ISSN 2413-6077
e-ISSN 2414-9985

I. Horbachevsky Ternopil National Medical University

International Journal of Medicine and Medical Research

Scientific-Practical Journal

Founded in 2015
Frequency: semiannually

Volume 11, No. 1

Ternopil – 2025

INTERNATIONAL JOURNAL OF MEDICINE AND MEDICAL RESEARCH

Founder:
I. Horbachevsky Ternopil National Medical University

Year of foundation: 2015

Recommended for printing and distribution
via the Internet by the Academic Council
I. Horbachevsky Ternopil National Medical University
(Minutes No. 8 of May 27, 2025)

State Registration:
Media identifier R30-02201.
Decision of the National Council of Television
and Radio Broadcasting of Ukraine No. 1551, Minutes No. 28, dated 23.11.2023.

The journal is included in the list of Professional Scientific Publications of Ukraine
Category "B" Specialties: 0511 – Biology; 0912 – Medicine; 0916 – Pharmacy; 0512 – Biochemistry
according to the Order of Ministry of Education and Science
No. 612, 7 May 2019 and 25 November 2019

The journal is presented international scientometric databases, repositories and scientific systems: Google Scholar, National Library of Medicine, Journal TOCs, ROAD, Base, DOAJ, Polska Bibliografia Naukowa, Ulrich's Periodicals Directory, Research4Life, Professional publications of Ukraine, National Library of Ukraine named after V.I. Vernadskyi, UCSB Library, Dimensions, German Union Catalogue of Serials, University of Oslo Library, University of Hull Library, SOLO – Search Oxford Libraries Online, European University Institute, Leipzig University Library, Cambridge University Library, Litmaps, Open Ukrainian Citation Index, Worldcat, J-Gate, CORE

International Journal of Medicine and Medical Research / Ed. by M. Korda. (Editor-in-Chief) et al. Ternopil: I. Horbachevsky Ternopil National Medical University, 2025. Vol. 11, No. 1. 121 p.

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CONTENTS

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 579.61:504.45.058:546.214
DOI: 10.63341/ijmmr/1.2025.06

Article's History:
Received: 22.12.2024; Revised: 19.03.2025; Accepted: 27.05.2025

Synergistic potential of aqueous ozone: Sublethal bacterial damage and enhanced antibiotic susceptibility

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Abstract. Combat-related injuries are frequently complicated by infections caused by multidrugresistant microorganisms, posing significant challenges to treatment. To improve clinical outcomes in such cases, alternative adjunctive therapeutic strategies are required. This study aimed to assess the antimicrobial potential of electrolytically generated aqueous ozone, focusing on its ability to induce sublethal damage in bacteria and enhance their susceptibility to antibiotics. A total of 357 multidrug-resistant clinical isolates were obtained from wound exudates and blood samples of 284 wounded soldiers. The most frequently isolated pathogens included *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus cereus*, and coagulase-negative *Staphylococcus* spp. Ozonated water was generated at concentrations ranging from 3.6 to 11.2 mg/L and subsequently standardised to approximately 4 mg/L for bacterial treatment. Selected isolates of *S. aureus* and *Escherichia coli* were exposed to aqueous ozone for 10 and 15 minutes. Sublethal damage was assessed by comparing bacterial growth on selective and nonselective media, revealing up to 89.2% sublethally injured *S. aureus* cells and up to 98.6% injured *E. coli* cells after 15 minutes of exposure. Initial estimations of the minimum inhibitory concentration using the Vitek-2 system were distorted by the combined effect of ozone and free chlorine, which forms during the electrolysis of saline solution. This prompted a shift to the Kirby-Bauer disc diffusion method. The results consistently demonstrated increased antibiotic susceptibility in treated isolates, as evidenced by larger inhibition zone diameters and a reduced number of antibiotics to which the isolates

Suggest Citation:
Pyatkovskyy T, Pokryshko O, Krasii N, Danylkov S. Synergistic potential of aqueous ozone: Sublethal bacterial damage and enhanced antibiotic susceptibility. Int J Med Med Res. 2025;11(1):6–13. DOI: 10.63341/ijmmr/1.2025.06

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remained resistant. Electrolytically generated aqueous ozone effectively compromises bacterial integrity, enhancing their susceptibility to antibiotics. It represents a promising adjunctive strategy for managing multidrug-resistant infections, particularly in resource-limited settings or during wartime

Keywords: antibacterial activity; antibiotic resistance; ozonated water; pathogenic bacteria; sublethal damage

Introduction

Combat-related injuries frequently present with multidrug-resistant infections that pose significant challenges to conventional antibiotic and antiseptic therapies. There is a growing need for alternative, low-cost antimicrobial strategies that can support infection control in resource-limited or high-risk environments. Exploring the potential of electrolytically generated aqueous ozone offers a promising direction for improving bacterial susceptibility and enhancing the effectiveness of standard treatments.

Ozone has long been recognised for its potent antibacterial properties and has been widely adopted across various industries for microbial control. In the food industry, A.C. Khanashyam *et al.* [1] highlighted its efficacy in improving food safety by inactivating a broad range of spoilage and pathogenic microorganisms. Similarly, X. Ren *et al.* [2] emphasised ozone's utility in water treatment, particularly in maintaining microbiological safety. In the wellness sector, A. Nagy [3] described its widespread application in spa and balneotherapy settings, where it contributes to maintaining hygienic conditions and reducing cross-contamination.

Despite these successful applications in non-medical settings, the adoption of ozone in clinical infection control remains limited. Traditional healthcare strategies have long relied on antibiotics and topical antiseptics as the primary tools for managing bacterial infections. However, as S. Lemmen & K. Lewalter [4] reported, the increasing global burden of antibiotic-resistant pathogens has severely undermined the effectiveness of these conventional methods, necessitating the exploration of adjunctive or alternative antimicrobial strategies. Although antiseptics represent a viable alternative to antibiotics, their use as a standalone solution for infection control remains problematic. As noted by A. Roth *et al.* [5], many antiseptics are constrained by limited efficacy in deep-seated infections due to poor tissue penetration, which reduces their utility in more complex clinical scenarios. J. Roy *et al.* [6] further emphasised that the repeated use of antiseptic agents may contribute to the development of microbial tolerance, raising concerns about long-term effectiveness. Additionally, J.J. Pérez-Santonja *et al.* [7] highlighted the cytotoxic effects of several commonly used antiseptics on human tissues, noting that their frequent application can impair wound healing processes. These concerns limit the suitability of antiseptics in sensitive clinical environments, particularly where tissue regeneration and healing are critical. Consequently, the search for alternative antimicrobial approaches that combine broad-spectrum efficacy with biocompatibility remains a key priority in contemporary medicine.

Electrolytic ozonation offers a compelling alternative by enabling the on-demand generation of ozonated water using only water and electricity, thereby eliminating the need for costly infrastructure or a continuous oxygen supply. H.Y. Li *et al.* [8] demonstrated that this method is both efficient and economical, providing a practical means of ozone production in settings where traditional ozonation systems – dependent on pure oxygen and specialised equipment – are impractical. Moreover, this technique addresses a major safety concern associated with gaseous ozone. As E. Grignani *et al.* [9] noted, exposure to ozone gas at high concentrations poses significant health risks, particularly respiratory toxicity. Electrolytic ozonation mitigates this hazard by avoiding the gas phase altogether, offering a safer alternative for clinical environments. With its advantages in cost, safety, and ease of implementation, electrolytic ozonation is emerging as a valuable tool in the development of novel antimicrobial strategies, particularly in the ongoing battle against antibiotic-resistant pathogens.

This study aimed to evaluate both the bactericidal and sublethal effects of ozonated water on clinical strains, as well as its impact on antibiotic susceptibility.

Materials and Methods

Sample collection and microbial identification. Wound discharge and blood samples were collected from wounded soldiers hospitalised at Ternopil Regional Clinical Hospital, Ternopil, Ukraine, between January and October 2024. Wound discharge samples were obtained using sterile cotton swabs and inoculated onto selective culture media. Blood samples were collected using vacuum blood collection tubes and analysed with the automated blood culture system BACT/ALERT 3D (bioMérieux, Marcy-l'Étoile, France). The resulting cultures were identified using the semiautomated Vitek-2 Compact 15 system (bioMérieux, Marcy-l'Étoile, France). The antibiotic susceptibility of treated and untreated isolates was assessed using the Kirby-Bauer disc diffusion method, alongside minimum inhibitory concentration (MIC) determination via the Vitek-2 Compact 15 system.

Aqueous ozone production and ozone concentration measurement. Ozonated water was generated on demand using sterilised tap water and a custom-built pre-production prototype employing water electrolysis on a diamond-coated anode. Ozone concentration in the water was assessed photometrically using a PoolLab 1.0 photometer (Water-i.d., Eggenstein, Germany), based on the intensity of colour change following reaction with N,N-diethyl-p-phenylenediamine sulphate. The ozone concentration was determined by comparing the absorbance of

the coloured light (at wavelengths of 530 and 620 nm) in the sample against that of untreated control, using calibration data programmed into the instrument. Tablet-based reagents were employed for measuring ozone levels. For bacterial treatment, the concentration was standardised to approximately 4 mg/L. When higher concentrations were detected, dilution was carried out to ensure that the treatment did not exceed this threshold.

Bacterial culture treatment and sublethal damage evaluation. The isolates were subcultured into meat-peptone broth for overnight incubation at 37°C. The resulting broth cultures were centrifuged at 3000 RPM using an 80-2 Benchtop Universal Laboratory Centrifuge (Jiangsu Jinyi Instrument Technology Co., Changzhou, China). The supernatant was discarded, and the cell pellets were resuspended in a sterile saline solution (0.9% NaCl). To minimise the presence of residual culture medium and reduce the organic load, the centrifugation and resuspension steps were repeated once. For ozone treatment, the supernatant was again discarded, and the pellets were resuspended in freshly prepared ozonated water (ozone concentration ~4 mg/L), followed by incubation at room temperature for 15 minutes. This was followed by serial dilution in sterile saline solution and plating of aliquots onto selective and non-selective culture media. The plates were incubated at 37°C for 24 hours. Sublethal injury of the tested strains was assessed by comparing colony counts between the selective and non-selective media [10]. This evaluation was conducted for *Staphylococcus aureus* and *Escherichia coli* isolates only. For *S. aureus*, non-selective blood agar and selective yolk salt agar (selective due to high salt concentration) were used. For *E. coli*, blood agar served as the non-selective medium, while MacConkey agar was used as the selective medium, with bile salts acting as selective agents by inhibiting the recovery of sublethally damaged cells. The percentage of sublethal injury was calculated using the following equation:

$$\%\ Injured\ cells = \frac{(CFU_{non-selective} - CFU_{selective})}{CFU_{non-selective}} \cdot 100. \quad (1)$$

For antibiotic susceptibility testing, pretreated suspensions of the selected strains were immediately spread onto Mueller-Hinton agar plates, and antibiotic-impregnated discs were applied in accordance with the Kirby-Bauer disc diffusion method. Control samples (untreated) followed the same protocol, using sterile saline in place of ozonated water. Antibiotic resistance status was determined based on the immediate post-treatment response; long-term resistance was not evaluated.

Statistical analysis. Data were collected and tabulated using MS Excel 2013. Categorical data were presented as percentages and proportions, while CFU counts were expressed in logarithmic values. Mean values and standard deviations (M ± SD) were calculated and used for statistical analysis. The equality of mean values between the two groups was assessed using Student's t-test. For comparisons among multiple groups, one-way analysis of variance (ANOVA) was performed using Statistica 8.0 software (StatSoft Inc., Tulsa, Oklahoma, USA).

Ethical approval. The research was conducted following the principles set out in the Declaration of Helsinki [11]. Ethical approval for the publication of this case report was obtained from the Ethics Committee of Ternopil National Medical University (Protocol No. 81, 3 April 2025).

Results and Discussion

Ozonated water, generated through electrolytic ozonation, had ozone concentrations ranging from 3.6 to 11.2 mg/L. A total of 357 clinical isolates were obtained from wound discharge and blood samples were collected from 284 wounded soldiers. The most frequently isolated pathogens included *Acinetobacter baumannii, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* among Gramnegative bacteria, while *S. aureus, Bacillus cereus,* and coagulase-negative *Staphylococcus* spp. were the predominant Gram-positive isolates. The distribution of these pathogens, along with the number and percentage of cases in which they were identified, is presented in Table 1.

Table 1. Distribution of isolated pathogens from wound discharge and blood samples

Pathogen	Wound discharge (n, %)	Blood isolates (n, %)
Acinetobacter baumannii	78 (21.85%)	5 (1.40%)
Bacillus cereus	28 (7.84%)	
Enterobacter cloacae	6 (1.68%)	
Enterococcus spp.	13 (3.64%)	1 (0.28%)
Escherichia coli	11 (3.08%)	
Klebsiella pneumoniae	51 (14.29%)	2 (0.56%)
Proteus mirabilis	6 (1.68%)	
Pseudomonas aeruginosa	38 (10.64%)	
Rothia kristinae	6 (1.68%)	
Staphylococcus aureus	64 (17.93%)	3 (0.84%)
Staphylococcus epidermidis	11 (3.08%)	
Staphylococcus spp.	13 (3.64%)	
Other	21 (5.88%)	
Total, n = 357	**346 (96.92%)**	**11 (3.08%)**

Source: compiled by the authors

During preliminary testing of antibiotic susceptibility using the Vitek-2 Compact system, bacterial suspensions were prepared in 0.45% NaCl, in accordance with the manufacturer's protocols. When assessing antibiotic susceptibility, the MICs of the untreated isolates were successfully determined using the Vitek-2 system. All 357 isolates demonstrated multidrug resistance, exhibiting resistance to three or more classes of antibiotics, thereby confirming the challenging nature of antimicrobial therapy in these cases. To evaluate the impact of aqueous ozone pretreatment, the required 0.45% sodium chloride solution was subjected to electrolysis using a portable ozone generator. However, chemical analysis revealed that the process generated not only ozone but also high concentrations of free chlorine (≥30 mg/L), another potent oxidising agent. This dual oxidative stress likely disrupted bacterial membranes and enzymatic systems. As a result, the Vitek-2 system misidentified *Staphylococcus aureus* as *Granulicatella adiacens* and *Erysipelothrix rhusiopathiae* – an unexpected but noteworthy observation. However, since the presence of chlorine introduced a confounding variable, the MIC results could no longer be attributed to the effect of ozone alone. For this reason, the Vitek-2 system was excluded from further ozone-specific susceptibility testing, and the Kirby-Bauer disc diffusion method was used instead. Representative results, illustrating the increased susceptibility of *S. aureus* to nitrofurantoin following ozonated water pretreatment, are shown in Figure 1.

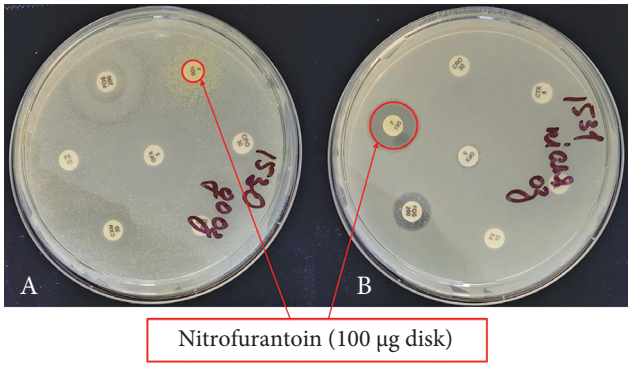

Figure 1. Results of the Kirby-Bauer disc diffusion method showing the effect of ozonated water pretreatment on antibiotic susceptibility of *S. aureus*
Notes: conversion to susceptibility is highlighted in red. A – untreated control; B – after 15-minute pretreatment with ozonated water
Source: compiled by the authors

To quantify this effect across all tested strains, the number of antibiotics to which each isolate was resistant was compared before and after ozonation. As summarised in Table 2, ozonated water pretreatment consistently reduced the number of antibiotics to which isolates exhibited resistance, highlighting its potential role in the susceptibility of multidrug-resistant bacteria to conventional antibiotics.

Table 2. Susceptibility of the isolates to antibiotics before and after treatment with ozonated water

Pathogen	Number of antibiotics to which the strain is resistant	
	before treatment with ozonated water	after treatment with ozonated water
Acinetobacter baumannii	12.64 ± 3.69	8.86 ± 3.81**
Enterobacter cloacae	9.50 ± 3.79	6.50 ± 3.37**
Enterococcus spp.	6.17 ± 1.58	5.11 ± 2.01*
Escherichia coli	5.76 ± 3.35	3.77 ± 1.89**
Klebsiella pneumoniae	12.42 ± 2.41	10.14 ± 3.39*
Proteus mirabilis	7.12 ± 2.13	5.57 ± 1.98*
Pseudomonas aeruginosa	11.57 ± 3.48	9.36 ± 3.54**
Staphylococcus aureus	10.71 ± 2.58	8.77 ± 2.64**
Staphylococcus epidermidis	8.21 ± 1.42	5.93 ± 1.10**

Notes: * – $p < 0.05$; ** – $p < 0.01$
Source: compiled by the authors

The extent of sublethal damage caused by ozonated water was quantified by comparing bacterial counts on selective and non-selective media for *S. aureus* and *E. coli*. For *S. aureus*, the initial concentration was approximately 8.9 log CFU/mL. After 10 minutes of treatment, there was no detectable reduction in blood agar, but a 1.04 log CFU/mL decrease was observed on yolk-salt agar, indicating that 90.97% of the surviving cells were sublethally injured. Following 15 minutes of treatment, a 1.65 log CFU/mL reduction was recorded on blood agar, and an additional 0.96 log CFU/mL reduction on yolk-salt agar was noted, corresponding to 89.19% sublethal injury among the treated population (Fig. 2).

For *E. coli*, the initial bacterial load was 8.97 log CFU/mL. After 10 minutes of ozonation, a reduction of 0.82 log CFU/mL on blood agar was observed, while a 1.59 log CFU/mL decrease was recorded on MacConkey agar, indicating that 97.44% of the population was sublethally damaged. With 15 minutes of treatment, the total reduction on blood agar reached 2.04 log CFU/mL, and the additional reduction on MacConkey agar was 1.77 log CFU/mL, representing 98.57% sublethally injured cells (Fig. 3).

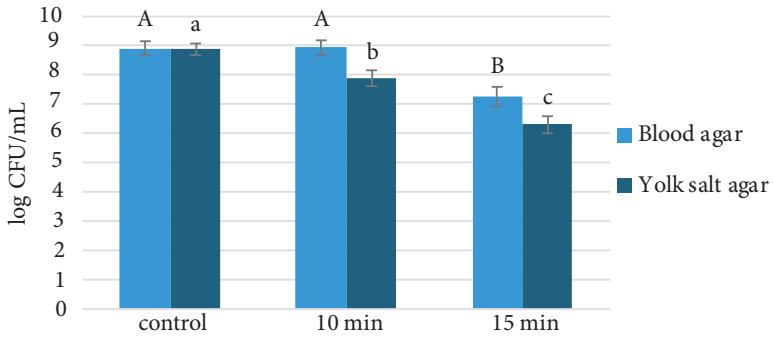

Figure 2. Effect of electrolytically generated aqueous ozone (~4 mg/L) on *S. aureus*
Notes: error bars indicate the standard deviation of the mean; letters above the bars denote a significant difference ($p < 0.05$)
Source: compiled by the authors

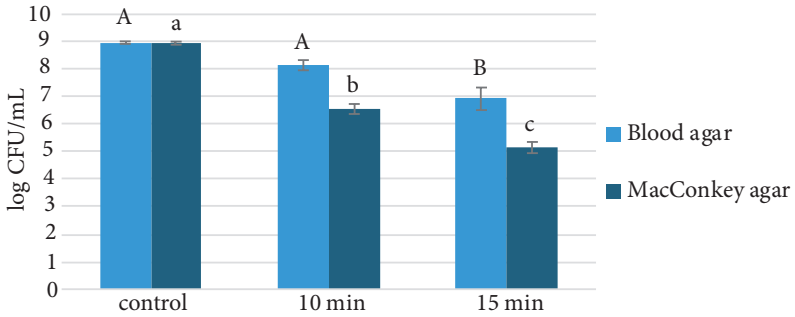

Figure 3. Effect of electrolytically generated aqueous ozone (~4 mg/L) on *E. coli*
Notes: error bars indicate the standard deviation of the mean; letters above the bars denote a significant difference ($p < 0.05$)
Source: compiled by the authors

The diversity of microbial isolates observed in this study is consistent with previous reports describing the microbiological landscape of combat-related injuries. I. Trutyak *et al.* [12] reported frequent isolation of *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and members of the *Enterobacteriaceae* family from mine blast and gunshot wounds, which aligns with the findings of the present study. G. Loban' *et al.* [13] highlighted the high prevalence of multidrug resistance among *A. baumannii* and *K. pneumoniae* isolates collected since the onset of the full-scale war in Ukraine, with resistance rates reaching 75%-80%. Likewise, K. Moussally *et al.* [14] documented substantial multidrug resistance in bacterial isolates from osteomyelitis cases in conflict zones, particularly among *S. aureus* and *P. aeruginosa*. The pathogen profile and resistance patterns observed in this cohort reflect broader trends in military medicine and underscore the ongoing challenge of managing infections in battlefield conditions. The high prevalence of multidrug-resistant pathogens necessitates the exploration of adjunctive antimicrobial strategies capable of enhancing bacterial susceptibility and disrupting resistance mechanisms.

The ozone concentrations obtained in this study (3.6-11.2 mg/L) are consistent with those reported in previous studies on electrolytic ozonation. Similar ranges (up to 5 mg/L) have been documented by E.I. Epelle *et al.* [15], where electrolytic ozonation was employed for microbial decontamination. However, some studies have reported higher ozone concentrations of 20-25 mg/L [16]. Differences in ozone yield may be attributed to variations in electrolysis parameters, electrode materials, water composition, and applied voltage. Compared with traditional ozonation systems, electrolytic ozonation offers the advantage of generating ozone on demand, without requiring a pure oxygen supply, making it a more cost-effective and scalable approach for antimicrobial applications [17].

Ozone is widely recognised for its antimicrobial properties, but its effects on bacterial physiology extend beyond direct inactivation. In this study, the authors observed that exposure to ozonated water not only reduced bacterial viability but also induced sublethal damage, as evidenced by differences in colony counts on selective and non-selective media. The observed differences in sublethal injury levels between Gram-positive and Gram-negative bacteria align with existing literature, suggesting that Gram-negative bacteria may be more susceptible to oxidative damage caused by ozone. This heightened vulnerability of Gram-negative bacteria may be attributed to the structural characteristics of their outer membrane, which contains lipopolysaccharides and unsaturated fatty acids that are particularly prone to oxidative attack. These results are consistent with earlier findings showing that reactive oxygen species, including ozone, cause significant damage to bacterial membranes, proteins, and DNA, ultimately leading to cell death or sublethal injury depending on the intensity and duration of exposure [18]. This suggests that, while some bacterial

cells survived ozone treatment, their cellular integrity and metabolic functions were compromised, making them more susceptible to additional stressors such as antibiotics. These findings support the idea that ozonated water could serve as an adjunct to conventional antimicrobial treatments, enhancing their efficacy against resistant pathogens.

Misidentification of microorganisms by the Vitek-2 system has been documented in several studies. S. Kim *et al.* [19] reported a case in which *Acinetobacter baumannii* was misidentified as *Alcaligenes faecalis*. Similarly, N. De Lappe *et al.* [20] described the misidentification of *Listeria monocytogenes*, while Z. Zong *et al.* [21] found that *Burkholderia pseudomallei* was incorrectly identified as *Burkholderia cepacia*. T.S. Park *et al.* [22] observed a misidentification of *Aeromonas veronii* biovar *sobria* as *Vibrio alginolyticus*, and T.K.F. Wang *et al.* [23] noted that a mucoid strain of *Salmonella enterica* serotype *Choleraesuis* was misidentified as *Hafnia alvei*. These examples illustrate the limitations of automated identification systems, particularly when dealing with atypical strains or those subjected to environmental stressors. In the present study, the misidentification of *Staphylococcus aureus* following treatment was likely influenced by oxidative stress caused by the combined presence of ozone and chlorine generated during the electrolysis of saline solution. While the specific contribution of each oxidant cannot be precisely determined, this outcome supports, at least partially, the hypothesis that oxidative treatments, including ozone exposure, may induce sublethal damage to bacterial cells. Such damage may interfere with biochemical identification systems and compromise diagnostic accuracy, highlighting the need for further investigation.

Although the observed increase in inhibition zone diameters and the reduction in the number of antibiotics to which the isolates appeared resistant suggest enhanced susceptibility, these changes should not be interpreted as a permanent reversal of antibiotic resistance. The effect is more accurately attributed to sublethal cellular damage induced by oxidative stress, which compromises bacterial defence mechanisms and temporarily sensitises the cells to antibiotics. This is consistent with previous findings in food microbiology, where reactive oxygen species such as ozone were shown to cause bacterial injury that is reversible under favourable conditions [24]. It is likely that, if the bacteria were provided with time and nutrients to recover, their original resistance profiles would re-emerge. Therefore, aqueous ozone should be viewed not as a standalone solution but as a temporary adjunct that enhances antibiotic efficacy during the acute phase of infection.

While this study demonstrates that pretreatment with aqueous ozone can enhance bacterial susceptibility to antibiotics through sublethal injury, recent findings also urge caution regarding the broader implications of sublethal ozonation. A study by C. Bai *et al.* [25] reported that sublethal concentrations of ozone (0-1.0 mg/L for 10 minutes) increased the frequency of conjugation and transformation among *E. coli* strains carrying resistance genes. These findings suggest that oxidative stress may promote horizontal gene transfer, potentially accelerating the spread of antibiotic resistance in aquatic environments. Although the ozone concentrations and experimental settings in this study differ, and the treatment was designed to support infection control in a clinical context, this evidence highlights the need for careful optimisation of ozone-based interventions. Ensuring adequate ozone dosing to achieve complete bacterial inactivation may be critical, particularly when applying ozone in environmental or water treatment settings, where sublethal exposure could have unintended ecological consequences.

Conclusions

This study demonstrates the promising potential of aqueous ozone, generated via electrolysis, as an effective adjunct in combating multidrug-resistant pathogens isolated from combat-related wounds. Among the Gram-negative bacteria, the most frequently isolated pathogens were *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. For Gram-positive bacteria, *Staphylococcus aureus*, *Bacillus cereus*, and coagulase-negative *Staphylococcus* spp. predominated. All isolates exhibited multidrug resistance, displaying resistance to three or more classes of antibiotics, highlighting the urgency for alternative or adjunctive antimicrobial strategies. The results indicated that pretreatment with electrolytically generated ozonated water (~4 mg/L) induced significant sublethal injury in both Gram-positive and Gram-negative bacteria. Specifically, *S. aureus* exhibited approximately 89% sublethal injury after 15 minutes of exposure, while *E. coli* showed an even higher level of damage, with nearly 99% of cells sublethally injured. Notably, this treatment enhanced the antibiotic susceptibility of multidrug-resistant isolates, as evidenced by the consistent reduction in the number of antibiotics to which the bacteria appeared resistant, and by increased inhibition zones in Kirby-Bauer disc diffusion tests. These findings highlight the potential of aqueous ozone as a complementary approach that can temporarily sensitise resistant pathogens and improve the effectiveness of existing treatments. Importantly, electrolytic ozonation offers practical advantages: it is low-cost, generates ozone on demand without the need to handle gaseous ozone, and can be implemented in resource-limited or field settings. However, the study also underscores the need for careful optimisation, as oxidative treatments may have unintended effects, such as temporarily altering bacterial identification profiles. Future research should explore the long-term clinical outcomes of combined ozone-antibiotic therapies and establish standardised protocols for safe and effective use in both civilian and military healthcare contexts.

Acknowledgements

The authors express their gratitude to the medical centre "Dr. Che Health Club" for the provided equipment and advice.

Funding
None.

Conflict of Interest
None.

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Синергічний потенціал водного розчину озону: сублетальні пошкодження бактерій та підвищена чутливість до антибіотиків

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Анотація. Бойові поранення часто ускладнюються інфекціями, спричиненими мультирезистентними мікроорганізмами, що створює значні проблеми для лікування. Для покращення результатів у таких випадках необхідні альтернативні допоміжні стратегії лікування. Метою цього дослідження було оцінити антимікробний потенціал електролітично згенерованого водного розчину озону, зосереджуючись на його здатності викликати сублетальне пошкодження бактерій та підвищувати чутливість до антибіотиків. Загалом було отримано 357 мультирезистентних клінічних ізолятів з виділень з ран та зразків крові 284 поранених військових. Найчастіше виділялися такі збудники, як *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus cereus* та коагулазонегативні *Staphylococcus* spp. Озоновану воду було згенеровано в концентраціях від 3,6 до 11,2 мг/л, потім стандартизовано до ~4 мг/л для бактеріальної обробки. Відібрані ізоляти *S. aureus* та *Escherichia coli* були піддані впливу водного розчину озону протягом 10 і 15 хвилин. Сублетальні пошкодження оцінювались шляхом порівняння росту бактерій на селективних та неселективних середовищах, виявивши до 89,2 % сублетально пошкоджених клітин *S. aureus* та до 98,6 % пошкоджених клітин *E. coli* через 15 хвилин. Попередні оцінки мінімальної інгібуючої концентрації з використанням системи Vitek-2 були спотворені комбінованим впливом озону та вільного хлору, що утворюється під час електролізу сольового розчину, що спонукало до переходу на диско-дифузійний тест Кірбі-Бауера. Результати послідовно показували підвищену чутливість до антибіотиків у оброблених ізолятах, про що свідчить збільшення діаметрів зон інгібування та зменшення кількості антибіотиків, до яких ізоляти залишалися стійкими. Електролітично згенерований водний розчин озону ефективно порушує цілісність бактерій, підвищуючи їхню чутливість до антибіотиків. Він пропонує перспективну додаткову стратегію для лікування мультирезистентних інфекцій, особливо в умовах обмежених ресурсів або у воєнний час

Ключові слова: антибактеріальна активність; стійкість до антибіотиків; озонована вода; патогенні бактерії; сублетальні пошкодження

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 613.88:614.213(540.51)
DOI: 10.63341/ijmmr/1.2025.14

Article's History:
Received: 23.09.2024; Revised: 15.02.2025; Accepted: 27.05.2025

Assessment of family planning awareness and behaviour in a tertiary Healthcare Centre in Vadodara

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Abstract. India's extensive family planning programme has made great strides, yet a disparity persists between women's desired fertility and their access to family planning services. The purpose of the present study was to assess the knowledge, attitude towards, and practices of family planning, as well as the unmet need among women in Vadodara, Gujarat, India. A cross-sectional study was conducted among 100 married women of reproductive age attending a tertiary care hospital in Vadodara. Data were collected using pre-tested questionnaires encompassing socio-demographic factors, family planning knowledge, attitudes, practices, and unmet needs. Findings revealed that while 64% of women were aware of family planning, knowledge was associated with age, literacy, and urban residence. All women with knowledge expressed approval, influenced by literacy and urban residence. Family planning practice reached 51%, with method choice varying by age, literacy, urban residence, and accessibility. Unmet needs for family planning were substantial at 28%. The findings of the present study highlighted the need for tailored education, improved access to family planning services, and targeted interventions. Tailored education can enhance knowledge and practice, especially among marginalised groups. Policymakers should prioritise rural access to effective methods. Non-governmental organisations can increase awareness and address unmet needs through community-based interventions. Understanding these factors is crucial for developing effective strategies to improve reproductive health outcomes and achieve desired family size

Keywords: contraception; unmet needs; reproductive health; women's health; health education

Introduction

India has made substantial strides in family planning (FP), reducing fertility rates through national programmes, public health initiatives, and social awareness campaigns. Despite its vast size and diverse population, India successfully decreased its fertility rate from 5.9 in 1961 to 2.2 in 2017 [1]. While according to P. Muttreja P & S. Singh [2] the challenges persist, such as regional disparities and unmet needs, continued investment in family

Suggest Citation:
Vala A, Panchal P, Sheth M. Assessment of family planning awareness and behaviour in a tertiary Healthcare Centre in Vadodara. Int J Med Med Res. 2025;11(1):14–21. DOI: 10.63341/ijmmr/1.2025.14

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planning can further enhance maternal and child health and overall well-being.

Aligned with the 2030 Agenda for Sustainable Development, India aims to ensure universal access to sexual and reproductive healthcare services, including family planning. Family planning is a cornerstone of India's Reproductive, Maternal, New Child Health + Nutrition (RMNCAH+N) strategy. The programme has made notable progress since its inception, contributing to population stabilisation and reducing maternal, infant, and child mortality. Recent indicators demonstrate a decline in maternal mortality ratio from 130 to 97 maternal deaths per 100,000 live births between 2014-2016 and 2018-2019 [3], with eight states achieving the SDG target of reducing maternal mortality ratio to below 70. The country's total fertility rate is now below the replacement level (2.1), according to the latest round of the National Family Health Survey 2019-2021, and the use of modern contraception methods among married women has increased from 47.8% to 56.5% [4].

India is committed to fulfilling its national commitments under the global FP2030 agreement, expanding family planning access and improving reproductive health. Ensuring access to skilled birth attendants is crucial for preventing maternal deaths, and India has achieved a high rate of births attended by qualified healthcare professionals, with nearly 90% of all births attended by doctors or nurses/midwives [5]. While progress has been made, B. Nanda *et al.* [6] found that challenges such as intimate partner violence, gender-based discrimination, and son preference persist. India has implemented measures to address these issues, including strengthening the enforcement of laws against sex selection and promoting programmes to end child marriage.

Family planning is a highly cost-effective intervention for global health and development. Investing in family planning yields significant economic returns. For every USD 1 invested in FP, there is a financial return of USD 20-120.4 [7]. Access to and utilisation of family planning services and corresponding contraception methods are essential for women's health and well-being, contributing to gender equity and poverty reduction. An unmet need for FP can lead to unintended pregnancy, unsafe abortion, and increased risk of death during labour and delivery, particularly among young women. The COVID-19 pandemic presented challenges to family planning services in 2020-2021. However, the Ministry of Health and Family Welfare prioritised family planning as essential and emphasised postpartum family planning and other spacing methods. Despite disruptions, many states reported increases in the use of various contraception methods, including intrauterine devices (IUDs), injectables, and oral contraceptives [8].

Research in Karnataka by I. Nasreen *et al.* [9] revealed a strong correlation between belief in family planning and its actual practice ($p < 0.0001$). Age was also found to be influential, with women aged 31-40 being less likely to adopt family planning methods compared to those aged 21-30 ($p = 0.012$). Common reasons cited for non-use included desired family size and cultural norms. Despite a reasonable understanding of modern contraception methods, Muslim women in the study area exhibited relatively low usage rates. Furthermore, the study on trends of prevalence of unmet need of family planning in India by K. Devaraj *et al.* [10] showed that India's unmet need for family planning halved between 1993 and 2021. While the national numbers improved, millions still lack access, with four states contributing significantly to the unmet need.

India's advances in family planning are notable, but ongoing efforts are necessary to address the persisting challenges and ensure universal access to reproductive healthcare services. By strengthening family planning programmes and addressing underlying social and economic factors, India can further improve maternal and child health outcomes and promote gender equality. The purpose of the present study was to evaluate the knowledge, attitudes, and practices regarding family planning and unmet needs of reproductive-age women in Vadodara, Gujarat.

Materials and Methods

A cross-sectional descriptive study was conducted at Shree Sayajirao General Hospital (SSGH), a tertiary care hospital in Vadodara, Gujarat, India. SSGH is a comprehensive healthcare facility that serves patients from a diverse range of geographic areas, including urban, rural, and tribal regions. Married women of reproductive age, specifically between 15 and 49 years old, were purposefully selected for participation in the study. These women were recruited from the Curative and Preventive General Practice (CPGP) Outpatient Department (OPD) at SSGH. To ensure the inclusion of eligible participants, several criteria were applied. Women who were unmarried, widowed, divorced, or had undergone a hysterectomy were excluded from the study. Additionally, women who were not willing to take part were not included.

Data was collected for the study over a two-month period, from September to October 2019. Before conducting face to face interviews with the subjects, informed consent was obtained. This involved providing the subjects with a detailed explanation of the study's purpose, how their data would be used, and their rights as participants. Structured questionnaires with close-ended questions were used to collect data from the subjects. These questionnaires were pre-tested and pre-validated to ensure their reliability and validity. A pilot test of the questionnaire was conducted at a primary health centre affiliated with Medical College Baroda to identify areas for improvement, such as reframing questions and categorising common responses. The questionnaires included questions related to socio-demographic variables, such as age, religion, education, occupation, residence, and income. Additionally, questions were asked about family planning knowledge, attitudes, and practices. The knowledge domain focused on topics such as family planning methods, birth spacing, and various contraceptive options. To assess attitudes, participants were presented with statements related to social and cultural beliefs regarding family planning. These statements were

accompanied by a rating scale, enabling subjects to specify their level of agreement or disagreement. To ascertain practices, the subjects were asked about their future childbearing desires, current contraception use, experience with conventional methods of contraception, and any unmet needs for family planning. The collected data was entered and analysed using password-protected Microsoft Excel software. This password-protected access was restricted solely to the investigators involved in the study, ensuring the confidentiality of the subjects' data. The quantitative data was analysed and presented in the form of rates and proportions, accompanied by graphical representations. The chi-square test was employed to analyse the statistical significance of the findings, and a 95% level of significance was set for interpretation.

Prior to initiating the study, necessary approvals were obtained from the Institutional Ethics Committee of Medical College Baroda and the Chief District Health Officer. The number for ethical approval is IECBHR/097-2019. These approvals ensured that the study adhered to ethical guidelines and protected the rights of the subjects. An eligible couple was defined as a married couple where the wife was of reproductive age, typically considered to be between 15 and 45 years old. This operational definition was a prerequisite for participation in this study. By including only eligible couples, the study ensured that analysis focused solely on this specific demographic group. Unmet needs for family planning are calculated in accordance with [11]:

(Women (married or in union) who are not using contraception, are fecund, and desire to either stop childbearing or postpone their next birth for at least two years + pregnant women whose current pregnancy was unwanted or mistimed + women in postpartum amenorrhea who are not using contraception and at the time they became pregnant, had wanted to delay or prevent the pregnancy ÷ Total number of women of reproductive age (15-49) who are married or in a union) × 100. (1)

Results and Discussion

A total of 100 females from the reproductive age group were enrolled in this study, with a mean (SD) age of 30.76 (6.75) years. Half (50%) of the females were in the age group of 21-30 years. Most (81%) of the females were followers of the Hindu religion. The knowledge about the contraception was associated with the age group. Knowledge about contraception was greater in the females with older age. However, age-group association was not observed in practice or attitude towards contraception. Out of the total females, 82% were females residing in urban areas. Knowledge and attitude regarding contraception was observed more among the urban residents as opposed to rural and tribal. Education of female subjects and their husbands was significantly associated with the knowledge, attitude towards, and practices of contraception use among the selected population (Table 1).

Table 1. Association of socio-demographic factors with KAP (knowledge, attitudes, and practices) of family planning

Variables	Knowledge about family planning				Practices of family planning method			Attitudes towards family planning method		
	Yes	Partial	No	p-value	Yes	No	p-value	Approve	Disapprove	p-value
Age group (in years)										
<20	02	04	00		02	02		02	04	
21-30	35	03	12	**0.0008**	23	18	0.44	35	15	0.58
31-40	25	06	00		24	12		27	12	
>40 years	02	03	00		02	03		02	03	
Religion										
Hindu	49	14	18	0.31	40	27	0.88	56	25	0.62
Muslim	15	02	02		11	08		12	07	
Wife's education										
Illiterate	06	0	03		09	00		03	06	
Primary	12	02	10		11	10		15	09	
Secondary	13	10	04	**0.002**	14	13	**0.01**	15	12	**0.02**
Higher secondary	11	02	03		07	06		11	05	
Graduate and above	22	02	00		06	10		24	00	
Husband's education										
Illiterate	03	00	03		03	03		03	03	
Primary	15	00	03		12	06		15	03	
Secondary	10	10	04	**0.004**	11	06	**0.03**	10	14	**0.02**
Higher secondary	14	05	00		08	05		14	05	
Graduate and above	22	06	05		17	11		26	07	
Residence										
Urban	55	13	14		18	15		56	26	
Rural	6	3	6	**0.04**	06	06	0.32	09	05	**0.001**
Tribal	03	00	00		03	00		03	00	

Continued Table 1

Variables	Knowledge about family planning				Practices of family planning method			Attitudes towards family planning method		
	Yes	Partial	No	p-value	Yes	No	p-value	Approve	Disapprove	p-value
Socio-economic status*										
Upper middle class	13	06	09	**0.02**	00	03	0.07	02	02	**0.003**
Middle class	17	02	08		14	09		19	08	
Lower middle class	32	06	03		18	16		36	05	
Lower class	13	06	09		19	07		11	17	

Notes: *modified BG prasad classification, update-2019
Source: compiled by the authors of this study

Among study participants, only 8% of subjects were nulliparous, and nearly 14% had a history of abortion in the past. A positive association was observed between the practices of family planning and attitudes regarding the use of the FP methods among the multiparous women. The history of abortion had a positive association with the knowledge and attitudes towards family planning methods. Subjects with a history of abortion had more knowledge and a positive attitude towards using the FP methods. The lesser number of children was associated with the KAP of the FP method. There was no association observed between knowledge and attitude with the number of male children (Table 2).

Table 2. Obstetric history of the subjects and its association with KAP of family planning

Variables	Knowledge about family planning				Practice of family planning method			Attitudes towards family planning method		
	Yes	Partial	No	p-value	Yes	No	p-value	Approve	Disapprove	p-value
Parity										
Nulliparous	6	2	0	0.30	6	0	**0.03**	8	0	**0.04**
Multiparous	58	14	20		45	35		60	32	
History of abortion										
Yes	14	0	0	**0.007**	5	3	0.70	14	0	**0.01**
No	44	14	20		40	32		46	32	
Number of living children										
0	06	02	00	**0.01**	06	00	**0.004**	08	00	**0.01**
1	26	04	05		07	16		26	09	
2	21	10	09		27	13		23	17	
3 and more	11	00	06		11	06		11	06	
Number of male children										
0	20	02	04	0.19	08	07	0.17	22	4	**0.001**
1	28	09	11		26	19		28	20	
2 and more	16	5	5		17	09		18	08	

Source: compiled by the authors of this study

Figure 1 shows the knowledge and practices regarding the various FP methods. Although nearly three-fourth of the women were aware of the barrier method, only one-fourth of them were practicing the method. Another common method was having knowledge of hormonal pills, permanent methods, IUCDs. Permanent method was the chosen method for contraception. Over three-fourths of the subjects had knowledge of FP from healthcare workers (79%), followed by internet (40%) and television (36%) (Fig. 2).

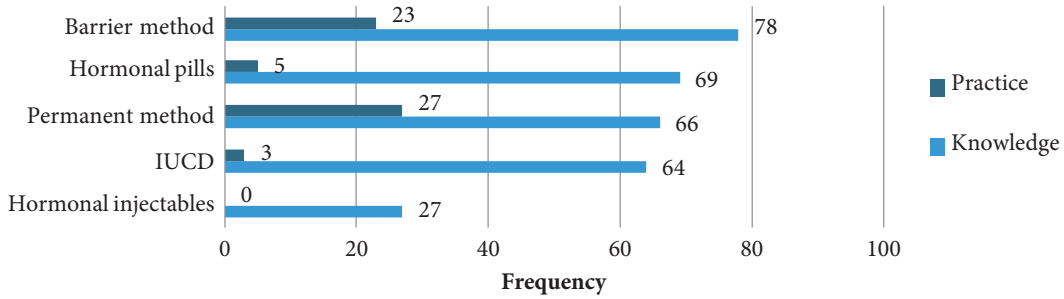

Figure 1. Knowledge and practice of various contraception methods among subjects
Source: compiled by the authors of this study

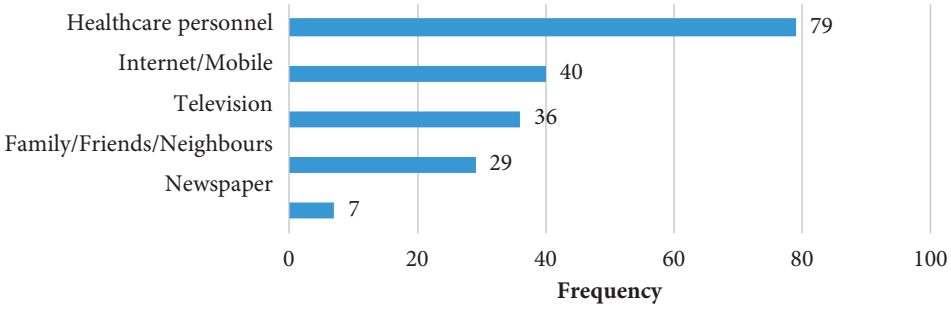

Figure 2. Source of knowledge of family planning methods among subjects
Source: compiled by the authors of this study

Table 3 presents association of knowledge of family planning method with the practice of FP method. No association of knowledge of FP method with the practices of FP method was observed. At the same time, the accessibility of FP method was positively associated with the practice of FP methods. According to Figure 3, 64% of females had the knowledge regarding the FP method, but only 51% of them were using the family planning methods. Increased age, education, urban residence, higher socio-economic class were positively associated with the KAP of FP method. The accessibility of the FP methods was also associated with the practices of FP methods.

Table 3. Factors associated with practices of family planning method

Variables	Practices of family planning method		p-value
	Yes	No	
Knowledge about family planning methods			
Yes	32	18	0.28
Partial	08	08	
No	11	09	
Knowledge about source of obtaining contraceptives			
Aware	46	28	0.18
Not aware	05	07	
Perceived knowledge of side effects			
Aware of side effects of contraception	23	12	0.24
Not aware of side effects	21	19	
Accessibility of family planning method			
Easily accessible	41	23	**0.01**
Not easily accessible	10	12	

Source: compiled by the authors of this study

The unmet need for family planning was found by formula (1):

$$\frac{\{(21+5+2)\cdot 100\}}{100} = 28\%. \quad (2)$$

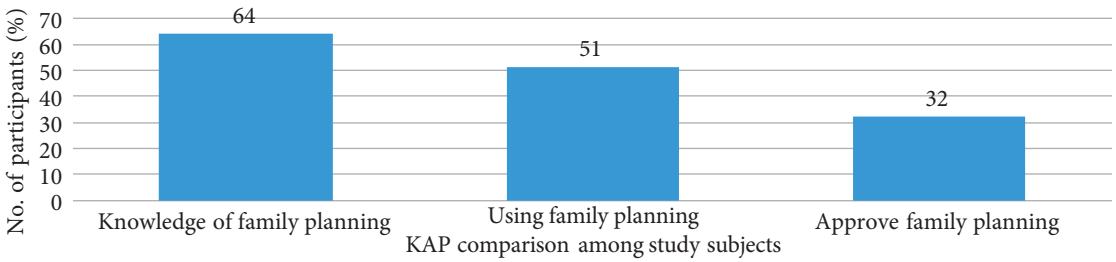

Figure 2. Source of knowledge of family planning methods among subjects
Source: compiled by the authors of this study

KAP of family planning measures are significant in improving the reproductive outcomes. Three of them play a vital role in improving the reproductive health. The present study showed that nearly 64% of subjects had knowledge

of family planning, while 16% had partial knowledge of family planning methods. The findings were greater than those presented in the study in Ethiopia by D. Bekele *et al.* [12]. The reason for such disparity may be explained by the national, cultural, and religious differences. Other reasons may include dependence on the age of the female, socio-economic status, education status, and accessibility of healthcare and social media, etc.

In the present study, the primary source of knowledge was healthcare personnel (79%), followed by internet/mobile (40%). The study findings are comparable to the findings in Northwest Ethiopia [13]. The knowledge was significantly associated with an older age group (31-40 years), literacy, and urban residency. These findings are in line with the study by M. Qazi *et al.* [14] in North India. Although there was significant association observed for age with the knowledge of contraception methods, there was no association observed between practices and attitudes. This could be attributed to their advanced experience and previous visits to healthcare facilities during their prior delivery. Another reason could be that with advancing age, there may be an increased need for contraception or extended birth spacing. These might be the possible reasons for the association.

Literacy of spouses was positively associated with the knowledge, attitudes, and practices of contraception. These findings were analogous to those of Y.R. Singh *et al.* [15] in Jaipur. Literacy increases the chances of exposure to more social media platforms, or more resources may increase the chances of knowledge for the family planning methods. Urban residence and higher socio-economic class were also associated with good knowledge and practice. Urban women were more likely to be jobholders and have more media exposure, which can increase the chances of having improved knowledge.

Out of the total, 51% of subjects under study were practising the family planning methods, which was smaller than in a study done in ASEAN countries [16] and greater than in Chhattisgarh [17]. In the present study, the most common contraception method was the barrier method, which is comparable to the F. Ewerling *et al.* [18], where most of the subjects were using modern contraception methods (76.1%), where condoms (11.8%) and OCPs (8.5%) were used frequently. A.S. Kasa *et al.* [19] revealed that residence, age, educational status, number of children, and monthly income were significantly associated with the practice of FP. The study findings were in line with the findings of the present study.

R.T. Wani *et al.* [20] found that the knowledge and attitude of the study subjects showed a poor correlation with the practice of family planning. Analogous findings were observed in the present study, where obstetric history, such as nulliparity, the number of children, and having one or more male children, was significantly associated with the approval of the family planning method. However, W. Simegn *et al.* [21] found that knowledge was positively associated with the usage of contraception methods. The reason for this may be the attitudes of the subjects towards using the family planning method. Many cultural beliefs prevent the usage of family planning methods.

The unmet need for family planning in the present study was 28%, which was lower than in the studies conducted in Tamil Nadu (39%) and South Nigeria (38%) [22-23]. The major reason for the unmet need can be the women understanding the FP method as a terminal method and not a spacing method, thereby preventing them from using the FP method. According to K. Machiyama *et al.* [24], the other reasons for unmet need are ambivalent fertility preferences, low perceived risk of getting pregnant, partner preference, etc. By considering the above factors, targeted interventions can be developed to encourage behaviour change among women regarding the use of family planning measures. This may help enhance family planning methods and positively impact fertility and demographic indicators.

Conclusions

The key findings of the present study were that older women demonstrated a greater level of knowledge of contraception methods compared to younger subjects. Urban residence and higher education levels were also positively correlated with knowledge of contraception methods. While age and residence did not significantly influence attitudes towards contraception, education level had a positive impact. Education level, residence, and accessibility of contraception methods were significantly associated with the practice of contraception methods. Higher education levels and urban residence were linked to higher rates of contraception use. Other factors like parity, history of abortion, and the number of living children were associated with KAP. Subjects with a history of abortion exhibited greater knowledge and positive attitudes towards family planning. The number of living children was negatively correlated with KAP. The study's limitations included its sample size, reliance on self-reported data and a hospital-based study which may limit the generalisability of the findings. Future research areas include longitudinal studies to track changes in KAP over time, comparative studies to examine KAP across different contexts, and qualitative studies to explore women's perceptions and experiences with family planning. Economic evaluations can also be conducted to assess the cost-effectiveness of family planning interventions.

Acknowledgements

The authors of the present study would like to acknowledge the Dean, Medical College Baroda and Medical Superintendent, SSG Hospital, Vadodara, Gujarat for their support during the data collection for this study.

Funding

None.

Conflict of Interest

None.

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Оцінка рівня обізнаності та поведінки щодо планування сім'ї у вищому медичному закладі у м. Вадодара

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Анотація. Широкомасштабна програма планування сім'ї в Індії досягла значних успіхів, але все ще зберігається диспропорція між бажаною фертильністю жінок та їхнім доступом до послуг з планування сім'ї. Метою цього дослідження було оцінити знання, ставлення та практику планування сім'ї, а також незадоволені потреби жінок у м. Вадодара, штат Гуджарат, Індія. Було проведено перехресне дослідження серед 100 заміжніх жінок репродуктивного віку, які відвідували лікарню третинного рівня у м. Вадодара. Дані збиралися за допомогою попередньо протестованих анкет, що охоплювали соціально-демографічні фактори, знання з питань планування сім'ї, ставлення, практики та незадоволені потреби. Результати показали, що хоча 64 % жінок знають про планування сім'ї, їхні знання пов'язані з віком, грамотністю та проживанням у місті. Усі жінки, які знають та схвалювали планування сім'ї, були більш освіченими та проживали у містах. Практика планування сім'ї складала 51 %, причому вибір методу залежав від віку, грамотності, міського проживання та доступності. Незадоволені потреби у плануванні сім'ї були значними – 28 %. Результати цього дослідження підкреслили потребу в цілеспрямованій освіті, покращенні доступу до послуг з планування сім'ї та цілеспрямованих втручаннях. Цілеспрямована освіта може підвищити рівень знань і практичних навичок, особливо серед маргіналізованих груп населення. Політики повинні надавати пріоритет доступу сільських жителів до ефективних методів планування сім'ї. Неурядові організації можуть підвищити рівень обізнаності та вирішити питання незадоволених потреб за допомогою втручань на рівні громад. Розуміння цих факторів має вирішальне значення для розробки ефективних стратегій, спрямованих на покращення результатів репродуктивного здоров'я та досягнення бажаного розміру сім'ї

Ключові слова: контрацепція; незадоволені потреби; репродуктивне здоров'я; здоров'я жінок; медична освіта

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616.379-008.64-06::617.736-005.98:616.153.45/.915
DOI: 10.63341/ijmmr/1.2025.22

Article's History:
Received: 18.10.2024; Revised: 23.03.2025; Accepted: 27.05.2025

Comparison of insulin resistance and lipid profile in clinically significant macular oedema versus non-clinically significant macular oedema in patients with type 2 diabetes mellitus

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Abstract. Lifestyle-related disorders, particularly diabetes, pose a significant global health challenge. Diabetic macular oedema, a microvascular complication, highlights the importance of managing insulin resistance and hyperlipidaemia for optimal clinical outcomes. Understanding the interplay between these factors is crucial for optimising therapeutic strategies and improving patient care. This cross-sectional study aimed to compare insulin resistance and lipid profiles between patients with clinically significant macular oedema and those with non-clinically significant macular oedema, both diagnosed with type 2 diabetes mellitus. This research can aid in the earlier identification and classification of macular oedema, enabling more timely and specific interventions. In general, 86 patients with type 2 diabetes

Suggest Citation:
Singh L, Sootinck M, Beg Z, Nigam B, Chandra A. Comparison of insulin resistance and lipid profile in clinically significant macular oedema versus non-clinically significant macular oedema in patients with type 2 diabetes mellitus. Int J Med Med Res. 2025;11(1):22–32. DOI: 10.63341/ijmmr/1.2025.22

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mellitus and macular oedema were divided into two groups: clinically significant macular oedema and non-clinically significant macular oedema. Comprehensive demographic data, medical histories, and current medication regimens were recorded. Glycaemic control and lipid profiles were assessed, while ophthalmological evaluations included visual acuity measurements and intraocular pressure assessments. Significant differences were observed between the two groups, particularly in diabetes duration, body mass index, blood glucose levels, and lipid profiles. Patients with clinically significant macular oedema had a longer duration of diabetes, a higher body mass index, and elevated blood glucose levels. Triglyceride levels were significantly higher, while high density lipoprotein levels were lower in the clinically significant macular oedema group. Multivariate analysis revealed significant associations between the odds of developing clinically significant macular oedema and diabetes duration, visual acuity, and high-density lipoprotein levels, suggesting their potential as risk factors for this condition

Keywords: diabetic macular oedema; dyslipidaemia; retinal diseases; diabetic neuropathies; retinal vein occlusion

Introduction

Diabetes, a leading lifestyle disorder, poses a significant global health challenge. Diabetes, a widespread chronic ailment caused by insufficient production or utilisation of insulin, impacts an estimated global adult population of approximately 537 million individuals. This figure is anticipated to increase to 643 million by 2030, and further to 783 million by 2045 [1, 2]. In South-East Asia (SEA), specifically, the prevalence of diabetes has exceeded all previous projections. Diabetic macular oedema (DMO) exacerbates the complications associated with diabetes mellitus (DM) by inducing visual impairment, frequently occurring in conjunction with diabetic retinopathy (DR) [3]. DMO, which impacts around 10% of diabetic patients, is identified as the predominant cause of vision-threatening DR in primary care settings. Furthermore, those who have diabetes are at an increased risk of developing cataracts during their youth, which further compromises the vision of individuals with diabetes mellitus [4].

Lipids and insulin are both pivotal factors in the pathogenesis and advancement of DMO and DR. An increased risk is correlated with elevated levels of total cholesterol and triglycerides, specifically low-density lipoprotein (LDL) cholesterol [5]. Conversely, high-density lipoprotein (HDL) cholesterol demonstrates a protective effect. Insulin resistance, a defining feature of type 2 diabetes, contributes to neurodegeneration and retinal vascular abnormalities by impeding glucose absorption and increasing inflammation and oxidative stress. The importance of dyslipidaemia and insulin resistance in the pathophysiology of DR and DMO is underscored by their interaction, which highlights potential therapeutic targets that could alleviate vision loss in diabetic patients [6].

Y.X. Xu *et al.* [7] recently conducted a cross-sectional study to investigate the relationship between diabetic retinopathy (DR) and various measures of insulin resistance (IR) in a cohort of 2,211 patients with type 2 diabetes. The study demonstrated a significant association between the estimated glucose disposal rate (eGDR) and both the presence and severity of diabetic retinopathy among the indicators analysed. The results suggest that eGDR may be a reliable indicator of DR, potentially surpassing other IR indices [8].

In a study by R. Behera *et al.* [9], the correlation between lipid profile and the occurrence and severity of DR, including clinically significant macular oedema (CSMO), was confirmed. With the exception of high triglyceride levels, elevated levels of total cholesterol, LDL, and triglycerides (TG), as well as decreased HDL levels, were found to increase the risk and severity of DR and CSMO. The findings highlight the complex relationship between metabolic factors, such as dyslipidaemia and insulin resistance, and the onset and progression of diabetic ocular complications. This underscores the potential for targeted interventions and risk-reduction strategies.

Understanding the interplay between insulin resistance, lipid profile, and macular oedema in patients with type 2 diabetes is of significant clinical importance. CSMO is a severe complication of diabetic retinopathy, leading to visual impairment and blindness [10]. However, distinguishing between clinically significant and non-clinically significant macular oedema (non-CSMO) is crucial for treatment decisions and prognosis. Investigating the differences in insulin resistance and lipid profiles between these two subgroups can provide valuable insights into the underlying pathophysiology and potentially guide personalised therapeutic approaches. Therefore, this study aimed to investigate the association of CSMO among patients with type 2 diabetes mellitus with insulin resistance and dyslipidaemia at a tertiary care centre in north India.

Materials and Methods

This cross-sectional study was conducted in the Department of Ophthalmology at Era's Lucknow Medical College, Lucknow, over two years (Aug 2021-Aug 2023). A total of 86 patients with macular oedema due to type 2 diabetes mellitus, aged over 18 years, and attending the Ophthalmology OPD at Era's Lucknow Medical College and Hospital were included in the study following ethical clearance and informed consent, following the Helsinki Declaration [11]. Exclusion criteria included patients undergoing insulin treatment and those taking lipid-regulating drugs (such as statins and fibrates), as well as patients receiving treatment for diabetic macular oedema, individuals who had undergone intraocular surgery or laser treatment or received intravitreal injections within the past three months. Additionally, patients with a history of using drugs affecting macular thickness (such as corticosteroids or nephrotoxic

drugs) within the past three months were excluded. Those with significant media haziness, which would prevent proper fundus visualisation, were also excluded. Patients diagnosed with diabetic macular oedema were categorised into two groups: Group CSMO and Group non-CSMO, each consisting of 43 patients. Following enrolment, participants' demographic details, including age and gender, were recorded. A comprehensive systemic examination was undertaken to collect medical histories of chronic conditions such as hypertension, ischaemic heart disease, nephropathy, and neuropathy. Concurrently, information on current medications was recorded. Patients observed an overnight fast before providing a 2 mL blood sample to assess glycaemic control and lipid levels. Parameters such as glycated haemoglobin (HbA1c), fasting blood sugar (FBS), postprandial blood sugar (PPBS), and homeostatic model assessment of insulin resistance (HOMA-IR) were meticulously recorded alongside serum lipid levels. A subsequent blood sample was obtained post-meal to evaluate postprandial blood glucose levels. An ophthalmological assessment was then conducted, including measurements of bestcorrected visual acuity using Snellen's chart and intraocular pressure (IOP) via Goldmann's Applanation Tonometer.

General examinations included height, weight, body mass index (BMI), and blood pressure measurements. Ocular assessments comprised evaluations of uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA), torchlight examination, distant direct ophthalmoscopy, slitlamp examination, and applanation tonometry. Fundus examination involved indirect ophthalmoscopy for a comprehensive view of the fundus, allowing for the exclusion of pathologies and retinal detachments. Using a +90D lens and a binocular slit-lamp microscope, a real inverted image was produced with a magnification of 0.75 times. Macular thickness was assessed using Cirrus HD Spectral Domain Optical Coherence Tomography (SD-OCT) from ZEISS, employing an optic disc cube generated from a three-dimensional dataset centred on the optic disc. Measurements were taken in various segments, including central, superior, inferior, temporal, nasal, inner superior, inner inferior, inner temporal, and inner nasal segments. Scans with a signal strength below six were excluded to ensure data reliability and accuracy.

Statistical analysis: The data was analysed using IBM SPSS Inc.'s Statistical Package for Social Sciences, version 21.0, based in Chicago, IL, USA. Data is presented in numerical form, including percentages and the mean value along with its standard deviation (SD). Comparisons were made using the chi-square test, independent samples – using t-test, with a p-value below 0.05 considered statistically significant. Additionally, odds ratios were calculated for various categorical evaluations.

Results

The study compared patient characteristics between those with CSMO and those with nonCSMO. A significant age difference was observed, with a majority of CSMO patients aged >60-70 years (51.2%), whereas the non-CSMO group had a higher proportion aged >50-60 years (62.8%, p = 0.003) (Fig. 1). Gender distribution also varied, with more males in the CSMO group (53.5%) and more females in the non-CSMO group (55.9%) (Fig. 2).

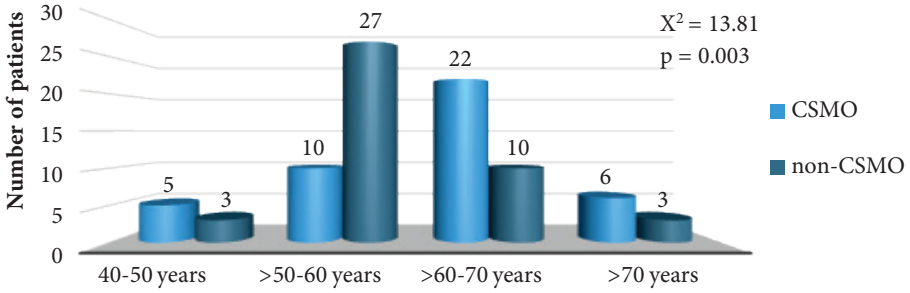

Figure 1. Distribution of patients with CSMO and non-CSMO across different age groups
Source: compiled by the authors

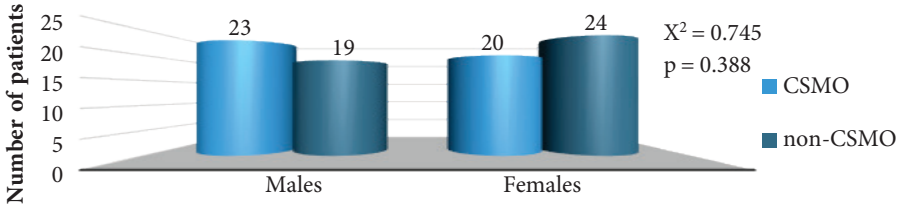

Figure 2. Comparison of gender distribution between patients with CSMO and non-CSMO
Source: compiled by the authors

The CSMO group demonstrated higher mean diabetes duration and BMI than the non-CSMO group. Although IOP was higher in the CSMO group, this difference was not statistically significant (Table 1).

Table 1. Baseline characteristics of CSMO and non-CSMO patients in both groups

Baseline characteristics		CSMO (n = 43)	non-CSMO (n = 43)	p-value
Age (years)	40-50	5 (11.6%)	3 (7.0%)	$X^2 = 13.81$ p = 0.003*
	>50-60	10 (23.3%)	27 (62.8%)	
	>60-70	22 (51.2%)	10 (23.3%)	
	>70	6 (14.0%)	3 (7.0%)	
Gender	Males	23 (53.5%)	19 (44.2%)	$X^2 = 0.745$ p = 0.388
	Females	20 (46.5%)	24 (55.9%)	
Duration (years)	Mean ± SD	17.28 ± 5.61	10.74 ± 1.85	<0.001*
BMI (males)		27.53 ± 1.52	26.59 ± 2.18	0.0228*
BMI (females)		27.86 ± 3.57	25.41 ± 1.99	0.0001*
IOP		15.97 ± 3.86	15.54 ± 3.81	0.606

Notes: * – significant; X^2 – Chi-Square test; mean values compared using t-test
Source: compiled by the authors

Analysis of diabetes duration revealed that the majority in the CSMO group had diabetes for over 20 years (51.2%), while most in the non-CSMO group had a duration of less than 20 years (74.4%). Odds ratios indicated an increasing likelihood of CSMO with longer diabetes durations. This finding suggests that patients with CSMO tend to be older compared to those without CSMO. Furthermore, the observed age difference implies that advancing age might be a risk factor for developing CSMO. This observation aligns with the current understanding that the prevalence of diabetic complications, including CSMO, increases with age due to prolonged exposure to hyperglycaemia and its detrimental effects on retinal vasculature. Regarding BMI, the odds of CSMO were higher in females with increased BMI, while in males, the odds of CSMO occurrence were below one across all BMI categories. Blood glucose levels, HbA1c, and insulin resistance were also found to affect the likelihood of CSMO (Fig. 3). Conversely, neither gender nor IOP demonstrated significant associations with CSMO. This finding suggests that both males and females have similar risks of developing CSMO and that IOP alone does not significantly impact CSMO development in diabetic patients (Fig. 4).

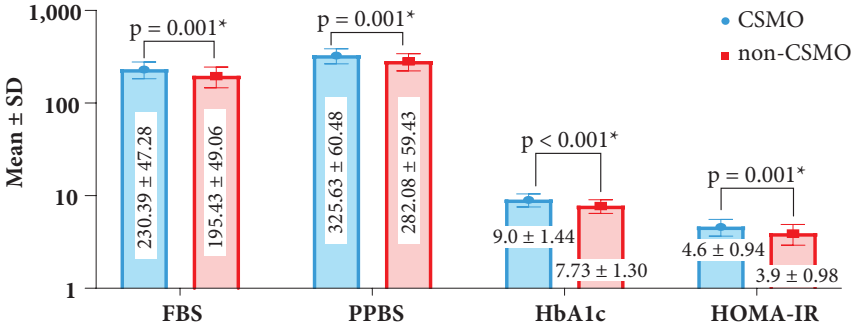

Figure 3. Comparison of blood sugar levels (FBS, PPBS, HbA1c) and HOMA-IR index between patients with CSMO and non-CSMO

Notes: * – significant
Source: compiled by the authors

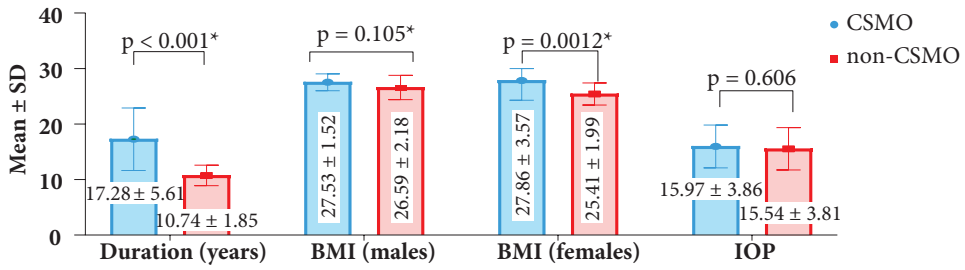

Figure 4. Comparison of mean duration of diabetes (years), BMI (males and females), and IOP between patients with CSMO and non-CSMO group

Notes: * – significant
Source: compiled by the authors

The prolonged duration of diabetes leads to cumulative microvascular damage in the retina, contributing to the pathogenesis of CSMO. This finding highlights the importance of early and sustained glycaemic control to prevent long-term complications, such as CSMO. Significant differences in BMI were observed between the two groups for both males and females, indicating an association between higher BMI and the presence of CSMO in both genders. Elevated BMI is often linked to poor glycaemic control and increased inflammatory markers, both of which can exacerbate retinal vascular permeability and lead to macular oedema. These results underscore the need for weight management as part of comprehensive diabetic care to reduce the risk of CSMO. Patients with CSMO exhibit significantly higher FBS, PPBS, and HbA1c levels, indicating poor glycaemic control. Elevated HOMA-IR values further suggest increased insulin resistance in these patients. These findings underscore the critical role of maintaining strict glycaemic control to prevent the onset of CSMO.

Assessment of glycaemic control revealed significantly higher values in the CSMO group; however, no significant differences were observed in total cholesterol (TC) and LDL levels. Table 2 indicates that patients with CSMO exhibit poorer glycaemic control, as evidenced by higher levels of FBS, PPBS, HbA1c, and HOMA-IR compared to non-CSMO patients. Additionally, CSMO patients have poorer lipid profiles, characterised by higher triglyceride levels and lower HDL cholesterol levels, although there were no significant differences in TC and LDL levels between the two groups. These findings suggest that poor glycaemic control and dyslipidaemia are associated with the presence of clinically significant macular oedema in diabetic patients (Fig. 5).

Table 2. Glycaemic control and Lipid profile assessment of CSMO and non-CSMO patients in both groups

Variables		CSMO	non-CSMO	p-value
Blood sugar	FBS	230.39 ± 47.28	195.43 ± 49.06	0.001*
	PPBS	325.63 ± 60.48	282.08 ± 59.43	0.001*
	HbA1c	9.00 ± 1.44	7.73 ± 1.30	<0.001*
	HOMA-IR	4.60 ± 0.94	3.90 ± 0.98	0.001*
Lipid profile	TC	260.11 ± 46.89	257.37 ± 41.47	0.774
	TG	175.97 ± 39.33	155.85 ± 31.48	0.010*
	HDL	41.95 ± 5.63	50.30 ± 7.85	<0.001*
	LDL	182.97 ± 46.07	175.90 ± 40.29	0.451

Notes: * – significant; mean values compared using t-test
Source: compiled by the authors

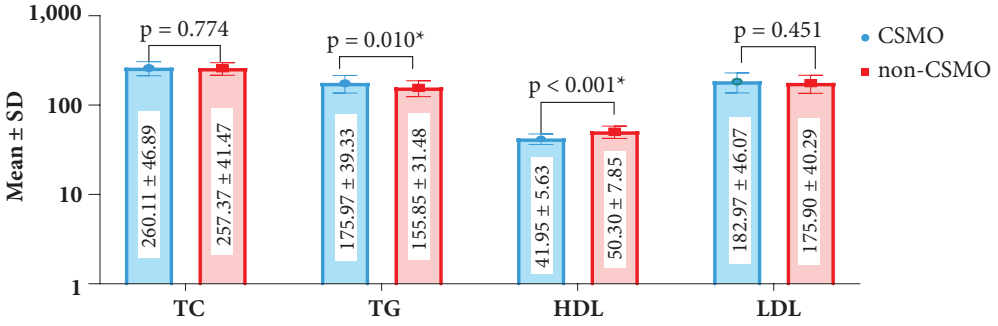

Figure 5. Comparison of lipid levels

Notes: * – significant
Source: compiled by the authors

Measurements of macular thickness in various regions indicated that central macular thickness was significantly higher in the CSMO group (269.79 ± 219.0 vs. 268.91 ± 1.0, p < 0.001), suggesting a potential association between central macular thickness and CSMO. The data indicate a significant increase in central macular thickness in CSMO patients compared to non-CSMO patients. This finding aligns with the characteristic central retinal swelling observed in CSMO. However, no significant differences were found in macular thickness measurements across the other regions (superior, inferior, temporal, nasal, and their inner counterparts), suggesting that macular oedema primarily affects the central region in these patients (Table 3).

Table 3. Macular thickness measurements of CSMO and non-CSMO patients in both groups

Macular thickness	CSMO	non-CSMO	p-value
Central	269.79 ± 219.0	268.91 ± 1.0	<0.001*
Superior	297.73 ± 246.0	298.51 ± 270.0	0.916
Inferior	298.17 ± 245.0	294.84 ± 265.0	0.587
Temporal	274.50 ± 236.0	283.40 ± 252.0	0.199
Nasal	302.30 ± 268.0	309.25 ± 290.0	0.141
Inner superior	324.74 ± 276.0	323.09 ± 310.0	0.881
Inner inferior	322.09 ± 300.0	321.67 ± 308.0	0.954
Inner temporal	306.91 ± 279.0	308.84 ± 295.0	0.813
Inner nasal	318.86 ± 290.0	322.50 ± 312.8	0.610

Notes: * – significant; mean values compared using t-test
Source: compiled by the authors

In the present study, individuals with total cholesterol levels exceeding 240 mg/dL (26 cases) exhibited significantly higher odds of CSMO, with an odds ratio of 9.39. Furthermore, a progressive increase in the odds of CSMO was noted with rising triglyceride levels. Surprisingly, abnormal LDL levels were associated with lower CSMO odds, while elevated HDL levels showed a contrasting trend, indicating higher odds of CSMO in the present study population. These findings underscore the complex relationship between lipid profiles and CSMO risk. Furthermore, the CSMO group had higher odds of developing a BCVA of <3/60 PL positive (Table 4). A multivariate model identified the duration of diabetes, BCVA, and HDL as significantly associated with CSMO, highlighting their potential as independent predictors (Table 5).

Table 4. Macular thickness and best-corrected visual acuity odds ratio in CSMO and non-CSMO patients in both groups

Variables		CSMO	non-CSMO	Odds ratio
Macular thickness	<250 μ (normal)	0	0	-
	>250-260 μ (mild)	9 (20.93%)	22 (51.16%)	Ref.
	>261-270 μ (moderate)	19 (44.18%)	16 (37.20%)	2.90
	>271 μ (severe)	15 (34.88%)	5 (11.62%)	9.17
Best-corrected visual acuity	6/6 to 6/9	0	0	-
	<6/9 to 6/18	10 (11.6%)	29 (45.3%)	Ref.
	<6/18 to 6/60	20 (23.3%)	49 (56.97%)	1.49
	<3/60 to PL+	56 (65.1%)	8 (9.3%)	20.30
	PL negative	0	0	-

Source: compiled by the authors

Table 5. Multivariate analysis of independent predictors for progression of CSMO from non-CSMO groups

Factors	Variable Type	β ± SE	p-value	OR (95% CI)
BMI	Linear	0.513 ± 0.382	0.153	1.86 (0.84-3.56)
Duration of diabetes	Linear	0.942 ± 0.338	0.005*	2.57 (1.33-4.95)
BCVA	Ordinal	-2.327 ± 1.181	0.049	0.10 (0.01-0.99)
PPBS	Linear	0.015 ± 0.012	0.213	1.02 (0.99-1.04)
HbA1c	Linear	0.666 ± 0.40	0.091	1.95 (0.89-4.28)
Insulin resistance #	Linear	0.616 ± 0.579	0.287	1.85 (0.60-5.76)
Triglyceride	Linear	0.044 ± 0.024	0.065	1.05 (1.00-1.10)
HDL	Linear	-0.327 ± 0.129	0.011*	0.72 (0.56-0.93)
Constant	Fixed value	-22.857 ± 11.876	0.052	1.67 (0.84-3.33)

Notes: * – significant; # – binary logistic regression after replacing fasting blood sugar and fasting insulin with insulin resistance; β ± SE – estimated coefficients (β) with standard errors (SE)
Source: compiled by the authors

Proximity to BCVA and duration of diabetes (β = 0.942, p = 0.005, OR = 2.57, 95% CI: 1.33-4.95) were identified as statistically significant predictors of CSMO progression among the factors analysed (β = -2.327, p = 0.049, OR = 0.10, 95% CI: 0.01-0.99). More specifically, the likelihood of developing CSMO increased 2.57-fold with the length of time a patient had the condition, whereas the likelihood decreased ten-fold with suboptimal BCVA. A protective effect was also indicated by the inverse association between elevated levels of HDL cholesterol and the progression of CSMO (β = -0.327, p = 0.011, OR = 0.72, 95% CI: 0.56-0.93). Statistically, CSMO progression could not be predicted by additional variables, including triglyceride levels, BMI, PPBS, HbA1c, or insulin resistance, as determined by this analysis. To identify diabetic patients at greater risk for the progression of CSMO and to enable the implementation of targeted interventions to preserve vision, it is critical to monitor their HDL cholesterol levels, duration of diabetes, and BCVA.

Discussion

Macular oedema, commonly linked to diabetes, reflects chronic damage to retinal neurovascular structures, progressing from peripheral to clinically significant central involvement. Previous studies have highlighted the role of insulin resistance and dyslipidaemia in macular oedema [12, 13]. This cross-sectional study explored the role of lipid levels and insulin resistance in 86 patients with T2DM presenting with macular oedema (43 CSMO, 43 non-CSMO). The majority of patients in the CSMO group were aged over 60 years (65.2%), whereas the majority of non-CSMO patients were aged under 60 years (69.8%). A significant difference was observed in the ages of patients in the two groups [14, 15]. Concerning gender, the majority of CSMO patients in the present study were male (53.5%), while the majority of non-CSMO patients were female (55.9%); however, this difference was not statistically significant. Both L. Feng *et al.* [15] and the present study on T2DM patients with macular oedema highlight the significant impact of age and gender on lipid levels and disease outcomes. L. Feng *et al.* [15] demonstrated age-related variations in lipid profiles with gender-specific trends, while the present study suggests that older age might be associated with more severe macular complications in diabetes. These findings emphasise the need for age and gender-specific approaches in managing lipid levels to prevent or manage diabetes-related complications effectively. In comparison to the present study, R. Raman *et al.* [14] reported that most CSMO and non-CSMO patients were male and did not find a significant difference between the two groups. K. Kamoi *et al.* [16] also did not find a significant difference in the age or gender of patients with CSMO and nonCSMO. Most other studies evaluating the relationship between macular oedema and lipid levels and/or insulin resistance have generally compared a diabetic population with macular oedema to a diabetic population without macular oedema [12, 17], or compared patients with DMO and diabetic retinopathy DR [13], typically in cross-sectional studies, which the present study similarly envisaged. In a study, P. Romero-Aroca *et al.* [18] reported that in the type 1 diabetic population, the mean age of patients with no diabetic retinopathy or macular oedema, those with diabetic retinopathy, and those with macular oedema showed an incremental trend, specifically 31.84, 43.54, and 50.05 years, respectively. In their study, most patients without diabetic retinopathy or macular oedema and those with diabetic retinopathy were male, whereas the majority of patients with macular oedema were female. G.S. Prakash & M. Kothari [19] reported the mean age of diabetic patients with and without CSMO as 57.02 and 56.42 years, respectively, and found no significant difference between the two groups. In both groups, males predominated. The inability to match the age profile of the patients was attributed to the COVID-19 pandemic, which resulted in a limited number of cases with a matched age and sex profile, as OPD services were affected and patient footfall remained low during this study period. Although the mean BMI of both male and female CSMO patients was higher than that of non-CSMO patients, the present study revealed that the odds of CSMO exhibited an incremental trend with increasing BMI. However, among males, the odds of CSMO were lower in those with higher BMI compared to those with lower BMI. The findings of the present study, at least for male patients, replicate the observations of E. Martín-Merino *et al.* [17], who also reported that obesity was associated with a lower risk of macular oedema in diabetic patients. However, regarding the association of higher BMI with CSMO compared to non-CSMO, R. Raman *et al.* [14] did not evaluate the BMI of patients in the two groups. P. Romero-Aroca *et al.* [18] also did not assess BMI or any other marker of obesity. Similarly, G.S. Prakash & M. Kothari [19] did not evaluate BMI or any other marker of obesity. Although K. Kamoi *et al.* [16] evaluated the role of BMI as a discriminatory factor between CSMO and non-CSMO, they failed to determine a significant difference between the two groups. In the present study, the duration of diabetes was significantly higher in patients with CSMO compared to those with non-CSMO. Upon stratified evaluation, the present study found that compared to individuals with a duration of diabetes of less than 10 years, those with a longer duration had higher odds of CSMO. These findings agree with the observations of R. Raman *et al.* [14], which similarly found a significant association of CSMO with the duration of diabetes. However, K. Kamoi *et al.* [16] reported that the duration of diabetes was longer in the non-CSMO group than in the CSMO group; still, they did not find this difference to be statistically significant. In their study, P. RomeroAroca *et al.* [18] found a longer duration of diabetes to be significantly associated with DR and DMO. G.S. Prakash & M. Kothari [19], like the present study, found a significant association between a longer duration of diabetes and CSMO. Regarding the relationship with IOP levels, the present study found that IOP was higher in patients with CSMO; however, this was not

statistically significant. R. Raman *et al.* [14] did not evaluate the role of IOP in their study. Limited data suggests its pathogenic role in the causation and progression of DMO. In the present study, fasting blood sugar, post-prandial blood sugar, HbA1c, and HOMA-IR were higher in patients with CSMO than in those with non-CSMO. With increasing levels of all these markers of glycaemic control and insulin resistance, the odds of CSMO exhibited an incremental trend. Consistent with the findings of the present study, R. Raman *et al.* [14] also found a significant association between poor glycaemic control and CSMO in both univariate and multivariate assessments. However, K. Kamoi *et al.* [16] did not find this association to be significant when evaluating HbA1c. P. Romero-Aroca *et al.* [18] reported that high HbA1c was a significant risk factor for both DR and DMO. G.S. Prakash & M. Kothari [19] found mean HbA1c levels to be significantly higher in patients with CSMO compared to the control group, with no significant association between fasting and post-prandial blood glucose levels and CSMO. In the present study, although mean TC, TG, and LDL levels were higher and mean HDL was lower in patients with CSMO compared to those with non-CSMO, the difference was statistically significant for TG and HDL levels only. Increasing total cholesterol and triglyceride levels were associated with an increase in the odds of CSMO. However, for LDL levels, the odds of developing CSMO were lower at higher LDL levels than those at optimal LDL levels. When HDL was considered, the present study found increased odds of developing CSMO. This finding could be attributed to the small sample size, indicating a need for further research. Regarding lipid levels, R. Raman *et al.* [14] discovered a significant association between high total serum cholesterol, high serum LDL cholesterol, and high serum non-HDL cholesterol with CSMO during univariate assessment. In the multivariate analysis, high serum LDL cholesterol, high serum non-HDL cholesterol, and a high cholesterol ratio were found to be related to CSMO. It is worth noting that E. Martín-Merino *et al.* [17] found a strong correlation between DMO and elevated levels of total cholesterol and LDL. However, they discovered that elevated triglyceride levels were strongly linked to a reduced risk of DMO. In the present study, higher LDL levels were associated with a lower risk of DMO. On the other hand, K. Kamoi *et al.* [16] did not find a significant discriminant role of lipid levels in distinguishing CSMO from non-CSMO. P. Romero-Aroca *et al.* [18] found no significant association of these lipids with DMO in their study. G.S. Prakash & M. Kothari [19] reported that lipid levels (higher TC, TG, LDL, VLDL and lower HDL were significantly associated with CSMO. In multivariate analysis, after adjusting for BMI, PPBS, HbA1c, insulin resistance, and triglyceride levels, BCVA and HDL emerged as independent predictors of CSMO only during diabetes. In their study, R. Raman *et al.* [14] found high serum LDL cholesterol, high serum non-HDL cholesterol, and high cholesterol ratio related to non-CSMO, poor glycaemic control, and high serum total cholesterol related to CSMO. Both the present study and the research by I. Vivsiana & M. Marushchak [20] explore the complexities of lipid profiles in patients with T2DM, emphasising the influence of additional comorbidities on lipid levels. Findings indicate significant differences in TG and HDL levels between T2DM patients with and without CSMO, linking higher TG and lower HDL levels to an increased likelihood of CSMO. Interestingly, higher LDL levels correlated with lower odds of CSMO, suggesting a more nuanced role of LDL in diabetic retinopathy. I. Vivsiana & M. Marushchak's [20] study reinforces the impact of comorbid conditions such as obesity and hypertension on worsening lipid profiles in T2DM patients, showing significantly higher levels of total cholesterol and TG among those with additional comorbidities. Together, these studies highlight the critical role of managing lipid levels in T2DM patients, particularly those with additional risk factors, to mitigate complications such as macular oedema and underscore the importance of targeted therapeutic strategies addressing dyslipidaemia in the presence of comorbid conditions. Similar to the present study, a significant reduction in the number of independent predictors for the prediction of CSMO was observed in both models. The present study also found poor BCVA to be associated with CSMO; however, this relationship does not require further explanation owing to its temporal nature. The present study's findings endorse the role of lipid dysregulation and insulin resistance in the progression of CSMO when compared with non-CSMO.

Conclusions

In this cross-sectional study, the analysis of baseline characteristics, glycaemic control, and lipid profiles between CSMO and non-CSMO groups provided critical insights. Key findings include a significant association between older age and longer duration of diabetes with the presence of CSMO, indicating that prolonged hyperglycaemia and ageing contribute to the development of this complication. Higher BMI, particularly in females, and poor glycaemic control, as reflected by elevated FBS, PPBS, HbA1c, and HOMA-IR levels, were significant risk factors for CSMO. These findings emphasise the importance of maintaining strict glycaemic control and managing weight to reduce the risk of CSMO. Lipid profile analysis revealed that higher triglyceride levels and lower HDL levels are associated with CSMO, highlighting dyslipidaemia as a contributing factor. The study also demonstrated that central macular thickness was significantly higher in CSMO patients, consistent with the characteristic retinal swelling observed in this condition. However, no significant differences were found in macular thickness across other regions, indicating that CSMO primarily affects the central retina. Multivariate analysis identified the duration of diabetes, BCVA, and HDL levels as independent predictors of CSMO progression. Specifically, a longer duration of diabetes and poorer BCVA increased the risk, while higher HDL levels had a protective effect.

These findings underscore the need for comprehensive diabetes management, focusing on early detection and sustained glycaemic control, weight management, and targeted lipid management to prevent the onset and progression of CSMO. Regular monitoring of these parameters in diabetic patients can help identify those at higher risk for CSMO, allowing for timely interventions to preserve vision and improve the quality of life for these individuals. The study highlights the multifactorial nature of CSMO, necessitating a holistic approach to diabetes care to mitigate this vision-threatening complication. The prospects for further research lie in conducting long-term longitudinal studies with larger sample sizes and focusing on personalised approaches to managing patients with T2DM to prevent or mitigate vision-threatening conditions such as CSMO.

Acknowledgements
None.

Funding
None.

Conflict of Interest
None.

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Порівняння інсулінової резистентності та ліпідного профілю при клінічно значущому та клінічно незначущому макулярному набряку у пацієнтів з цукровим діабетом типу 2

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Анотація. Розлади, пов'язані зі способом життя, зокрема діабет, є серйозними викликами для глобального здоров'я. Діабетичний макулярний набряк, як мікросудинне ускладнення, підкреслює важливість управління інсуліновою резистентністю та гіперліпідемією для досягнення ефективних клінічних результатів. Розуміння взаємодії цих факторів є ключовим для оптимізації терапевтичних стратегій та покращення медичної допомоги. Це перехресне дослідження мало на меті порівняти інсулінову резистентність і ліпідні профілі

між клінічно значущим макулярним набряком і клінічно незначущим макулярним набряком у пацієнтів з цукровим діабетом типу 2. Дослідження може призвести до раннього виявлення та класифікації макулярного набряку, що дозволяє здійснювати більш своєчасні та специфічні втручання. Загалом, 86 пацієнтів з діабетом типу 2 з макулярним набряком були поділені на дві групи: клінічно значущий макулярний набряк та клінічно незначущий макулярний набряк. Було зафіксовано комплексні демографічні дані, медичні історії та поточні режими медикаментозного лікування. Оцінювалися рівень глікемічного контролю та ліпідні профілі, а офтальмологічні оцінки включали вимірювання гостроти зору та оцінки внутрішньоочного тиску. Була виявлена значна різниця між групами клінічно значущого макулярного набряку і клінічно незначущого макулярного набряку, особливо у тривалості діабету, індексі маси тіла, рівнях глюкози в крові та ліпідних профілях. Пацієнти з клінічно значущим макулярним набряком демонстрували більшу тривалість діабету, вищий індекс маси тіла та підвищені рівні глюкози в крові. Рівні тригліцеридів були значно вищими, тоді як рівні ліпопротеїнів високої щільності були нижчими у пацієнтів з клінічно значущим макулярним набряком. Мультиваріантний аналіз виявив значні асоціації між ймовірністю клінічно значущого макулярного набряку та тривалістю діабету, гостротою зору та рівнями ліпопротеїнів високої щільності, що вказує на їх потенційні ризики для розвитку клінічно значущого макулярного набряку. Дослідження підкреслює важливість управління інсуліновою резистентністю та дисліпідемією у пацієнтів з цукровим діабетом типу 2 для зменшення ризику клінічно значущого макулярного набряку

Ключові слова: діабетичний макулярний набряк; дисліпідемія; захворювання сітківки; діабетичні нейропатії; оклюзія вен сітківки

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616.717.45-001.5-089
DOI: 10.63341/ijmmr/1.2025.33

Article's History:
Received: 01.01.2025; Revised: 16.04.2025; Accepted: 27.05.2025

Internal fixation of humeral shaft fractures using a dynamic compression plate: A prospective study

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Abstract. Fractures of the humeral shaft present a challenge due to their unique anatomical and biomechanical characteristics. Fixation with a dynamic compression plate is a widely adopted technique for the surgical management of these fractures, aiming to achieve stable fixation and promote early mobilisation. This study aimed to evaluate the clinical and functional outcomes of dynamic compression plate fixation in humeral shaft fractures. This prospective study included 40 patients with displaced humeral shaft fractures, including Grade I and II open fractures. Preoperative assessments comprised clinical examinations and radiographic evaluations. Surgical fixation was performed using a dynamic compression plate, and postoperative follow-up was conducted at 2 weeks, 6 weeks, 3 months, and 6 months. Functional outcomes were assessed using the Modified Stewart & Hundley classification, and statistical analysis was

Suggest Citation:
Bhol A, Thakur T, Dewangan P, Kumar V, Gupta P. Internal fixation of humeral shaft fractures using a dynamic compression plate: A prospective study. Int J Med Med Res. 2025;11(1):33–41. DOI: 10.63341/ijmmr/1.2025.33

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carried out. The study cohort had a mean age of 32.64 years (±4.77) and was predominantly male (65%). The most common cause of injury was road traffic accidents (55%). Type A fractures were the most frequent (42.5%), with 70% involving the right upper limb. The mean time to union was 4.58 ± 1.06 months. At 6 months, 10 patients had excellent outcomes, 21 had good, 8 had fair, and 1 had a poor outcome ($p < 0.0001$). Preoperative complications included multiple injuries. Postoperative complications were minimal, with only one case of malunion reported. The findings suggest that dynamic compression plate fixation is an effective method for the management of humeral shaft fractures, demonstrating significant improvements in alignment and functional outcomes, with low complication rates and favourable union times. These results support the reliability of dynamic compression plating in optimising treatment approaches and improving patient outcomes

Keywords: surgical fixation; fracture healing; orthopaedic surgery; clinical outcomes; range of motion

Introduction

The current study is of significant importance as it relates to the optimal management of humeral shaft fractures, which, despite their relative prevalence, present unique challenges in the selection of appropriate treatment. There is a critical need to balance the advantages of surgical interventions, such as plate osteosynthesis and intramedullary nailing, which enable early mobilisation and anatomical restoration, against the benefits of non-operative approaches, which take advantage of the humerus's high healing potential, in light of evolving trends in orthopaedic care. Furthermore, this study is particularly relevant as it examines the efficacy of dynamic compression plating (DCP) fixation in the management of these fractures, providing insights into its reliability, safety, and potential to optimise patient outcomes. This research has the potential to improve patient recovery, reduce complications, and support individualised treatment strategies in orthopaedic practice while also contributing to clinical knowledge.

J.J. Olson *et al.* [1] noted that humeral shaft fractures account for 3-5% of all adult fractures, with the majority occurring in the middle third of the bone. S. Goyal *et al.* [2] observed that although many humeral fractures heal successfully with non-operative methods, the trend has shifted towards internal fixation to facilitate early mobilisation and restore function more rapidly. M. Hardy & L.M. Feehan [3] emphasised the effectiveness of conservative treatments, such as functional bracing, skeletal traction, and shoulder spica casts, particularly in cases where the humerus's inherent healing capacity is sufficient. Similarly, A.U. Burki *et al.* [4] highlighted the success of functional bracing in achieving favourable outcomes in humeral diaphysis fractures, further underscoring the humerus's potential for non-surgical recovery.

U. Kandemir *et al.* [5] reported that plate osteosynthesis is widely regarded as the gold standard for treating humeral shaft fractures due to its capacity to provide rigid fixation. However, they cautioned that careful protection of the radial nerve is essential during the procedure. R.K. Bhartiya *et al.* [6] suggested that intramedullary nailing (IMN) is a viable alternative, particularly for osteoporotic bone, as it preserves the fracture haematoma, allows for load-sharing, and involves minimally invasive techniques. D. Angachekar *et al.* [7] concluded that both DCP and IMN produced comparable functional outcomes in humeral shaft fractures. The choice between these methods should depend on the surgeon's expertise and the specific needs of the patient. Similarly, R.K. Chandan *et al.* [8] found that alth ough both DCP and interlocking nailing (ILN) achieved similar union rates and functional results, DCP had the advantage of fewer complications, yielding better outcomes in terms of pain management and shoulder function. In agreement, B. Hussain *et al.* [9] concluded that DCP not only facilitated faster bone union but also offered superior functional outcomes and fewer complications compared to ILN in patients with humeral shaft fractures.

This study aimed to evaluate the clinical and functional outcomes of DCP fixation in the management of humeral shaft fractures, considering recent advancements in implant design and surgical techniques. By bridging the gap between traditional approaches and modern innovations, the findings aim to inform clinical decision-making and raise the standard of care in orthopaedic practice.

Materials and Methods

This prospective study was conducted in the Department of Orthopaedics, Dr. KNS Memorial Institute of Medical Sciences, Barabanki. The sample was comprised of 40 patients using humeral shaft fractures treated with a dynamic compression plate. The study adhered to the ethical principles outlined in the Declaration of Helsinki [10]. Prior to commencement, approval was obtained from the local Institutional Review Board (Letter No. MIMS/2022/EX/211), and informed consent was obtained from all participants. Patients were included according to the following criteria: displaced fractures of the humeral shaft, age above 18 years, Grade I or II open fractures, multiple injuries, nerve injury, angulation greater than 15 degrees, and non-compliance with conservative treatment. Exclusion criteria included Grade III open fractures, nonunion, delayed union, and pathological fractures. A preoperative evaluation was carried out, including medical history, clinical examination, and standard radiographs of the humerus (AP and lateral views) encompassing the shoulder and elbow joints. Initial management involved the application of a U-slab until surgery. If required, electroneuromyography was performed to exclude nerve compression, traction injury, or complete nerve damage. Routine investigations were undertaken, and informed consent along with physician clearance fo

fitness was obtained. These investigations included: X-ray of the humerus (AP and lateral views) with shoulder and elbow joints; blood tests (CBC, ESR, PT INR); urine analysis (albumin, sugar, microscopy); blood grouping and Rh typing; HIV, HBsAg, and HCV tests; liver and kidney function tests (LFT & KFT); chest X-ray and ECG; blood sugar levels; RT-PCR test for COVID-19. Postoperatively, patients were followed up at intervals of 2 weeks, 6 weeks, 3 months, and 6 months. X-rays were taken at 6 weeks, 3 months, and 6 months to assess fracture healing (Fig. 1). Functional outcomes (classified as excellent, good, fair, or poor) were evaluated using a modified Stewart & Hundley classification.

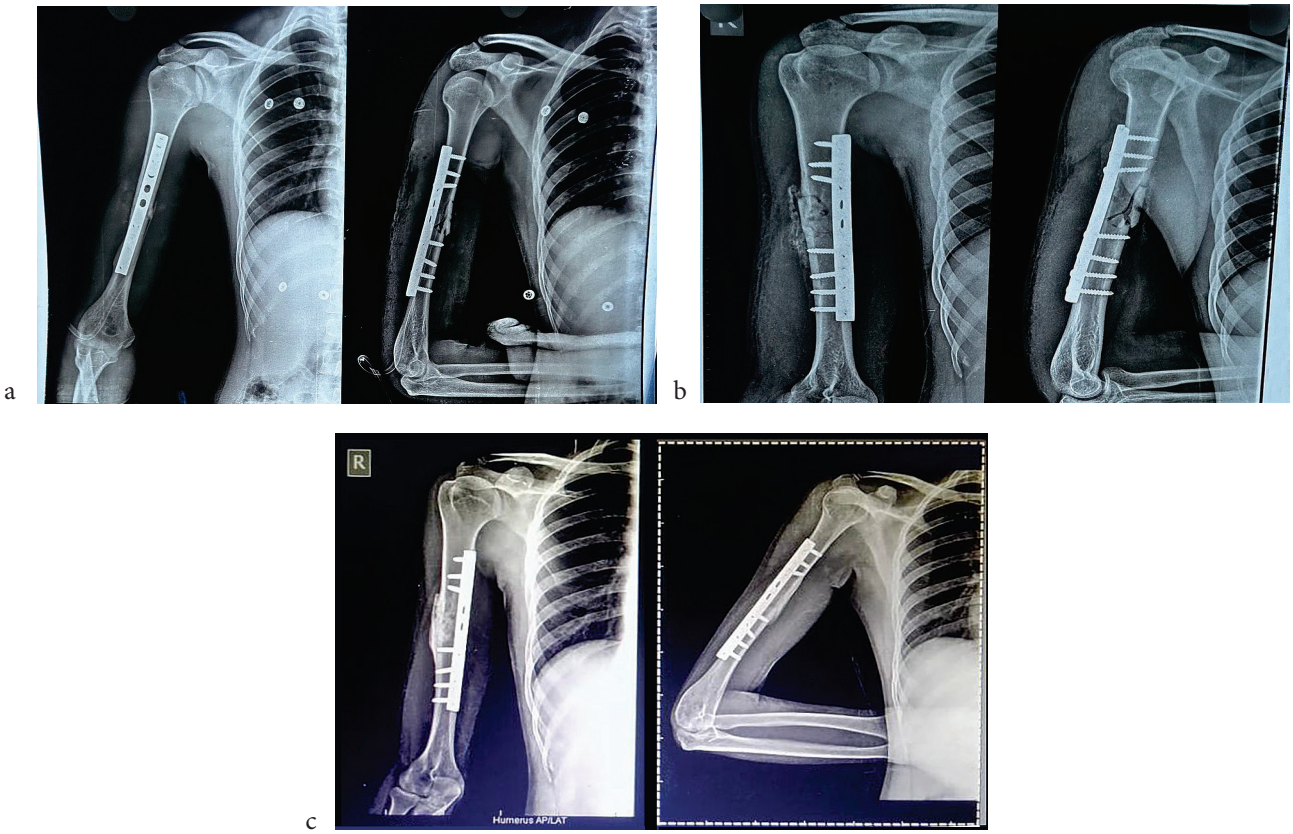

Figure 1. X-rays of patients
Notes: a – 1-month post-op; b – 3-month post-op; c – 6-month post-op
Source: compiled by the authors

A limitation of the study was the absence of an assessment of rotational movements (external and internal rotation) in the shoulder joint. Although the study focused on abduction/adduction and flexion/extension, the inclusion of rotational movements would have enabled a more comprehensive evaluation of functional recovery. Statistical analysis was conducted using SPSS software (version 26.0; SPSS Inc., Chicago, Illinois, USA) for Windows. All continuous variables (e.g. mean age, duration of surgery, blood loss, range of movements, and time to union) were expressed as mean (standard deviation) or range, depending on the data distribution. Analysis known as the analysis of variance (ANOVA) was used to compare the means of two or more groups. A p-value <0.05 or <0.001 was considered statistically significant.

Results and Discussion

The DCP is preferred over the locking compression plate (LCP) for humeral shaft fractures due to its ability to provide axial compression, promoting primary bone healing and superior load-sharing. Unlike the LCP, which offers rigid fixation independent of bone quality, the DCP is more effective in non-osteoporotic, simple, and wedge-type fractures, ensuring early mobilisation and faster recovery. This study highlighted the efficacy of DCP fixation.

Among the 40 patients, the predominant age group was 26-30 years (37.50%), with an average age of 32.64 ± 4.77 years. The majority were male (65%), while females accounted for 35%. Regarding occupation, most participants were labourers (45%). The most common cause of injury was road traffic accidents (RTA), accounting for 55%. Regarding pre-operative complications, Grade I open fractures were observed in 3 cases (7.5%), while Grade II open fractures were significantly more common, affecting 37 patients (92.5%). Fracture classifications revealed that 42.50% had Type A fractures. Injuries predominantly affected the right limb (70%), with the left limb being involved in 30% of cases (Table 1).

Table 1. Clinico-demographic characteristics of the enrolled patients (n = 40)

Clinico-demographics	Frequency	%
Age (years)		
18-25	6	15.00
26-30	15	37.50
31-35	11	27.50
36-40	8	20.00
Mean ± SD	32.64 ± 4.77	
Gender		
Male	26	65.00
Female	14	35.00
Occupation		
Professional/White collar	3	7.50
Skilled trades/Blue collar	12	30.00
Labourers	18	45.00
Student	7	17.50
Nature of injury		
RTA	22	55.00
Fall from height	13	32.50
Animal hit	5	12.50
Fracture classification (AO)		
Type A	17	42.50
Type B	11	27.50
Type C	12	30.00
Limb involved		
Right (dominant)	28	70.00
Left (non-dominant)	12	30.00

Source: compiled by the authors

Regarding the pre-operative complications, Grade I open fractures were observed in 3 (7.50%) of the cases, whereas Grade II open fractures were observed in 37 (92.5%) patients. Nerve injury was identified in 7.5% of the patients. Additionally, a significant proportion of the patients (25%) sustained multiple injuries (Fig. 2). Apart from Type A fractures, in Type B (wedge) fractures, the DCP plate is applied in neutralisation mode, whereby interfragmentary screws first secure the wedge fragment, and the plate then acts to protect against torsional and bending forces. In Type C (multifragmentary) fractures, the DCP plate is used in bridge plating mode, spanning the fracture site while maintaining alignment of the proximal and distal fragments, thereby allowing indirect healing through callus formation.

In the initial treatment phase, 60.00% of patients were managed with a U-slab, 7.50% underwent surgical debridement, and 32.50% received alternative treatment. The average duration of surgery was 148.00 ± 13.47 minutes, with an average blood loss of 217.00 ± 43.22 mL, indicating the considerable surgical intervention required for these patients (Table 2). The range of movement in patients improved significantly over the follow-up periods of 6 weeks, 3 months, and 6 months (Table 3).

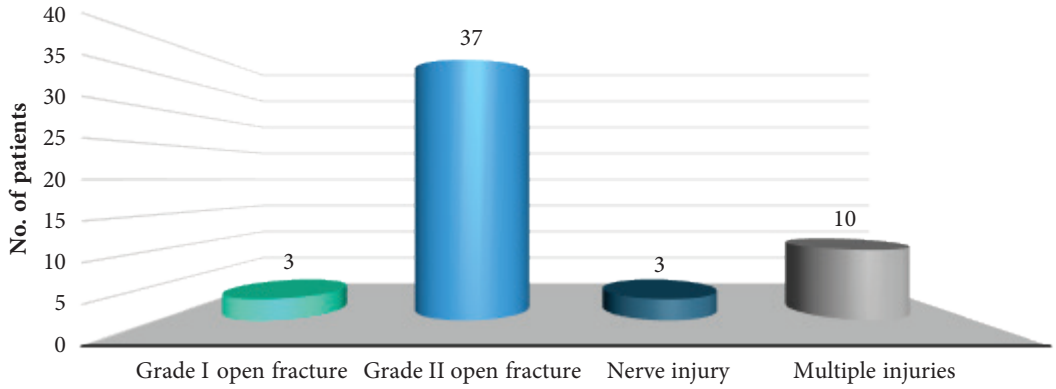

Figure 2. Pre-operative complications of the enrolled patients

Source: compiled by the authors

Table 2. Initial treatment of the enrolled patients

Initial treatment	Frequency	%
U-slab	24	60.00
Debridement	3	7.50
Other treatments	13	32.50
Duration of surgery (min)	148.00 ± 13.47	
Blood loss (mL)	217.00 ± 43.22	

Source: compiled by the authors

Table 3. Range of movement at follow-up evaluations

Range of movement	At 6 weeks	At 3 months	At 6 months	p-value
Shoulder abduction/ adduction	150.12 ± 10.34 (141-160)	156.23 ± 8.78 (144-166)	162.45 ± 5.67 (152-172)	F = 21.10 p < 0.0001*
Shoulder flexion/ extension	141.56 ± 12.45 (130-152)	146.78 ± 10.29 (134-157)	150.90 ± 8.87 (141-162)	F = 7.743 p = 0.0007*
Elbow flexion/extension	130.89 ± 10.98 (120-144)	135.34 ± 8.45 (125-146)	140.23 ± 6.34 (131-152)	F = 11.28 p < 0.0001*

Source: compiled by the authors

The outcomes based on the Modified Stewart & Hundley classification demonstrated significant improvement over time. At 6 weeks, none of the patients achieved an excellent outcome; at 3 months, 5 patients had attained this level, increasing to 10 patients at 6 months. The overall improvement was statistically significant, with a p-value of less than 0.0001 (Table 4). The mean time to union was 4.58 ± 1.06 months. A contributing factor to the delayed union in some cases may have been the presence of multiple injuries in 10 patients. Polytrauma is associated with extended healing times due to systemic inflammatory responses, impaired bone metabolism, and increased physiological stress. Furthermore, patients with multiple injuries often experience restricted mobilisation and prolonged recovery periods, which can delay fracture consolidation and elevate the risk of complications. Only one case (2.50%) of malunion was reported. Overall, complication rates were low, with no reported cases of nonunion, delayed union, or radial nerve palsy, indicating that most patients experienced satisfactory healing without major complications (Table 5).

Table 4. Modified Stewart & Hundley classification of the enrolled patients

Modified Stewart & Hundley classification	At 6 weeks	At 3 months	At 6 months	p-value
Excellent	0	5	10	X = 33.81 p < 0.0001*
Good	7	11	21	
Fair	23	20	8	
Poor	10	4	1	

Source: compiled by the authors

Table 5. Time to union and complications among enrolled patients

Time to union and complications	Frequency	%
Mean time to union (months)	4.58 ± 1.06	
Post-operative complications		
Nonunion	0	0.00
Delayed union	0	0.00
Superficial infection	0	0.00
Deep infection	0	0.00
Malunion	1	2.50
Radial nerve palsy	0	0.00

Source: compiled by the authors

The current study recorded an average age of 32.64 ± 4.77 years, with a predominantly male population (65%). The most common age group was 26-30 years (37.50%). Consistent with Deepak *et al.* [11], humeral shaft fractures were more frequent among young and middle-aged individuals, with a male predominance. The average age aligns with the findings of R.V. Griend *et al.* [12], although H.T. Hee *et al.* [13] reported a slightly higher average. In contrast to G.M. Sharma *et al.* [14], the gender distribution in the present study also indicates male predominance. Fracture classifications included 42.50% Type A, 27.50% Type B, and 30% Type C, similar to findings by Ş. Yiğit [15]. Both studies found consistent injury mechanisms and AO classifications across populations.

The present study found that 70% of injuries involved the right limb and 30% the left, differing from C.D. Deepak *et al.* [11], who reported equal proportions. Road traffic accidents accounted for 65% of fractures, consistent with findings by F.S.L. Meekers & P.L.O. Broos [16]. Similarly, G.M. Sharma *et al.* [14] noted dominant-side involvement in 62.7% of cases, with road traffic accidents accounting for 55.8%, supporting the present findings. The present study illustrates notable improvements in the range of motion following rehabilitation, with shoulder abduction/adduction increasing from 150.12 ± 10.34 degrees to 162.45 ± 5.67 degrees, shoulder flexion/extension from 141.56 ± 12.45 degrees to 150.90 ± 8.87 degrees, and elbow flexion/extension from 130.89 ± 10.98 degrees to 140.23 ± 6.34 degrees. M. Ghrairi *et al.* [17] found higher internal and external rotation torque peaks in male judo athletes, which aligns with the present study across genders, albeit with variations in assessment speed and normalisation methods. The use of normalisation techniques and alternative testing positions in the current study may explain the higher dominant-side ratios observed, compared to the seated-testing approach employed by M. Ghrairi *et al.* [17]. F.B. Marcondes *et al.* [18] also observed stable external/internal rotation ratios in female judo athletes, further supporting the present findings. However, P. Drid *et al.* [19] reported no significant differences between dominant and non-dominant sides in European judo athletes, which contrasts with the present study's minor asymmetries. Furthermore, comparisons with athletes in other sports, such as water polo and baseball, revealed distinct torque distribution patterns, highlighting sport-specific training adaptations. This aspect is recognised as a limitation of the present study.

Using the Modified Stewart & Hundley classification, this study showed notable improvements in patient outcomes over time. Initially, no patients had excellent outcomes at 6 weeks, but by 3 months, 5 patients achieved excellent outcomes, increasing to 10 at 6 months. Overall, significant improvement was observed ($p < 0.0001$). G.M. Sharma *et al.* [14] reported 18.6% achieving excellent results, 62.8% good, 13% fair, and 4.65% poor outcomes. In the initial treatment phase, 60.00% of the 40 patients were treated with a U-slab, 7.50% underwent debridement, and 32.50% received alternative treatments. The average duration of surgery was 148.00 ± 13.47 minutes, with an average blood loss of 217.00 ± 43.22 mL, indicating significant surgical intervention. In contrast, Ş. Yiğit [15] reported shorter intervals from fracture to surgery (5.9 days vs 57.4 days), reduced operative times (92.2 minutes vs 119.2 minutes), and lower blood loss (281.2 mL vs 377 mL) in patients who underwent primary surgical treatment compared with those managed conservatively, although bone grafting rates were similar. These differences underscore the variability in treatment strategies and outcomes across studies.

The study demonstrated promising outcomes with a mean time to union of 4.58 ± 1.06 months. Notably, no cases of nonunion, delayed union, superficial infection, deep infection, or radial nerve palsy were observed, resulting in an incidence rate of 0.00% for these complications. Comparatively, M.D. McKee *et al.* [20] found a nonunion incidence of 2-4%, while Sarmiento *et al.* [5] reported a 5% rate of delayed union. Infections were also lower in the present study compared with the 1-2% superficial and 1% deep infection rates documented by J.W. Mast *et al.* [21]. Only one case of malunion (2.50%) was reported, which is favourable compared with the 5% rate noted by L. Klenerman [22]. Overall, the study's outcomes indicate a lower complication rate and effective management of humeral shaft fractures using DCP, consistent with or superior to previously reported literature. According to S. Raghavendra & H.P. Bhalodiya [23], approximately 11.8% of individuals experience radial nerve palsy following humeral shaft fractures. C.D. Deepak *et al.* [11] reported a 5% incidence of superficial infection following surgical treatment with DCP, which was managed with standard dressing and antibiotics, resulting in successful recovery within two weeks.

Thus, in the present study, significant improvements in the range of motion and functional outcomes were observed during follow-up, with an optimal time to union and low complication rates, including no cases of nonunion, delayed union, or radial nerve palsy. These findings demonstrate the efficacy of DCP fixation in achieving favourable alignment, rapid recovery, and reduced complications, supporting its reliability for the management of humeral shaft fractures.

Conclusions

The present study highlights the effectiveness of DCP fixation in the treatment of humeral shaft fractures, particularly in a male and predominantly youthful population. The results indicate that this surgical method not only ensures precise fracture alignment but also enhances functional outcomes and range of motion during the follow-up. Based on the Modified Stewart & Hundley classification, the majority of patients achieved excellent or good outcomes, while others experienced a steady and substantial recovery. The effectiveness of DCP fixation in facilitating timely recovery was evident in the average time to fracture union of 4.58 months, which was well within the anticipated parameters. It is important to note that the study reported minimal complications, with only one instance of malunion and no cases of nonunion, delayed union, infections, or radial nerve palsy. The safety and reliability of this method in surgical management are emphasised by the low complication rate. Moreover, the research underscores the significance of individualised treatment strategies, particularly for youthful and active individuals who prioritise early mobilisation and functional restoration. The absence of major complications and the substantial improvements in the range of motion across all measured joints indicate that DCP fixation is a highly reliable and effective option. These results are consistent with the current body of literature and offer substantial evidence to support the use of DCP fixation as the preferred treatment for humeral

shaft fractures. This approach ensures patients an optimal recovery, reduced complications, and an improved quality of life. Future research should focus on comparing DCP fixation with alternative surgical methods, such as intramedullary nailing or minimally invasive techniques, to determine the most effective approach for different fracture patterns and patient profiles. Additionally, long-term follow-ups are essential to assess the durability of functional outcomes and late complications. Studies involving larger, more diverse populations and incorporating advanced imaging or biomechanical analyses may provide deeper insights into optimal fixation strategies and tailored treatment protocols for humeral shaft fractures.

Acknowledgements
None.

Funding
None.

Conflict of Interest
None.

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Внутрішня фіксація перелому діафіза плечової кістки динамічною компресійною пластиною: проспективне дослідження

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Анотація. Лікування переломів плечової кістки є складним завданням через її унікальні анатомічні та біомеханічні характеристики. Фіксація динамічною компресійною пластиною є широко розповсюдженим методом хірургічного лікування таких переломів, спрямованим на досягнення стабільної фіксації та сприяння ранній мобілізації. Метою цього дослідження було оцінити клінічні та функціональні результати фіксації динамічною компресійною пластиною при переломах плечової кістки. Проспективне дослідження включало 40 пацієнтів зі зміщеними переломами плечової кістки, в тому числі з відкритими переломами I та II ступенів. Передопераційне обстеження включало клінічне обстеження та рентгенографічні дослідження. Хірургічна фіксація виконувалась за допомогою динамічної компресійної пластини, а післяопераційне спостереження проводилось через 2 тижні, 6 тижнів, 3 місяці та 6 місяців. Функціональні результати оцінювались за модифікованою класифікацією Stewart & Hundley, також було проведено статистичний аналіз. Середній вік досліджуваної когорти становив 32,64 років (±4,77), серед пацієнтів переважали чоловіки (65 %). Найчастішою причиною травм були дорожньо-транспортні пригоди (55 %). Переломи типу A були найчастішими (42,5 %),

причому 70 % стосувалися правої верхньої кінцівки. Середній час до зрощення становив 4,58 ± 1,06 місяця. Через 6 місяців 10 пацієнтів мали відмінний результат, 21 – добрий, 8 – задовільний і 1 – поганий ($p < 0,0001$). Передопераційні ускладнення включали множинні травми. Післяопераційні ускладнення були мінімальними, повідомлялося лише про один випадок незрощення. Отримані дані свідчать про те, що фіксація динамічною компресійною пластиною є ефективним методом лікування переломів плечової кістки, який демонструє значне покращення вирівнювання та функції, з низьким рівнем ускладнень та кращим часом зрощення. Ці результати підтверджують надійність динамічної компресійної пластини в оптимізації підходів до лікування та покращенні результатів лікування пацієнтів

Ключові слова: хірургічна фіксація; загоєння переломів; ортопедична хірургія; клінічні результати; діапазон рухів

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616.831-005.1-06:616.831-009.11-031.47-085.84(669.1)
DOI: 10.63341/ijmmr/1.2025.42

Article's History:
Received: 12.11.2024; Revised: 17.03.2025; Accepted: 27.05.2025

Effects of transcutaneous electrical nerve stimulation, phonophoresis, and interferential current therapy on hemiplegic shoulder pain among Nigerian stroke survivors

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Abstract. Hemiplegic shoulder pain is a widespread and debilitating symptom experienced by stroke survivors, affecting their rehabilitation outcomes and quality of life. Addressing effective treatment options for this condition is essential to improve patient care. The purpose of this study was to determine how hemiplegic shoulder pain in stroke survivors was affected by phonophoresis, transcutaneous electrical nerve stimulation, and interferential current stimulation. This was a pre- and post-test experimental study conducted among 45 stroke survivors. Hemiplegic shoulder pain was assessed on the Numerical Pain Rating Scale and data were analysed using ANOVA. The results of the study reported a notable variation ($F = 35.101$, $p < 0.05$) across the physical modalities (transcutaneous electrical nerve stimulator, ultrasound device, and interferential current stimulator) in improving hemiplegic shoulder pain of the subjects. However, phonophoresis was

Suggest Citation:
Obaseki Ch, Hammed A, Omorotiomwan I, Usman S, Omodele A. Effects of transcutaneous electrical nerve stimulation, phonophoresis, and interferential current therapy on hemiplegic shoulder pain among Nigerian stroke survivors. Int J Med Med Res. 2025;11(1):42–8. DOI: 10.63341/ijmmr/1.2025.42

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found to have superior effect on hemiplegic shoulder pain of stroke survivors, with the post-hoc analysis revealing that phonophoresis is the most promising protocol for treating hemiplegic shoulder pain of stroke survivors. The findings of this study suggest that training clinicians in the proper application of ultrasound devices for phonophoresis can significantly enhance treatment outcomes for hemiplegic shoulder pain in stroke survivors

Keywords: neurological rehabilitation; post-stroke pain; physical modalities; pain modulation

Introduction

Hemiplegic shoulder pain (HSP) is one of the most frequent clinical manifestations following stroke. Along with symptoms of pain, HSP is also accompanied by abnormal muscle tone, reduced grip and shrug strength, and impaired sensation. The occurrence of HSP following a stroke incident can further increase the burden of recovery, limit the functional ability of stroke survivors, and affect their quality of life. Effective management of this condition is crucial as it influences the ability of stroke survivors to regain functionality. Despite the availability of various physical modalities for pain relief, the comparative effectiveness of different treatment protocols is still being explored.

The use of non-pharmacological interventions, such as transcutaneous electrical nerve stimulation (TENS), phonophoresis, and interferential current therapy for the management of chronic pain has gained increased attention. V.C. Whitehair *et al.* [1] examined the acute effects of TENS and transcutaneous neuromuscular electrical stimulation (t-NMES) on pain-free passive range of motion in patients with hemiplegic shoulder pain. The authors found no significant difference in pain-free passive shoulder range of motion between TENS, t-NMES, and the group that received no stimulation. The researchers argued that the shorter duration of electrical stimulation and placement of the electrodes may be responsible for their result. S. Ersoy *et al.* [2] reported that suprascapular nerve blockage, in comparison to TENS, decreased pain scores more significantly among patients with HSP. In contrast to these studies, Y. Li *et al.* [3] investigated the effects of a combined intervention of transcranial Direct Current Stimulation (tDCS) and TENS on HSP, revealing that the combination of tDCS and TENS yielded a greater improvement in pain rating compared to the sole application of tDCS. This finding demonstrated the efficacy of TENS in relieving HSP among stroke survivors. TENS has also been reported to be efficacious in alleviating other chronic pains.

The researchers have also investigated the efficacy of phonophoresis/therapeutic ultrasound in the management of hemiplegic shoulder pain. P. Dajpratham *et al.* [4] compared the efficacy of ultrasound therapy and high-intensity laser therapy for the management of hemiplegic shoulder pain. Their study revealed that ultrasound therapy significantly improved outcomes of pain and shoulder internal rotation among the patients. While both interventions provided comparable analgesic effects, ultrasound therapy demonstrated a greater impact on improving shoulder range of motion (ROM). Additionally, patients who received ultrasound therapy reported a reduced need for analgesic medications compared to those treated with high-intensity laser therapy. In addition to conventional exercise protocols, F. Eslamian *et al.* [5] compared the efficacy of IFC and electrical acupuncture on shoulder pain among stroke survivors. The group who received electrical acupuncture had better pain improvement compared to the subjects treated with received IFC. While these studies demonstrated the potential of phonophoresis and interferential current in the management of HSP, recent studies notably lack in-depth coverage on the efficacy of these interventions.

However, studies have also demonstrated the efficacy of these physical modalities in the management of other chronic pains. A systematic review by É.P. Rampazo *et al.* [6] on the effects of interferential current in patients with non-specific chronic low back pain reported moderate-quality evidence that interferential current reduces intensity of low back pain as well as disability immediately after treatment, compared to placebo. The researchers also reported low-quality evidence that interferential current therapy reduces pain intensity when compared to TENS. Similarly, K.S. Jung & T.S. In [7] reported that interferential current therapy significantly reduced pain and disability as well as improved balance among patients with chronic low back pain. Another systematic review by F.A. Yang *et al.* [8] on the efficacy of phonophoresis in reducing pain among individuals with knee osteoarthritis, reported that phonophoresis yielded significant reduction in pain scores when compared to therapeutic ultrasound with placebo gel. M.S. Omara *et al.* [9] reported that while both TENS and phonophoresis were efficacious in reducing pain intensity among the subjects, phonophoresis produced more significant effects. A. Oparin *et al.* [10] proposed cryomassage as an alternative therapy for pain management.

To the best of the researchers' knowledge, there is no satisfactory existing database establishing the effects of TENS, phonophoresis, and interferential current therapy on HSP of stroke survivors in Nigeria. Furthermore, basic data on stroke survivors with HSP, which is one of the most challenging manifestations following stroke, are almost non-existent. This suggests the need for academic efforts to provide such data to enhance proper management of HSP among Nigerian clinicians. Notably, it is unclear what the empirical situation has been as to identifying the best modality to adopt in the treatment of HSP in Nigeria. The present study was necessitated by the identified gap in knowledge and research endeavours. It was necessary to compare the effectiveness of TENS, phonophoresis, and IFCS on HSP of Nigerian stroke survivors, which constituted the purpose of the present study.

Materials and Methods

This study employed an experimental design with pre- and post-tests. 66 hemiparetic stroke survivors, ranging within the biological age from 45 to 65, who were treated at the University of Benin Teaching Hospital's Neurology Unit and Physiotherapy Department from July 1 to September 30, 2023, comprised the study's population. 45 stroke survivors with HSP of an average duration of 4 weeks and Numerical Pain Rating Scale (NPRS) between 4 and 10 took part in this study. Subjects were included in this study using purposive sampling technique. Conversely, subjects with acute inflammation of the shoulder joints, peripheral neuropathy, impaired cognition (with score on mini-mental scale lower than 24), and fracture of the upper extremities were excluded from the study. Subsequently, sampling technique employed in the study was a simple randomisation using balloting with replacement to divide the subjects equally into three groups (TENS, IFCS, and the phonophoresis groups). The subjects received analogous analgesics treatment, as directed by their physicians. There was no significant difference in the baseline hemiplegic shoulder pain rating between the control and intervention groups.

TENS is an electrotherapeutic agent used for pain relief. The study employed conventional TENS with high frequency of 150 Hz and a short pulse duration of 100 μs in the normal mode. Therapeutic ultrasound is an electrophysical agent. The present study employed the 1 MHz frequency. The frequencies used in therapy are normally within 1.0-3.0 MHz (1 MHz = 1 million cycles per second). Furthermore, therapeutic ultrasound was applied to the subjects' hemiplegic shoulders with topical analgesics (ketoprofen) to induce phonophoresis. IFCS is a type of electrical stimulation using paired electrodes from two separate circuits that carry medium-frequency and high-frequency (4,000 Hz) alternating currents. The present study used the high frequency of 4,000 Hz. NPRS was used to assess different levels of pain. The subjects were prompted to mark a point on a 10 cm line to indicate their pain intensities. All the instruments used in this study were proved scientifically to be standardised, valid, and have good reliability. The validity of the instruments was attested to by specialists in physiotherapy and neurology as suitable for the study. The researchers also cross-checked the instruments and ascertained that their adequate working conditions before use.

Prior to the administration of the instruments, the subjects were given a thorough explanation of the test procedure, along with the goals and specifics of the study, and they were asked to sign an informed consent form before taking part in the study. The committee of research ethics of the University of Benin Teaching Hospital, Nigeria granted ethical approval for the study (ADM/E 22/A/VOL. VII/1483032). The HSP of the subjects was measured prior to and after the 4-week application of the treatment modalities. The difference in the HSP of stroke survivors following application of TENS, phonophoresis, and IFCS was analysed using ANOVA. In addition, Tukey's was employed in instances where significant main or interaction effects of the modalities were identified. A p-value of <0.05 was accepted as statistically significant. Statistical Package for the Social Sciences (SPSS) version 23.0 was used for the analyses performed in the present study.

Results and Discussion

Table 1 displays the results of the ANOVA used to determine the significance of the variation in the subjects' HSP is after TENS, phonophoresis, and IFCS treatment. At 0.05 ($p < 0.05$), the F-value of 35.101 with 5 and 89 degrees of freedom was found to be statistically significant. This suggested that the individuals' HSP was significantly differently affected by the tools. To determine the exact difference, a post-hoc test was to be performed due to this disparity.

Table 1. Analysis of variance (ANOVA) displaying variations in the subjects' HSP after utilising physical modalities

	Sum of squares	Df	Mean square	F	Sig.
Between groups	216.456	5	43.291	35.101	0.000
Within groups	103.600	84	1.233		
Total	320.056	89			

Notes: Df – degree of freedom; Sig. – the two-tailed p-value linked to the null hypothesis that the groups had the same variance; F – the F-test ratio of sample variance
Source: compiled by the authors of this study

The post-hoc test is presented in Table 2. None of the pairwise mean difference comparisons in Table 2 showed statistically significant differences except for pre-IFCS vs post-ultrasound (3.93333*), pre-ultrasound vs post-IFCS (1.26667*), pre-ultrasound vs post-ultrasound (4.66667*), pre-TENS vs post-ultrasound (4.40000*), post-IFCS vs pre-ultrasound (-1.26667*), post-IFCS vs post-ultrasound (3.40000*), post-ultrasound vs pre-IFCS (-3.93333*), post-ultrasound vs pre-ultrasound (-4.66667*), post-ultrasound vs pre-TENS (-4.40000*), post-ultrasound vs post-IFCS (-3.40000*), post-ultrasound vs post-TENS (-3.53333*), and post-TENS vs post-ultrasound (3.53333*). Accordingly, only the ultrasound (phonophoresis) affected the variation in the subjects' HSP, since the pairwise mean did not have any variables overall.

Table 2. The Tukey's post-hoc test demonstrating variations in the instruments based on the subjects' HSP

(I) Group	(J) Group	Mean difference (I-J)	Std. Error	Sig.
Pre-IFCS	Pre-ultrasound	-0.73333	0.40552	0.466
	Pre-TENS	-0.46667	0.40552	0.858
	Post-IFCS	0.53333	0.40552	0.776
	Post-ultrasound	3.93333*	0.40552	0.000
	Post-TENS	0.40000	0.40552	0.921
Pre-ultrasound	Pre-IFCS	0.73333	0.40552	0.466
	Pre-TENS	0.26667	0.40552	0.986
	Post-IFCS	1.26667*	0.40552	0.029
	Post-ultrasound	4.66667*	0.40552	0.000
	Post-TENS	1.13333	0.40552	0.068
Pre-TENS	Pre-IFCS	0.46667	0.40552	0.858
	Pre-ultrasound	-0.26667	0.40552	0.986
	Post-IFCS	1.00000	0.40552	0.146
	Post-ultrasound	4.40000*	0.40552	0.000
	Post-TENS	0.86667	0.40552	0.279
Post-IFCS	Pre-IFCS	-0.53333	0.40552	0.776
	Pre-ultrasound	-1.26667*	0.40552	0.029
	Pre-TENS	-1.00000	0.40552	0.146
	Post-ultrasound	3.40000*	0.40552	0.000
	Post-TENS	-0.13333	0.40552	0.999
Post-ultrasound	Pre-IFCS	-3.93333*	0.40552	0.000
	Pre-ultrasound	-4.66667*	0.40552	0.000
	Pre-TENS	-4.40000*	0.40552	0.000
	Post-IFCS	-3.40000*	0.40552	0.000
	Post-TENS	-3.53333*	0.40552	0.000
Post-TENS	Pre-IFCS	-0.40000	0.40552	0.921
	Pre-ultrasound	-1.13333	0.40552	0.068
	Pre-TENS	-0.86667	0.40552	0.279
	Post-IFCS	0.13333	0.40552	0.999
	Post-ultrasound	3.53333*	0.40552	0.000

Source: compiled by the authors of this study

Stroke is a debilitating condition and a leading cause of disability globally. H.I. Adebisi *et al.* [11] and M. Duray & E. Baskan [12] reported that stroke substantially affects the upper limb function and grip strength. HSP is one of the widespread complications of stroke and is reported to be common among stroke survivors, with prevalence ranging within 22-47% [13]. According to the present study, there were notable differences ($p < 0.05$) across the physical modalities (transcutaneous electrical nerve stimulator, ultrasound device, and interferential current stimulator) in improving the HSP condition of the subjects. This result aligns with previous findings of M. Moniruzzaman *et al.* [14], D. Suriya-Amarit *et al.* [15], and M. Zhou *et al.* [16], who reported significant effects of these physical modalities in reducing HSP. M. Moniruzzaman *et al.* [14] evaluated the efficacy of both TENS and ultrasound therapy in the management of HSP and reported that both interventions significantly improve pain outcomes among patients with HSP. D. Suriya-Amirat *et al.* [15] reported that patients treated with interferential current reported greater reduction in HSP compared to subjects who received placebo. M. Zhou *et al.* [16] reported that both TENS and neuromuscular electrical stimulation were effective in improving HSP among stroke survivors. The consistency of these findings with the present study reinforces the efficacy of physical modalities in the management of HSP among stroke survivors. It is hypothesised that these interventions improve pain outcomes through mechanisms such as modulation of nociceptive signals and stimulation of endogenous opioid release. C.G.T. Vance *et al.* [17] and É.P. Rampazo & R.E. Liebano [18] considered these mechanisms in their research. M.K.N. Takla & S.S. Rezk-Allah [19] reflected the enhancement of local blood circulation and muscle relaxation improvements.

The present study found phonophoresis to have superior effect on HSP of stroke survivors. Previous findings reported that phonophoresis significantly improved the HSP of stroke survivors as well as among other populations, such as in patients with myofascial pain syndrome [20, 21]. M.S. Rahman & M.T. Uddin [20] observed that, when administered with pregabalin, therapeutic ultrasound yielded more significant reduction in post-stroke shoulder pain compared to therapeutic ultrasound in isolation. This may be explained by the similarity in the study methodology, including subject characteristics, or correspondence in HSP measuring instruments. Another explanation could also be the affinity in the gradients or clinical characteristics of stroke morbidity. Still, there are

two ways to interpret the substantial improvement in HSP observed in this study after ultrasound therapy. Firstly, the decrease in HSP in this study affirmed the efficacy of ultrasound device in the management of HSP compared with TENS and IFCS. Secondly, the use of topical analgesics (ketoprofen) as coupling medium together with ultrasound device (phonophoresis) could also illustrate the improved HSP noticed in the present study. T. Amornpinyokiat [21] also showed that phonophoresis was more effective in reducing pain in myofascial pain syndrome, compared to conventional ultrasound therapy. This finding further highlighted the improved efficacy in pain reduction following the use of a topical analgesic in combination with ultrasound therapy.

In summary, the present study revealed that the physical modalities of TENS, interferential current therapy, and phonophoresis were efficacious in reducing pain intensity of HSP among stroke survivors. According to the post-hoc analysis, phonophoresis was the most effective of these modalities and offered greater relief of pain compared to interferential current and TENS. The superior result obtained from phonophoresis application in the present study may be attributed to the analgesic effect of ketoprofen used as the coupling medium. The findings of the present study align with those from prior studies that reported the efficacy of physical modalities such as TENS, neuromuscular electrical stimulation, and high-intensity laser therapy.

Conclusions

The findings of the present study revealed that all three physical modalities significantly reduce HSP, with notable differences in their efficacy. Among the interventions, phonophoresis demonstrated superior effectiveness in alleviating HSP. Therefore, phonophoresis is the most promising protocol in the intervention of HSP of stroke survivors. The combination of topical analgesics (ketoprofen) as coupling medium together with ultrasound device could be the reason why phonophoresis provides superior relief of HSP after stroke compared to TENS and IFC. Thus, clinicians should be trained in the proper usage of physical modalities, especially ultrasound device, for management of HSP of stroke survivors. Limitation of this study lied in the inability to monitor subjects' activities outside the study setting. Specifically, the use of prescribed analgesics and adherence to home programmes were not accounted for, which could have influenced the outcomes. Inadequate clinical examinations also prevented the severity of the stroke from being factored in. Future studies can aim to explore synergistic effects of combining phonophoresis, TENS, or interferential current with other rehabilitation techniques, such as neuromuscular electrical stimulation or manual therapy, to determine if a multi-modal approach yields better outcomes for HSP management. Studies should also investigate the long-term efficacy of pain relief provided by these modalities.

Acknowledgements

The authors of the present study would like to acknowledge the management, staff, and patients at the Physiotherapy Department, University of Benin Teaching Hospital, Benin City, Nigeria for their assistance and involvement with this study.

Funding

None.

Conflict of Interest

None.

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Вплив транскутанної електричної стимуляції нервів, фонофорезу та інтерференційної струмової терапії геміплегічного болю у плечі у нігерійців, які пережили інсульт

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Анотація. Геміплегічний біль у плечі – поширений і виснажливий симптом, з яким стикаються люди, що перенесли інсульт, і який впливає на результати їхньої реабілітації та якість життя. Пошук ефективних методів лікування цього стану має важливе значення для покращення догляду за пацієнтами. Метою цього дослідження було визначити, як фонофорез, транскутанна електрична стимуляція нервів та стимуляція інтерференційними струмами впливають на геміплегічний біль у плечі у людей, які пережили інсульт. Було проведене до- і післятестове експериментальне дослідження серед 45 осіб, які пережили інсульт. Геміплегічний біль у плечі оцінювався за числовою шкалою оцінки болю, а дані аналізувалися за допомогою дисперсійного аналізу. Результати дослідження показали значні відмінності ($F = 35{,}101$, $p < 0{,}05$) між фізичними методами лікування (транскутанний електричний стимулятор нервів, ультразвуковий пристрій та стимулятор інтерференційного струму) у зменшенні геміплегічного болю в плечі у досліджуваних. Однак було виявлено, що фонофорез має кращий вплив на геміплегічний біль у плечі у людей, які пережили інсульт, а постфактум аналіз показав, що фонофорез є найбільш перспективним протоколом лікування геміплегічного болю в плечі у людей, які пережили інсульт. Результати цього дослідження свідчать про те, що навчання лікарів правильному застосуванню ультразвукових пристроїв для фонофорезу може значно покращити результати лікування геміплегічного болю в плечі у пацієнтів, які пережили інсульт

Ключові слова: неврологічна реабілітація; постінсультний біль; фізичні модальності; модуляція болю

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616.12-008.331.1-036.22(540.51)
DOI: 10.63341/ijmmr/1.2025.49

Article's History:
Received: 10.01.2025; Revised: 14.04.2025; Accepted: 27.05.2025

Prevalence and risk factors of hypertension in urban and rural populations of Vadodara, Gujarat

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Abstract. Hypertension, one of the most common non-communicable diseases, is associated with various modifiable risk factors. This study was carried out to compare the prevalence and risk factors of hypertension in urban and rural populations above 30 years of age. An OPD-based cross-sectional study was conducted at the Urban Health Training Centre (UHTC) and Rural Health Training Centre (RHTC) of the Medical College, affiliated to a tertiary care hospital, from May to July 2023, enrolling 100 participants each from UHTC and RHTC, aged more than 30 years. Using a pre-tested questionnaire, socio-demographic, personal and family details, lifestyle risk factors, blood pressure and anthropometric measurements were taken. The proportion of hypertensive patients was 41% in urban and 27% in rural (z-value: 2.11, p-value: <0.05), of which more than half were males in both urban (58%) and rural (59%). A major proportion of hypertensive patients was found in the age group of above 70 years in both urban (10 out of 12

Suggest Citation:
Sooraj A V, Pandya C, Shringarpure K, Yohannan S, Damor J. Prevalence and risk factors of hypertension in urban and rural populations of Vadodara, Gujarat. Int J Med Med Res. 2025;11(1):49–56. DOI: 10.63341/ijmmr/1.2025.49

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participants) and rural populations (7 out of 10 participants). Out of the diagnosed cases, 90% of urban and 70% of rural patients were on regular medication. Family history of hypertension (z-value: 3.43, p-value: <0.05), diabetes (z-value: 2.73, p-value: <0.05) and lifestyle risk factors like lack of physical activity (z-value: 2.93, p-value: <0.05), and stress (z-value: 3.39, p-value: <0.05) were significantly higher in urban areas, whereas smokeless tobacco consumption (z-value: 4, p-value: <0.05) and high salt diet (z-value: 3.37, p-value: <0.05) were significantly higher in rural areas. This study provides insights into how different environmental factors and cultural differences affect prevalence and risk factors associated with hypertension and helps in targeted public health interventions. The result will contribute to a better understanding of how environmental and cultural factors influence hypertension in a rapidly industrialising state, offering insights that can guide public health policies and more targeted interventions aimed at reducing the burden of hypertension in both settings in Gujarat

Keywords: non-communicable diseases; blood pressure; lifestyle disorder; proportion; urbanisation; comparison

Introduction

Hypertension (high blood pressure), one among the most common Non-Communicable Diseases (NCDs), stands out as a leading cause of death, earning the moniker of the "silent killer" as it contributes to cardiovascular diseases, stroke, chronic kidney disease, and other severe complications [1, 2]. The World Health Organization's (WHO) global report on hypertension 2023 [3] highlights the global prevalence of hypertension as 33% (34% in males and 32% in females), that has estimated to cause 7.5 million deaths worldwide annually [4]. According to a study done by S.F. Koya *et al.* [5], hypertension awareness and control are alarmingly low in many regions in India, despite its increasing prevalence due to urbanisation and lifestyle shifts.

A.E. Schutte *et al.* [6] similarly reported that in low- and middle-income countries, the management of hypertension is lagging behind global standards, contributing to rising mortality rates. One of the primary unresolved issues is the urban-rural disparity in hypertension prevalence, particularly in rapidly urbanising regions. C. Ricci *et al.* [7] have provided essential insights into how hypertension contributes to all-cause and cause-specific mortality. The study by C. Ke *et al.* [8] revealed that hypertension increases the odds of cardiovascular deaths due to ischemic heart disease (IHD) and stroke, by six- to eight-fold, and that the mortality burden is growing more rapidly in rural areas. The study by R. Mohammad & D.W. Bansod [9] showed that there was a higher prevalence of hypertension among men compared to women with a higher proportion in urban residents and the prevalence increased with age. H. Song *et al.* [10] highlighted the urban-rural disparity in the prevalence of factors influencing hypertension such as age, gender, occupation, literacy, dietary habits, diabetic status, high BMI, lack of physical activity, alcohol and tobacco consumption. J. Pan *et al.* [11] emphasised the differences in the adherence to treatment in hypertensive patients of urban and rural areas, with a significantly lower adherence in the rural areas compared to urban settings. Despite the extensive research on hypertension, there remains a gap in studies focusing on local popular dynamics within India, particularly in states like Gujarat. Vadodara district, which exemplifies a coexistence of urban and rural population, presents an ideal microcosm to investigate these differences.

This study aimed to fill the gap by investigating the proportion of hypertension and risk factors such as age, gender, obesity, tobacco use, physical inactivity, high salt intake, and alcohol consumption, which have been consistently associated with hypertension across different settings, in urban and rural population of age more than 30 years in Vadodara district of Gujarat.

Materials and Methods

An OPD based cross-sectional study was conducted at Urban Health Training Centre (UHTC) and Rural Health Training Centre (RHTC) of Medical College affiliated to tertiary care hospital. UHTC is situated at a locality in Vadodara city which covers around 56,000 population. RHTC is situated at a village near the outskirts of Vadodara city and covered a population of around 37,000. A total of 200 participants were enrolled through purposive sampling, 100 each from UHTC and RHTC of age more than 30 years from May to July, 2023. Pregnant women and those individuals not willing to participate were excluded from the study.

This study adhered to the Code of Ethics of the American Sociological Association [12] and appropriate permission was obtained from the Medical Officer in-charge of RHTC and UHTC to conduct the study by explaining its purpose and outcome. After taking informed consent from the willing participants by explaining nature of the study and guaranteeing anonymity, a pretested questionnaire was used to gather data on socio-demographic characteristics including age, gender, education, occupation, family history of hypertension, and collected information on lifestyle risk factors such as consumption of alcohol and tobacco products, excessive salt intake, and lack of physical exercise.

Operational definitions: A person is found to have family history of hypertension if one or both parents had the condition. Males were classified as heavy drinkers if they consume more than two alcoholic drinks per day and females were considered as heavy drinkers if they consume more than one drink per day [13]. A person was defined as a smoker if they currently smoke any form of tobacco including cigarette, beedi, or cigar. Smokeless tobacco use includes consumption of products like pan, gutka, tobacco-lime mixtures or any other form of tobacco. Regular exercise was described as engaging in physical activity for at least 30

minutes per day, a minimum of 5 days per week [14]. Excessive salt intake refers to consuming more than 6 grams of sodium chloride per day. Adequate sleep was characterised by having quality sleep for 7 hours or more [15].

Blood pressure (BP) was measured in the right arm using mercury sphygmomanometer (Diamond, manufactured in India) in sitting position after 5-10 minutes of rest and no immediate intake of hot drinks like tea or coffee within last 30 minutes. Electronic weighing machine (Electronic Personal Scale SCS-0180, manufactured in China) was used to record the weight. Height was measured using a measuring tape fixed to the wall while the subject stood on a level surface with heels together, barefoot. Waist circumference was taken with the subject standing upright, using a non-elastic plastic tape positioned midway between the lower rib margin and the iliac crest, ensuring the tape was pulled snug but not pressing into the skin. Waist circumference risk classification was done according to the WHO criteria [16], waist circumference ≥94 cm was considered to be increased risk category in males and waist circumference ≥80 cm was considered to be increased risk category in females. Body mass index (BMI) was calculated and classified according to standard WHO criteria [17]. Those with BMI ≥25 kg/m^2 was considered to be high risk group for hypertension.

The Joint National Committee 7 (JNC-7) criteria [18] was used for the definition and classification of hypertension. According to that, hypertension was defined as having a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher, those individuals having BP under this category were reassessed and average of three readings were taken. Already diagnosed cases were counted and first time diagnosed cases were asked to come for follow up and further management.

Quantitative data was expressed in mean (±Standard Deviation). Proportion of hypertension and prevalence of risk factors in urban and rural population were expressed in percentages. Data entry and analysis was done using Microsoft Excel Version 2408. Standard Error of Difference between two proportions was used to examine the differences in proportion of hypertension and identifying significant difference in prevalence of risk factors within each population subgroups. P-value <0.05 was considered to be significant.

Results and Discussion

A total of 200 participants were enrolled in the study, 100 each from urban and rural areas with a mean (±Standard Deviation) age of 54.1 (±12.3) years in urban and 51 (±12.1) years in rural. More than half of the study population were males (53%) in urban whereas more than half were females (52%) in the rural population. Higher proportion of hypertensive patients were males in both urban (58%) and rural (59%) areas. Considering the age distribution, maximum number of participants belonged to the age group 50-59 years in urban and 40-49 years in rural while proportion of hypertensive patients was more in the age group of above 70 years in both urban (10 out of 12 participants) and rural population (7 out of 10 participants). Seven percent of the total hypertensives in urban and 4% in rural were young hypertensives. Socio-demographic distribution of the participants is shown in Table 1.

Table 1. Socio-demographic distribution of the participants in urban and rural population

Gender distribution of the study prticipants						
Gender	**Urban**			**Rural**		
	n	**Hypertensive n**	**%**	**n**	**Hypertensive n**	**%**
Males	53	24	45	48	16	33
Females	47	17	36	52	11	21
Age distribution of the study participants						
Age (in years)	**Urban**			**Rural**		
	n	**Hypertensive n**	**%**	**n**	**Hypertensive n**	**%**
30-39	14	3	21	20	1	5
40-49	20	6	30	29	2	7
50-59	31	10	32	19	9	47
60-69	23	12	52	22	8	36
>70	12	10	83	10	7	70
Total	**100**	**41**	**41**	**100**	**27**	**27**

Notes: n = 100, therefore n is same as proportion
Source: compiled by the authors

The total proportion of hypertensive patients was found to be 34%, with 41% in urban and 27% in rural population and this difference was found to be statistically significant (z-value: 2.11, p-value: <0.05). Only 16% in urban and 21% in rural population were normotensives and a large proportion of study participants in both urban (52%) and rural (49%) were pre-hypertensives according to JNC-7 classification (Table 2). There were 6 and 8 patients from the urban and rural area, respectively, who were diagnosed first time as hypertensive and asked to come for follow up and further management.

Table 2. Classification of the participants according to JNC-7 classification

Blood pressure classification	Total		Urban		Rural	
	n	%	n	%	n	%
Normotensive	37	18.5	16	16	21	21
Pre hypertensive	101	50.5	52	52	49	49
Hypertension – stage I	40	20	21	21	19	19
Hypertension – stage II	22	11	11	11	11	11
Total	**200**		**100**		**100**	

Source: compiled by the authors

In urban area, out of the total hypertensives, 90% of the patients were on regular medication while the remaining 10% did not take medicines regularly. 80% of the patients were taking medicines from government sources and the rest were taking medicines from private sources and majority (75%) of the patients on irregular medication were taking medicines from private sources. In the rural area, only 70% of the total hypertensives were on regular medication and the rest were on irregular medication. 89% of the patients were taking medicines from government sources and only 11% of the patients were taking from private sources. This difference in the medication adherence in urban and rural population was found to be statistically significant (z-value: 3.64, p-value: <0.05).

Lack of physical activity (z-value: 2.93, p-value: <0.05), family history of hypertension (z-value: 3.43, p-value: <0.05), prevalence of diabetes (z-value: 2.73, p-value: <0.05) and stress (z-value: 3.39, p-value: <0.05) were significantly higher in urban areas compared to rural areas whereas smokeless tobacco consumption (z-value: 4, p-value: <0.05) and high salt diet (z-value: 3.37, p-value: <0.05) were significantly higher in rural areas (Table 3). The prevalence of major risk factors of hypertension given by the Centres of Disease Control and Prevention including high salt intake, lack of physical activity, alcohol and tobacco use, obesity, family history of hypertension and diabetic status were determined and in addition to that, stress and lack of good sleep (sleep <7 hours/day) [15] were also assessed and given in Figure 1, which shows a high prevalence of over-weight/obesity (BMI ≥25 kg/m^2) , high risk waist circumference and consumption of tobacco products in both the areas.

Table 3. Assessing the differences in the proportion of risk factors by Standard Error of Difference between two Proportions

Risk factors	Urban		Rural		z-value	p-value
	n (%)	95% CI	n (%)	95% CI		
Tobacco smoking	39	(29.40-49.27)	27	(18.61-36.80)	1.82	>0.05
Smokeless tobacco consumption	30	(21.24-39.98)	57	(46.71-66.86)	4	<0.05
Alcohol consumption	6	(2.23-12.60)	9	(4.20-16.40)	0.81	>0.05
Family history of hypertension	53	(46.27-65.73)	30	(21.24-39.98)	3.43	<0.05
Lack of physical activity (<30 min/day)	77	(67.51-84.83)	58	(47.71-67.80)	2.93	<0.05
High salt diet	45	(35.03-55.27)	68	(57.92-76.98)	3.37	<0.05
BMI ≥25 kg/m2	52	(41.78-62.10)	43	(33.14-53.29)	0.95	>0.05
Waist circumference (males ≥94 cm & females ≥80 cm)	52	(41.78-62.10)	41	(31.26-51.29)	1.56	>0.05
History of DM	43	(33.14-53.29)	25	(16.88-34.66)	2.73	<0.05
Stress	70	(60.02-78.76)	47	(36.94-57.24)	3.39	<0.05
Inadequate sleep (<7 hours)	36	(26.64-46.21)	26	(17.74-35.73)	1.54	>0.05

Notes: p-value <0.05 is considered to be significant
Source: compiled by the authors

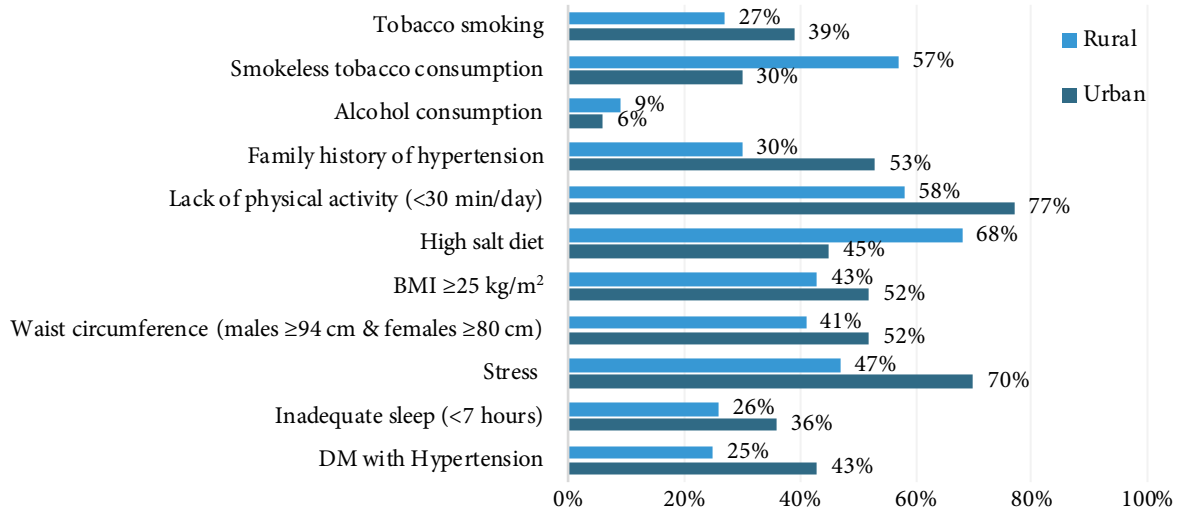

Figure 1. Prevalence of risk factors in urban and rural population
Source: compiled by the authors

This study highlights the burden of hypertension in the urban and rural field practice area. The proportion of hypertension, according to JNC-7 criteria, was found to be 34% which aligns with the estimates given by WHO Global Report on hypertension [3] which was 33%. In addition, this study revealed significant differences between urban and rural populations, even though overall prevalence was higher in urban areas (41%), rural areas still had a substantial burden (27%). These findings were comparable with the findings of a study by I.M. Ismail *et al.* [19], who reported a higher prevalence of hypertension among urban residents (23.7%) compared to rural dwellers (18.3%) in coastal regions of South India. The study by R. Anchala *et al.* [20] found a higher prevalence of hypertension in urban areas (33.8%) compared to rural areas (27.6%), which often shows higher hypertension rates due to urbanisation and life style changes. Similarly, the Office of Registrar General of India [21] also shows a higher prevalence in urban areas (25%) compared to rural areas (10%). This difference in proportion could be conditioned by dietary habits, physical activity, and increased stress levels in cities as per this study.

Present study identified that more than half of the hypertensive patients in both urban (58%) and rural (59%) areas were males, which was comparable to a study by U. Venkatesh *et al.* [22], where the prevalence of hypertension was found higher in males (18.2%) than in females (16.1%). Similar trend was found in a study by S. Singh *et al.* [23] in urban Varanasi, where the prevalence of hypertension was 40.9% in males and 26% in females. This gender disparity needs further evaluations and it could be due to the difference in occupational stress, addictions, and lifestyle choices. Knowledge about these gender specific variations will be helpful in targeted interventions and prevention.

Major proportion of hypertensive patients were in the age group of above 70 years followed by 60 to 69 years in both the areas which was found similar to the study by Y. Ostchega *et al.* [24] that showed 74.5% of older adults over 60 years of age have hypertension. Another study by E. Oliveros *et al.* [25] found that 65% of men and 75% of women were found to develop hypertension by the age of 70 years. These findings suggest that age is a well-established risk factor for hypertension and as age increases, the risk of hypertension also increases, leading to a decline in cardiovascular endurance as indicated by a study done by S. Vadzyuk & P. Tabas [26]. This study also identified a small proportion (7% in urban and 4% in rural) of young hypertensives (30-39 years) while a study by Z. Geevar *et al.* [27] in Kerala have found the prevalence of hypertension among young adults as 11.2% which is higher than the findings of this study. This emphasises the need of early detection and management across all age groups.

A notable finding was the presence of undiagnosed hypertensive cases. 6 (6%) participants in urban and 8 (8%) participants in rural population had elevated blood pressure (>140/90 mmHg) but were not previously diagnosed. This trend was found similar to a study by B. Boro & S. Banerjee [28] in which the prevalence of undiagnosed cases was found higher in rural areas than in urban areas, while, a study conducted by P.D. Appadurai *et al.* [29] in South Indian districts found that the proportion of undiagnosed hypertensive cases were more in urban than in rural. Those cases were encouraged to seek follow up care to prevent complication and reduce the burden of hypertension related morbidity. This shows that the government initiative proposed for screening of hypertension and diabetes in all participants above the age of 30 years may indeed help in early identification of these non-communicable disease and manage them timely.

Among the diagnosed cases, medication adherence was significantly higher in the urban population (90%) than in the rural population (70%) which was comparable with a study by P.R. Katapadi & D.D. Bant [30] in which the antihypertensive adherence was more in urban (76%) than in rural (71%), and a study by D. Mathur *et al.* [31] in Rajasthan found that the proportion of non-adherent patients were more in rural (39.7%) than in urban (14.4%)

population. This difference could be due to better access to health care facilities in urban and higher health seeking behaviour of the urban population. This discrepancy demands health promotion and counselling in the rural areas to improve medication adherence. A qualitative insight to look into these perceptions is warranted.

Considering the major risk factors of hypertension, the present study identified that lack of physical activity, family history of hypertension, prevalence of diabetes and stress were significantly higher in urban areas as compared to rural areas while smokeless tobacco consumption and high salt diet were significantly higher in rural areas. A similar study by R.R. Marinayakanakoppalu & A.C. Nagaralu [32] found that there was a statistically significant difference in the proportion of individuals having extra salt intake, family history of hypertension, overweight and obesity in urban and rural population of India. This disparity highlights the impact of lifestyle in urban areas while cultural habits and lack of awareness regarding the disease in rural settings.

These findings signify the comparable difference in the burden of hypertension and its associated risk factors in urban and rural settings across various parts of the country. Similar difference was observed in the medication adherence, with a lower medication adherence in the rural areas adding to the disease associated mortality. This emphasises the critical need for comprehensive public health strategies to address hypertension and its prevailing risk factors in different contexts.

Conclusions

This study highlights a significant difference in the prevalence and risk factors of hypertension between urban and rural population. Urban areas showed a higher prevalence of hypertension (41%) compared to rural areas (27%), and this difference was found to be statistically significant. Proportion of male and female participants were comparable in both urban and rural settings, with higher rates of hypertension in males than in females in both the settings. Hypertension was more prevalent among older age group, particularly those above 70 years, in both urban and rural population, with about half of the participants having pre-hypertension in both the areas. Medication adherence was found better in urban areas, with 90% of hypertensive patients taking regular medications, compared to only 70% in rural areas. This disparity underscores the importance of improving health care access and health seeking behaviour in rural settings. Risk factors such as lack of physical activity, family history of hypertension, diabetes, and stress were significantly higher in the urban areas, reflecting the lifestyle and environmental factors associated with urbanisation. In contrast, rural participants showed higher rates of smokeless tobacco consumption and a high salt diet compared to urban areas, while other risk factors were equally prevailing in both the areas. Identifying the risk factors for hypertension and tracking of participants with these risk factors may help in early diagnosis and thereby prevent complications. Targeted interventions should be done by tailoring public health efforts to the specific needs of urban and rural population and the strategies should address risk factors prevalent in each setting. Further research into role of socio-economic, cultural and health care access factors is required to be conducted in both the settings, for a better understanding of the urban-rural disparities in the prevalence and associated risk factors of hypertension.

Acknowledgements

The authors sincerely acknowledge the participants of the study for their time and efforts, UHTC and RHTC Medical Officers for permitting to conduct this study, Dean and Senior faculties of Medical College, Baroda for guiding to complete this study.

Funding

None.

Conflict of Interest

None.

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Поширеність та фактори ризику артеріальної гіпертензії серед міського та сільського населення Вадодари, штат Гуджарат

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Анотація. Артеріальна гіпертензія, одне з найпоширеніших неінфекційних захворювань, асоціюється з різними модифікованими факторами ризику. Це дослідження було проведено з метою порівняння поширеності та факторів ризику артеріальної гіпертензії серед міського та сільського населення старше 30 років. Перехресне дослідження за участю амбулаторних пацієнтів було проведено в Міському навчальному центрі охорони здоров'я (МНЦОЗ) та Сільському навчальному центрі охорони здоров'я (СНЦОЗ) Медичного коледжу при лікарні третинного рівня з травня по липень 2023 року, в якому взяли участь по 100 осіб з МНЦОЗ та СНЦОЗ у віці понад 30 років. За допомогою попередньо протестованої анкети було зібрано соціально-демографічні, особисті та сімейні дані, фактори ризику способу життя, виміряно артеріальний тиск та антропометричні показники. Частка пацієнтів з артеріальною гіпертензією становила 41 % у містах і 27 % у сільській місцевості (z-значення: 2,11, p-значення: <0,05), з яких більше половини були чоловіками як у містах (58 %), так і в сільській місцевості (59 %). Найбільша частка пацієнтів з артеріальною гіпертензією була виявлена у віковій групі старше 70 років, як серед міського (10 з 12 учасників), так і серед сільського населення (7 з 10 учасників). Серед діагностованих випадків 90 % міських і 70 % сільських пацієнтів регулярно приймали ліки. Сімейний анамнез артеріальної гіпертензії (z-значення: 3,43, p-значення: <0,05), діабету (z-значення: 2,73, p-значення: <0,05) та фактори ризику, пов'язані зі способом життя, такі як недостатня фізична активність (z-значення: 2,93, p-значення: <0,05) та стрес (z-значення: 3,39, p-значення: <0,05) були значно вищими в міській місцевості, тоді як споживання некурильного тютюну (z-значення: 4, p-значення: <0,05) та дієта з високим вмістом солі (z-значення: 3,37, p-значення: <0,05) були значно вищими в сільській місцевості. Це дослідження дає уявлення про те, як різні фактори навколишнього середовища та культурні відмінності впливають на поширеність і фактори ризику, пов'язані з гіпертонією, і допомагає в розробці цілеспрямованих заходів у сфері охорони здоров'я. Результати дослідження сприятимуть кращому розумінню того, як екологічні та культурні фактори впливають на артеріальну гіпертензію у швидко індустріалізованому штаті, пропонуючи ідеї, які можуть спрямовувати політику громадського здоров'я та більш цілеспрямовані втручання, спрямовані на зменшення захворюваності на артеріальну гіпертензію в обох середовищах у штаті Гуджарат

Ключові слова: неінфекційні захворювання; артеріальний тиск; порушення способу життя; частка; урбанізація; порівняння

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 614.213/.253:331.101.32(540.51)
DOI: 10.63341/ijmmr/1.2025.57

Article's History:
Received: 02.12.2024; Revised: 06.03.2025; Accepted: 27.05.2025

Assessment of job satisfaction among nursing staff in a tertiary care hospital of Central Gujarat, India – a cross-sectional study

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Abstract. In a hospital setting, nurses are ground-line workers who take care of patients round the clock, and therefore it is crucial that they are satisfied with their work. The purpose of the present study was to assess job satisfaction among nursing staff from personal, interpersonal, and job perspectives. This cross-sectional questionnaire-based study was conducted using pre-validated and free to use Muthayya's job satisfaction questionnaire. A total of 195 nurses were included in the study, while 192 – consented to take part and filled out the given form. Study population was predominantly female and had over 20 years of work experience. It was established that 70.31% of participants were satisfied in the job aspect, 84.38% – in personal aspect, and 76.56% – in interpersonal aspect. The study showed overall satisfaction of 80.20%. Greater levels of satisfaction were noted among individuals with over 20 years of experience and General Nursing and Midwifery (GNM) qualifications ($p < 0.001$). Gender and job satisfaction, however, had no significant association ($p = 1$). Less facilities at workplace, less authority to nursing staff for effectively carrying their job responsibility, getting lesser remuneration, pressure from patients' relatives' sides were the predictors adversely affecting the job satisfaction level among nursing

Suggest Citation:
Bambhava M, Patel S, Parmar V, Shah S, Verma A. Assessment of job satisfaction among nursing staff in a tertiary care hospital of Central Gujarat, India – a cross-sectional study. Int J Med Med Res. 2025;11(1):57–65. DOI: 10.63341/ijmmr/1.2025.57

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staff. Most of the surveyed nursing staff of the tertiary care hospital of Vadodara were satisfied. Provision of adequate facilities, ensuring equitable remuneration, and fostering a positive working environment significantly enhanced job satisfaction among nursing staff, ultimately leading to improved performance and higher-quality patient care in hospitals

Keywords: healthcare worker; burnout; mental health; job responsibilities; personal satisfaction

Introduction

It is essential to evaluate job satisfaction among the nursing staff as it directly correlates with the efficiency and performance of employees on the job which would further improve the quality of the services provided to the patients [1]. Nurses are crucial links between the physicians, therapists, patients' family, and other paramedical staff in hospitals. Job satisfaction in nursing profession is increasingly being recognised as a measure to include in quality improvement programs whereas low job satisfaction, work accidents, low work engagement, burnout, work related stress of nurses can result in increased attrition rate and absenteeism, affecting the efficiency and effectiveness of healthcare services. Furthermore, job dissatisfaction at workplace can affect mental health of employees. However, research on job satisfaction among nurses in India, particularly in tertiary care hospitals like those in Vadodara city, is still limited. Understanding the factors that influence job satisfaction in this demographic is essential to address gaps in workplace policies and improve the overall healthcare provision system.

Y.K. Almualm *et al.* [2] investigated job satisfaction among nurses in governmental and private healthcare settings, emphasising recruitment and retention challenges. Positive influences on job satisfaction included autonomy, salary, professional interactions, task clarity, supervision quality, collegial relationships, and organisational policies. Conversely, dissatisfaction arose from heavy workloads, inadequate pay, limited professional development opportunities, poor supervisory support, lack of autonomy, and insufficient resources and benefits. A. Ayed *et al.* [3] investigated the relationship between work environment factors and professional quality of life (ProQoL) among ICU nurses, identified key determinants of job satisfaction such as demographic variables (e.g., age, gender, education, and experience) and workplace dynamics, including decision-making involvement, leadership support, and nurse-physician collaboration. P. Ozdoba *et al.* [4] found analogous correlations between socio-demographic and occupational characteristics with professional values and job satisfaction among nurses in the eastern part of Poland. R. Topchyan & C. Woehler [5] found that job experience and female gender were significant predictors for level job satisfaction among teachers. T. Yuan *et al.* [6] highlighted the mediating roles of job satisfaction and work engagement in the relationship between ProQoL profiles and outcomes like turnover intentions and life satisfaction, and H. Wei *et al.* [7] also confirmed these findings. B.J. Ali & G. Anwar [8] concluded that recognition and respect from employers, promotions, engagement of employees in decision-making, and compensation were some factors enhancing job satisfaction. Y. Ejigu *et al.* [9] identified inadequate pay and benefits, limited career advancement opportunities, heavy workloads, unsupportive supervision, and inflexible workplace policies as major factors undermining job satisfaction.

The present study focused on evaluating the job satisfaction of nurses by assessing various factors including job related aspects, personal factors, and interpersonal dynamics. By identifying these factors and evaluating the association of demographic variables such as experience and qualifications with job satisfaction levels, this study offered actionable recommendations for improving the work environment.

Materials and Methods

This was a cross-sectional questionnaire-based study. The primary study tool was Muthayya's job satisfaction questionnaire [6, 10], a pre-validated and free to use survey questionnaire used to study staff satisfaction, which is applied to measure job satisfaction in a variety of sectors, including healthcare (nursing). Questionnaire included demographic basic details of participants, job satisfaction related to such aspects as job, personal, and interpersonal. The original scale contained 34 questions, but after adapting to the hospital setting, 32 questions were used for the present study. The questions were translated into local language and the questionnaire was validated using the Spearman-Brown prediction formula (1), producing the value of 0.80 (2), which was indicative of the satisfactory reliability of the scale:

$$New\ Reliability = \frac{kr}{1+(k-1)r}, \quad (1)$$

where k – the factor by which the number of items in the test is increased or decreased (new number of items divided by the original number of items (in the present study, k was 32/34 = 0.941); r – the observed reliability of the original test.

$$New\ Reliability = \frac{0.941 \cdot 0.81}{1+(0.9411-1)0.81} = \sim 0.80. \quad (2)$$

The job aspect encompassed information regarding remuneration, employment opportunities, absence of technical expertise, promotional prospects, facilities for work, workload, conflicting work roles at the place of employment, monotonous nature of work, work expectations of superiors, and the authority vested in the job. The personal aspect covered a range of information pertaining to inadequacy, security, non-acceptance within the department, under-employment, the desire to change jobs, and a perceived lack of authority. The interpersonal aspect encompassed the pressure at one's work and attitude towards

superiors. Questions had answer options in the form of Agree (2), Not sure (1), and Disagree (0). Maximum score each respondent could reach was 64. The cut-off value for satisfied and dissatisfied was maintained at 32, with higher scores indicating lower levels of satisfaction.

The data was collected through the implementation of self-administered questionnaires, which were filled out by each member of the nursing staff. Prior to taking part in the study, the participants were clearly explained the purpose of the study, emphasising the voluntary nature of participation. Participants were assured of their anonymity and confidentiality throughout the study, and it was explicitly communicated that no harm would result from the participants' involvement. The present study was conducted in November 2021 to May 2022 at government tertiary care hospital, Vadodara. Pilot study was conducted among 15 nurses. The pilot study established the prevalence of job satisfaction at 86%, as ascertained using the open Epi software. The calculation of the required sample size was determined by the 86% prevalence of job satisfaction and a 95% confidence interval. The calculated sample size was thus established at 185. However, this figure was augmented by a further 5% to account for subjects who were lost to follow-up, thereby bringing the total sample size to 195. The inclusion criterion was the nursing staff of tertiary care hospitals who had completed their probation period. The exclusion criteria were nursing staff who did not consent to take part and members of the nursing staff with any pending or ongoing disciplinary proceedings. Out of 195 nurses, three nurses did not gave consent for taking part in study, and therefore only 192 nurses were included in the analysis. Informed consent was obtained from each participant, and the study was approved by the institutional ethics committee (IECBHR/04-2021).

Summary statistics were employed to describe the sociodemographic characteristics of the samples. Chisquare/Fisher's exact test analysis was employed to observe the relationship between factors like years of work experience, gender of nursing staff, and educational qualification with job satisfaction. Coefficient correlation was used to find any relationship between job, personal, and interpersonal aspects. Statistical analysis and entry of data was performed by Data Analysis tool in Microsoft Excel 2021 and Jamovi version 2.4.14. A significance level of 95% ($p < 0.05$) was considered statistically significant throughout the study.

Results and Discussion

According to demographic data (Table 1), a total of 195 nurses were included in this study, out of which 192 nurses consented to take part in the study. Of the total sample, 11.45% were males and 88.55% were females with age ranging from 21 to 58 years, with a mean age of 45.1 years. Most participants (64.06%) had over 20 years of experience, with the average work experience at 19.1 years.

Table 1. Demographic data

Age (M = 45.1; SD = 9.11; range = 21-58)	N (%)
Gender	
Male	22 (11.45)
Female	170 (88.55)
Nursing Seniority	
<5 years	16 (8.30)
6-10 years	11 (5.72)
11-15 years	25 (13.02)
16-20 years	17 (8.90)
>20 years	123 (64.06)

Notes: M – mean; SD – standard deviation
Source: compiled by the authors of this study

Overall, 80.20% of the nursing staff were satisfied with their job. About 84.38% of nurses (CI: 78.46-89.21%) expressed satisfaction with the personal component of their jobs, followed by the interpersonal aspect (76.56%; CI: 69.92-82.36%), and the job aspect (70.31%; CI: 62.98-76.39%). Only 10.76% of nurses were unsure about their level of job satisfaction (Fig. 1). Table 2 demonstrates that the job aspect had moderate positive correlation with personal and interpersonal aspect, whereas personal and interpersonal aspects correlated poorly with each other.

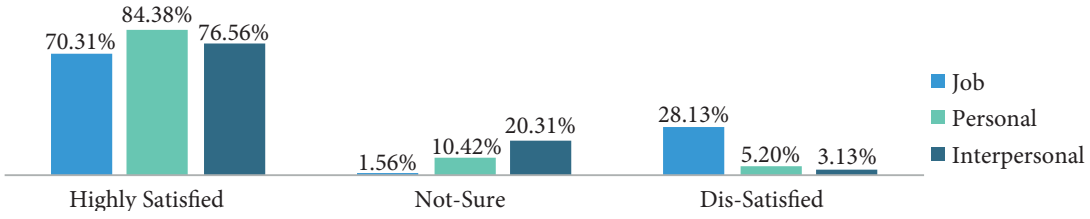

Figure 1. Job satisfaction level according to domains
Source: compiled by the authors of this study

Table 2. Corelation model of three domains

		Job aspect	Personal aspect	Interpersonal aspect
Job aspect	Spearman's rho	–		
	df	–		
	p-value	–		
Personal aspect	Spearman's rho	0.671	–	
	df	190	–	
	p-value	<0.001	–	
Interpersonal aspect	Spearman's rho	0.610	0.530	–
	df	190	190	–
	p-value	<0.001	<0.001	–

Notes: df – degree of freedom; rho – rank correlation coefficient
Source: compiled by the authors of this study

Table 3 shows that nurses with over 20 years of experience were more satisfied (about 90.24%) compared to those with under 20 years of experience (about 69.56%), and the difference was statistically significant ($p < 0.001$). There was no statistically significant difference between job satisfaction and gender of nursing staff ($p = 1$). The educational qualification of the respondents was divided into two categories: Bachelor of Science in nursing (BSc nursing) and General Nursing and Midwifery (GNM). Nurses who qualified in GNM were more satisfied (about 85.63%) than those nurses who had BSc nursing qualification (about 36.36%), and the difference was statistically significant ($p < 0.001$).

The findings suggested that improving workplace facilities can significantly enhance job satisfaction for most nurses (98.43%). Interestingly, only a small proportion (0.52%) of nurses reported that a reduced workload contributed to boredom in the workplace (Table 4).

Table 3. Job satisfaction related with level of experienced, gender and qualification

Variable	Group	Dissatisfied	Satisfied	Frequency (n = 192)	X^2 test/ Fisher's exact test	p-value	95% CI
Years of experience	>20 years of experience	12	111	123	13.3	<0.001	8.233-33.773
	<20 years of experience	21	48	69			
Gender	Female	29	141	170	0.0173	1	-13.409-23.867
	Male	4	18	22			
Qualification	BSc Nursing	7	4	11	17.7	<0.001	15.896-75.158
	GNM	26	155	181			

Source: compiled by the authors of this study

Table 4. Survey respondents who expressed agreement with questions on the job aspect

	Questions related to the job aspect	Respondents (n = 192)	%
1.	You are dissatisfied with promotion opportunities	36	18.75
2.	Due to lack of technical knowledge, you are at disadvantage	76	39.58
3.	You are overloaded with work	57	29.68
4.	You a forced to do things at your workplace which are against your better judgment	69	35.93
5.	You are confused about the role you must play when doing your job	14	7.29
6.	You feel that the patients do not care about your suggestions	74	38.54
7.	You should be provided with better facilities for decent work	189	98.43
8.	You are paid less than employees in another department	109	56.77
9.	Having less work causes you to feel boredom at workplace	1	0.52
10.	You have fewer opportunities to do your best in this job	71	36.97
11.	You are not getting required administrative information to carry out job	89	46.35
12.	Each day of work appears as though it will never end	79	41.14
13.	You feel that your progress at your job is not what it could be	84	43.75
14.	You feel that your job does not give you the chance to do things that you could do best	26	13.54
15.	You have clear idea of expectations from seniors regarding your work performance	36	18.75

Source: compiled by the authors of this study

A considerable proportion of respondents (63.02%) reported that perceiving a limited ability to execute their assigned responsibilities adversely affected their job satisfaction. Notably, 7.29% of nurses expressed agreement with the sentiment that their role is not perceived as valuable within their department (Table 5).

Table 5. Survey respondents who expressed agreement with questions on the personal aspect

	Questions related to the personal aspect	Respondents (n = 192)	%
1.	You think you could have done a better job in a different department	64	33.33
2.	You feel like you are not fully capable of handling your job	22	11.45
3.	You do not feel secure at your workplace	43	22.39
4.	You feel disliked and rejected by your co-workers	14	7.29
5.	You feel that your department is only given secondary consideration by the government	85	44.2
6.	You would be happy if your current job lasted for a long time	23	11.97
7.	You feel that your current job is not suitable for people like you	17	8.85
8.	You feel that your job is not valuable in your department	14	7.29
9.	You think you should have gotten a better job for your qualifications	66	34.3
10.	You feel that you lack the opportunity to think and work independently in your job	61	31.77
11.	You think you should change your current job	19	9.89
12.	You feel that you have little power to carry out the responsibilities assigned to you	121	63.02

Source: compiled by the authors of this study

Nearly half (49.47%) of nurses reported that pressure from patients' relatives negatively affected their work efficiency. Furthermore, 9.89% of nurses reported limited opportunities for career advancement and inadequate remuneration, highlighting significant concerns regarding job satisfaction and professional development (Table 6).

Table 6. Survey respondents who expressed agreement with questions on the interpersonal aspect

	Questions related to the interpersonal aspect	Respondents (n = 192)	%
1.	Your superiors appreciate the arduous work you put in	52	27.08
2.	Your superiors encourage you to give suggestions for improvement in your department	39	20.31
3.	You feel that pressure from patient's relatives affects the efficiency of your work	95	49.47
4.	You feel that whenever you have a problem you cannot talk to anyone better experienced than you in your department	33	17.18
5.	You feel like you do not have a good chance to move on in life and make enough money	19	9.89

Source: compiled by the authors of this study

One crucial aspect of organisational behaviour that is often considered and discussed is job satisfaction. The goal is to promote both mental and physical health from a wide perspective that includes organisational and human resource management perspective. Organisational productivity and profitability have a positive relationship with job satisfaction. Basically, individuals that are highly satisfied with their workplace are found to perform better at job [11]. Although during the 2010-2020, lots has changed in the healthcare system, affecting the way nurses work in their organisations and treat patients. Strong teamwork and communication among healthcare professionals can lead to better patient health outcomes, while continuous education and training can empower nurses to provide more effective care. In the present study, participants had a relatively wide age range from 21 to 58 years, were predominantly female and most had over 20 years of experience. Findings of the current study indicated that level of job satisfaction was not influenced by the gender of the nursing staff. H. Tsuchihashi *et al.* [12] investigated analogous demographic characteristics of nurses in Japan, concluding that male nurses were highly engaged at job and therefore satisfied compared to female nurses. In contrast to that, N. Panchal *et al.* [13] observed that female nurses were more satisfied than male nurses.

The correlation between the three domains – job aspect, interpersonal aspect, and personal aspect – was statistically significant, with $p < 0.001$. The findings indicated that job satisfaction levels were strongly influenced by years of professional work experience. This may suggest that more years of experience serves as a proxy for age. T. Bonsaksen *et al.* [14] also suggested a positive relationship between older age and job satisfaction, although this relationship was not observed by Y. Pang *et al.* [15] in Korean nurses. The present study also identified a significant difference in job satisfaction levels based on the qualification of nursing staff, with General Nursing and Midwifery (GNM)-qualified nurses reporting higher satisfaction compared to Bachelor of Science in Nursing (BSc Nursing)-qualified staff. This difference might be attributed to

fact that BSc Nursing qualification is considered superior to GNM in India, and therefore nurses with BSc Nursing qualification might feel underutilised in their roles.

Most nurses working at the tertiary care hospital reported a pronounced level of job satisfaction in the present study. Analogously, a study conducted by Abdullah *et al.* [16] in a tertiary care hospital of Khyber Pakhtunkhwa found that over three-fourths of the nursing staff were overall satisfied with their jobs, and self-administered questionnaires were used to assess satisfaction levels. Previous studies on job satisfaction employed various standardised questionnaires, such as the Mueller and McCloskey Satisfaction Scale (MMSS) used by Y. Zhong *et al.* [17] to study nursing staff in China, and the Job Satisfaction Scale (JSS) and Speakman Job Satisfaction Scale (SJSS) used by M.K. Rosenberg & T. Bonsaksen [10] to evaluate physiotherapists in Norway, Job Satisfaction Survey (JSS) by Spector was used by N. Panchal *et al.* [13] to assess job satisfaction in Uttarakhand, India. However, these questionnaires were often lengthy, time-consuming, and focused more on the stress levels of healthcare staff, which could introduce bias into the findings. To mitigate potential biases, the study utilised the semi-structured B.C. Muthayya's Job Scale, which evaluates nurses' experiences in relation to their jobs, relationships, and personal lives.

The findings suggested that most nurses reported strong levels of satisfaction across the personal, interpersonal, and job aspects. These findings were comparable with a study conducted among Employees of Grameen Bank [18], which concluded that most of the employees were satisfied with their regular duties, overall job security, and responsibilities. Another study conducted in Czech Republic also found greater level of satisfaction among employees in organisational and supportive culture [19]. However, these findings were at odds with those of a study conducted in several regions of Ethiopia among community health workers, which revealed that only 48.6% of workers were satisfied overall [9]. This figure is lower than that of the current study.

Highly influential factor of job satisfaction is suitable work environment and better facilities, also the present study showed less boredom during working hours which lightened the work-load of nurses. By prioritising the creation of a supportive work environment, offering better facilities, and implementing strategies to reduce boredom, healthcare institutions can effectively lighten the workload of nurses. This not only enhances job satisfaction and retention rates, but also ultimately improves the quality of patient care. This finding aligns with those of A. Nurmeksela *et al.* [20], who suggested focusing on improving nursing practices by managing and organising nurses' work in a way that makes their employees feel supported, motivated, and secure. In their study among Jordanian nurses, A.H. Al-Nawafleh *et al.* [21] highlighted the fact that interpersonal relations play a vital role in retention of nurses, thereby affecting job satisfaction, which can be improved by providing supportive environment at workplace. Y.M. Yasin *et al.* [22] identified factors influencing job satisfaction, such as positive leadership styles, supervisory support, recognition of achievements, streamlined job responsibilities, a sense of ownership in work, and strong peer support. These factors were found to enhance job satisfaction and reduce staff turnover.

Nurses may feel disadvantaged if they lack technical knowledge, overload with work, do things against better judgement, feel unappreciated by patients, lack required administrative information, perception of endless workdays, sense of stagnant progress, feel undervalued in job qualification, lack independence in work, appreciation from superiors, and encouragement for suggestions and improvement. These were moderately influential factors that adversely affected the job satisfaction of nursing staff in the present study. T. Woo *et al.* [23] investigated factors that adversely affected job satisfaction, such as work overload, interrelationship with peers, and boredom at workplace. Additionally, S.A. Bhat & P. Patni [24] found that several factors negatively affected job satisfaction, including a lack of support, feeling undervalued, a lack of recognition, a poor work-life balance, and limited growth opportunities. H. Shao *et al.* [25] found that job security, low pay, unfavourable work environments, workload, and a lack of promotion or career advancement, lack of recognition were among the elements contributing to job dissatisfaction.

The study highlighted that job satisfaction among nurses is strongly influenced by years of professional experience, qualification levels, and workplace conditions. A supportive environment, adequate facilities, and reduced workload contribute significantly to higher job satisfaction and retention rates, ultimately improving patient care quality. However, factors such as work overload, lack of recognition, and limited career growth opportunities negatively affect overall job satisfaction, emphasising the need for organisational improvements.

Conclusions

The present study was conducted to assess job satisfaction among nursing staff in terms of personal, interpersonal, and job-related aspects, with the purpose of identifying factors that influence their satisfaction. By addressing these factors, any organisations can create a work environment that fosters employee contentment and enhances job satisfaction, ultimately helping the organisation achieve its objectives. The findings of this study revealed that most of the members of the nursing staff were satisfied with their job. Most nurses surveyed were more satisfied with the personal aspect compared to interpersonal and job aspects, although factors like work experience, better facilities at work, authorisation to perform individual responsibility, and pressure from the relatives' side affected the quality of work in nursing profession. The provision of adequate facilities, fair pay, and a positive work atmosphere all significantly affect the satisfaction of the members of the nursing staff with their jobs. Consequently, this enhances their performance and elevates the standard of patient care in hospitals.

Building an adaptive healthcare workforce and long-lasting improvements in patient outcomes depends on addressing these variables, highlighting how significant they are in healthcare management and policy initiatives. However, the present study was conducted in a single healthcare facility, which may have affected the generalisability of the findings to other settings or regions. The cross-sectional design also restricts the ability to establish causal relationships between job satisfaction factors and their impact on performance and patient care quality. Future research could benefit from longitudinal studies and broader sampling to address these limitations and provide a more comprehensive understanding of the issue.

Acknowledgements
None.

Funding
None.

Conflict of Interest
None.

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Оцінка задоволеності роботою медсестринського персоналу в лікарні третинного рівня в Центральному регіоні штату Гуджарат, Індія – перехресне дослідження

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Анотація. У лікарняних умовах медичні сестри є первинним персоналом, який цілодобово піклується про пацієнтів, і тому важливо, щоб вони були задоволені своєю роботою. Метою даного дослідження було оцінити задоволеність роботою серед середнього медичного персоналу з особистої, міжособистісної та професійної точок зору. Це перехресне дослідження на основі анкетування проводилося з використанням попередньо валідизованого та вільного для використання опитувальника задоволеності роботою. Загалом у дослідженні взяли участь 195 медичних сестер, з яких 192 дали згоду на участь і заповнили анкету. У дослідженні брали участь переважно жінки зі стажем роботи понад 20 років. Встановлено, що 70,31 % учасників були задоволені робочим аспектом, 84,38 % – особистим аспектом і 76,56 % – міжособистісним аспектом. Дослідження показало загальну задоволеність на рівні 80,20 %. Вищий рівень задоволеності спостерігався серед осіб з досвідом роботи понад 20 років та кваліфікацією «сестринська справа та акушерство» ($p < 0,001$). Однак між статтю та задоволеністю роботою не було значущого зв'язку ($p = 1$). Менше зручностей на робочому місці, менше повноважень для ефективного виконання своїх обов'язків, менша оплата праці, тиск з боку родичів пацієнтів – все це предиктори, що негативно впливають на рівень задоволеності роботою серед медперсоналу. Більшість опитаних медичних сестер лікарні третинного рівня у Вадодарі були задоволені своєю роботою. Надання належних умов, забезпечення справедливої компенсації та створення позитивного робочого середовища значно підвищили рівень задоволеності роботою серед медперсоналу, що в кінцевому підсумку призвело до покращення показників роботи та підвищення якості обслуговування пацієнтів у лікарнях

Ключові слова: медичний працівник; вигорання; психічне здоров'я; посадові обов'язки; особиста задоволеність

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616.314-089.23
DOI: 10.63341/ijmmr/1.2025.66

Article's History:
Received: 29.01.2025; Revised: 22.03.2025; Accepted: 27.05.2025

Improving physical performance when using REHASPLINT orthodontic appliances

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Abstract. Bite correction with the use of orthodontic appliances helps to improve blood circulation by affecting the position of the vertebral artery, normalising muscle tone, reducing pain, and restoring joint mobility. The present study was devoted to the impact of REHASPLINT orthodontic appliances on the physical performance of patients with traumatic brain injuries and traumatic cervical syndrome. The study involved a clinical experiment with 10 patients aged 25 to 38 years. The physical strength assessment included pull-ups, hanging on a crossbar, pushing a medical ball (9 kg), and squeezing a wrist expander. The testing was conducted in two stages: without and with orthodontic mouthguards. The results of the study confirm that the use of mouthguards helps to improve muscle function and overall physical performance by optimising bite biomechanics. The study showed that the use of orthodontic mouthguards during exercise contributes to a significant improvement in the physical performance of participants. When performing pull-ups, the average result increased from 7.3 to 10.7 pull-ups, which indicates an increase in upper body strength by 46.58%. The time spent holding the bar increased from 54.3 to 76.4 seconds, which demonstrates an improvement in endurance and muscle control by 40.7%. When pushing a 9 kg medicine ball, the average distance increased from 4.63 to 5.45 metres, indicating an increase in strength and coordination by 17.73%. Compression of the wrist expander showed an increase in the average result from 128.9 to 152.1 compressions in 60 seconds, increasing arm strength and endurance by 18.04%. The impact of orthodontic mouthguards is most noticeable in exercises requiring coordination and stability, such as holding on to the bar and pushing a ball. The data obtained emphasise the effectiveness of orthodontic mouthguards in the rehabilitation of patients with traumatic brain injury and traumatic cervical syndrome. The use of mouthguards can be recommended to improve the physical capabilities of military personnel and patients during rehabilitation

Keywords: traumatic brain injury; traumatic cervical syndrome; vertebral artery; cerebral blood flow; orthodontic mouthguards; physical performance; physical rehabilitation

Introduction

Despite significant advances in weaponry, the development of innovative methods of warfare, and the growing role of unmanned aerial vehicles, it cannot be argued that a reduction in the number of wounded soldiers automatically leads to a reduction in the incidence of traumatic brain injuries. In fact, these injuries remain one of the most

Suggest Citation:
Tymchenko A, Tymchenko S. Improving physical performance when using REHASPLINT orthodontic appliances. Int J Med Med Res. 2025;11(1):66–77. DOI: 10.63341/ijmmr/1.2025.66

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common problems among soldiers in today's military conflicts. Modern protective equipment reduces the likelihood of penetrating wounds but increases the impact of the shock wave, making it one of the leading causes of traumatic brain injury. Blast injuries are divided into several types: primary (shock wave), secondary (fragments of debris), tertiary (body acceleration), and quaternary (high temperatures and toxic gases). Tertiary trauma, which results from the acceleration of the body after an explosion, is one of the most common causes of traumatic brain injury in combat. Due to the high force of the explosions, many soldiers are either killed or seriously injured, including those in a vegetative state. Scientists L.-Z. Kong *et al*. [1] argue that the symptoms of mild traumatic brain injuries are often nonspecific and may not be noticed by doctors. Thus, despite the improvement of protective equipment and the development of technology, traumatic brain injuries remain a significant problem that requires a comprehensive approach to prevention, diagnosis, and treatment.

L. Sushchenko *et al*. [2] note that military personnel suffering from traumatic brain injuries often face insufficient adaptation of rehabilitation programmes to their specific needs, which highlights the need for further research and development of specialised therapeutic approaches. The severity of the consequences of traumatic brain injury directly depends on the type of injury and the timeliness of medical care. These consequences can range from full recovery to severe disabling disorders or death, depending on the mechanism of injury and the speed of response to treatment. Among the most common complications of traumatic brain injuries are motor disorders, spasticity, and cognitive impairment, which seriously limit the patient's ability to learn, work, and adapt socially. The effectiveness of rehabilitation largely depends on the complexity of approaches that include physical exercises, cognitive training, vestibular rehabilitation, kinesitherapy, and aerobic exercise. These methods stimulate neuroplasticity and help restore functional capabilities.

Mild forms of traumatic brain injury tend to remain hidden, making it difficult to diagnose and treat effectively. Methods of restoring intracranial injuries are still under development, and in military settings, the treatment of traumatic brain injuries is focused mainly on neuropsychiatric symptoms rather than full recovery. Primarily, pharmacological and physical therapy, as well as rehabilitation, including cognitive and behavioural therapy, are used to restore cognitive and social functions. Despite advances in neuroregeneration, serious neurological consequences, such as long-term cognitive impairment and chronic pain, require a long course of rehabilitation and social adaptation to successfully reintegrate injured servicemen and women into professional and social life. Researchers N.E. Carlozzi *et al*. [3] argue that recovery from traumatic brain injury is often complicated by concomitant mental disorders, such as post-traumatic stress disorder and depression, as well as bodily injuries. In such cases, servicemen and women often require long-term inpatient treatment, followed by specialised rehabilitation and support after discharge.

Cranial injuries resulting from traumatic brain injury can contribute to the development of various types of malocclusions. According to C. Kariya *et al*. [4], cranial injury is the main factor causing malocclusion and cranial compensation that develops after temporomandibular joint disorder. Malocclusions can cause pathological occlusal relationships, playing a vital role in the development of temporomandibular joint dysfunction. These abnormalities cause proprioceptive changes that reflexively lead to tension and spasm of the masticatory muscles, which contribute to their dysfunction. Y. Rybert *et al*. [5] argue that patients with temporomandibular joint disorders in the setting of orthodontics require a thorough examination and the use of modern methods of diagnosis and treatment aimed at normalising the musculoarticular complex and correcting the bite.

The relevance of studying the possibilities of improving the physical performance of servicemen with traumatic brain injuries using REHASPLINT orthodontic appliances is due to the high prevalence of malocclusion in servicemen with traumatic brain injuries and their significant impact on overall health, including the function of muscles, joints and the nervous system. Despite the potential benefits of using orthodontic mouth guards, there is a lack of research directly examining their impact on physical performance during physical activity in servicemen and women with traumatic brain injury. Most of the available studies focus on the general aspects of treatment of occlusal disorders, without a specific focus on the military population and its specific needs. In addition, insufficient attention has been paid to the long-term effects of RehaSplint on the recovery of physical performance, which is important for military personnel who need rapid rehabilitation. There is also a need for a more detailed study of the mechanisms of action of these devices on muscles and joints, as well as their impact on overall physical fitness. Addressing these gaps can significantly improve approaches to the treatment and rehabilitation of servicemen and women with traumatic brain injuries, providing more effective methods of restoring their physical capabilities. In this regard, the aim of this study was to investigate the effect of orthodontic mouthguards on the physical performance of patients during physical activity.

Literature Review

The traumatic cervical syndrome that occurs after a traumatic brain injury includes biological and neurological consequences that manifest as neck pain, headaches, and impaired nervous, mental, otological, and visual functions. Scientists N. Tanaka *et al*. [6] state that in 20-40% of patients, pain can persist for years, and chronic forms can cause arthritis, nerve root irritation, and vestibular disorders. According to R. Sillevis & A. Hansen [7], cervicogenic headache occurs due to biomechanical dysfunction of the cervical spine, which causes nerve compression and muscle

tension. This condition is accompanied by pain and limited neck mobility. Treatment involves correcting the position of the joints and restoring normal muscle tone. Cervicogenic dizziness caused by functional problems of the neck is manifested by pain, nausea, visual and hearing impairments, as well as temporomandibular joint problems and psychological disorders. In addition, problems with the temporomandibular joint and psychological disorders may occur. Impaired motor activity of the cervical muscles is manifested in a decrease in strength, endurance and stability, as well as in changes in muscle behaviour, including a decrease in the activity of deep postural muscles and a delay in the onset of muscle reactions.

The study by E.A. Katz *et al.* [8], which involved 7 patients diagnosed with cervical lordosis, demonstrated that the loss of cervical lordosis may play a role in the development of changes associated with the hemodynamics of the circle of Willis and cerebral arteries, as well as in reducing blood flow in the brain. Loss of cervical lordosis is a condition characterised by a decrease in the natural curvature of the cervical spine. The main causes of this condition are poor posture, trauma (e.g., whiplash), degenerative disc disease, and spondylolisthesis. Symptoms may include muscle tension, discomfort in the neck and arms, and possible neurological disorders due to nerve compression. Loss of lordosis disrupts the biomechanics of the spine, increasing the load on muscles and joints, which can lead to chronic pain and serious complications if left untreated. The results of the study showed that the correction of cervical lordosis loss was associated with an increase in cerebral artery parameters, indicating an immediate increase in blood flow in the brain.

Systematic reviews by N. Bowler *et al.* [9] confirm the high effectiveness of cervical spine manipulations in reducing neck pain and headaches. However, these procedures are associated with the risk of serious neurovascular complications, such as transient ischaemic attack, stroke, or even death, which is most often caused by dissection of the vertebral artery and, less often, the internal carotid artery. According to H. Kranenburg *et al.* [10], understanding the mechanical factors, including the characteristics of blood flow in the cervical arteries in different positions and movements of the cervical spine, can help reduce the risk of ischaemic disorders, such as stroke, after mobilisation or manipulation procedures on the cervical spine. In conformity with M. Waheed *et al.* [11], modern technologies facilitate operations with minimal incisions, which reduces the risk of complications and speeds up the recovery process. Spine surgery includes methods of treating pathologies of the cervical and lumbar spine aimed at improving the condition of patients. The main procedures include laminectomy to normalise function and reduce pain, decompression to relieve pressure on nerve roots, kyphoplasty and vertebroplasty to restore vertebral height in compression fractures, spinal fusion to stabilise vertebrae with titanium screws and plates, and endoscopic surgery to avoid tissue damage and speed up recovery.

M. Renke *et al.* [12] argue that cerebral blood flow is a key indicator of the functional state of the brain, as it provides oxygen and nutrients to the brain tissue. Prolonged blood flow disorders caused by vascular occlusion or stenosis can lead to irreversible damage to brain tissue, such as the formation of an ischaemic core. The results of studies by S. Hung *et al.* [13] showed that hypoperfused tissue around the ischaemic core remains potentially viable. The fate of this tissue depends on the level of perfusion: if the blood supply improves, the tissue can recover; if not, the ischaemic core can grow, but the degree of its growth varies.

O. Maitas *et al.* [14] focus on the importance of the vertebral artery in the blood supply to the brain. It passes through the canals in the transverse processes of the cervical vertebrae and, entering the skull through the large occipital foramen, connects with the artery of the opposite side, forming the basilar artery. The vertebral artery is divided into four segments (V1-V4), each of which has specific anatomy and treatment. Segment V1 (from the subclavian artery to the transverse foramen of C5 or C6) is easily treated percutaneously if it is straight. Segment V2 (from C2 to C6) passes through the bone canal, and its short distance to the subclavian artery makes treatment more accessible. Segment V3 (from C2 to the dura) is tortuous, which complicates intervention, requiring the avoidance of balloon stents and the use of short self-expanding stents. Segment V4, the intracranial segment, connects the vertebral arteries to the basilar artery and supplies blood to the spinal cord. Thus, the vertebral arteries ascend, passing through the transverse foramen of the cervical vertebrae and merging to form a single basilar artery that continues to the circle of Willis and the cerebral arteries. Given the close anatomical connection between the cervical spine, vertebral arteries and the cerebral vasculature, E.A. Katz *et al.* [8] suggested that improvement of cervical hypolordosis contributes to an increase in collateral hemodynamics of the cerebral arteries and improved blood flow.

Therefore, traumatic cervical syndrome requires a comprehensive approach to diagnosis and treatment. As a result of traumatic brain injuries, traumatic neck syndrome can lead to serious biological and neurological consequences that significantly affect the quality of life of patients. Scientific studies emphasise the importance of timely diagnosis and correction of traumatic cervical syndrome and related conditions to prevent serious complications such as chronic pain and neurological disorders. Manipulations on the cervical spine can be effective, but they should be accompanied by careful medical monitoring to reduce the risk of complications. In general, a comprehensive approach to the treatment of traumatic cervical syndrome and related conditions is necessary to improve treatment outcomes and quality of life. Further research in this area is needed to improve diagnostic and treatment methods, which will reduce the risk of complications and improve the prognosis for patients with traumatic cervical spine injuries.

Materials and Methods

The study was based on the ideas of A.T. Still [15], who viewed the body as a single, integrated system where structure and function are interconnected. Still viewed malocclusion as not just a local problem but part of a complex interaction between the body structure and its functions. He emphasised that an imbalance in the bite can cause tension in the jaws, neck, and even spine, affecting overall health, including the function of internal organs. Steele believed that such disorders should be corrected not only by mechanical means but also by activating the body's natural self-healing mechanisms. He emphasised the importance of manual therapy in improving blood circulation, relieving muscle tension and restoring the harmonious functioning of the nervous system.

The clinical trial involved ten men aged 25 to 38 who were treated at the Kyiv Regional Centre for Mental Health with contusions between March 2024 and January 2025. Patients were monitored during the rehabilitation period. They sustained closed traumatic brain injuries, encompassing cerebral contusions and diffuse axonal damage, predominantly due to blast trauma. The ICD diagnostic for individuals with traumatic cervical syndrome is S13.4 (sprain and strain of the cervical spine) and G44.86 (cervicogenic headache), indicating cervical spine trauma with accompanying neurological symptoms. All patients had a diagnosis on admission that included a range of disorders, such as traumatic brain injury and traumatic cervical syndrome.

Participants with a complicated psychiatric or somatic history were excluded from the study to ensure homogeneity of the sample and minimise the impact of external factors on the results. This approach allowed focusing on the key objectives of the study and exclude the possible impact of comorbidities that could distort the interpretation of the data. A complicated psychiatric history was defined as cases of severe mental disorders, such as schizophrenia, bipolar disorder, or severe depression, which required active medication. The presence of such conditions could have a significant impact on the perception of therapy, patient compliance, and physiological parameters, which would create methodological difficulties.

Somatic anamnesis was defined as diseases that could significantly affect the general condition of the body and the interpretation of the study results. Such conditions included severe chronic diseases of the cardiovascular system, respiratory system, kidneys, and liver, as well as malignant tumours and autoimmune disorders. This selection criterion was aimed at excluding the influence of factors that could complicate the analysis of the effectiveness of the therapy. This approach ensured more accurate and reliable data, which is especially important for the further development of recommendations for the use of treatment methods.

The study used a comprehensive approach to assessing the patients' condition. The first stage involved collecting a detailed medical history, which allowed getting a complete picture of the participants' health status, medical history, past injuries, current complaints and individual characteristics of the body. This stage was important for identifying concomitant factors that could affect the results of therapy. A physical examination was conducted, encompassing a general assessment, evaluation of the musculoskeletal system, neurological status, and function of the maxillofacial area, during which post-traumatic malocclusion was identified in several patients, despite the absence of premorbid bite abnormalities, indicating secondary functional lesions resulting from the injury. This stage allowed assessing the physical condition of the patients and determine the initial indicators for further monitoring. Then, the patients were trained in the use of orthodontic mouthguards. Patients were provided with detailed instructions on how to wear and care for the devices correctly to ensure their maximum effectiveness. This approach not only increased the compliance of the participants but also helped to eliminate possible errors in the application. The complexity of the activities ensured a comprehensive approach to the study, which contributed to obtaining reliable and clinically relevant data.

Orthodontic appliances provided by the German company Bausch GmbH in cooperation with its Ukrainian partners Premier-Dental were used for orthodontic therapy. This assistance was organised as part of a charity initiative aimed at supporting medical institutions in Ukraine. In particular, the devices were handed over to the Kyiv Regional Mental Health Centre located in Vorzel. Physical strength testing was carried out twice with an interval of one week, during which individuals utilised orthodontic mouthguards with daily therapeutic exercises. The exercises consisted of neuromuscular training, including deep neck flexor movements, scapular stabilisation drills, and grip-strengthening activities with hand grippers or putty. This regimen enabled an assessment of the synergistic impact of various therapies on physical performance. At the first stage of the study, testing was carried out without the use of mouthguards, which made it possible to establish baseline physical strength indicators. The second stage included the use of orthodontic mouthguards, which allowed comparing the results and identify changes associated with their use.

The testing involved various techniques aimed at assessing strength and endurance. These exercises provided a comprehensive approach to assessing the participants' physical strength. Comparison of the results of both stages of the study allowed better understanding the impact of orthodontic mouthguards on physical activity. The following methods of physical strength assessment were used in the study are:

1. Pull-ups. The maximum number of pull-ups that patients could perform in one approach was assessed. This test allows assessing the strength of the upper body, especially the muscles of the back and arms, as well as overall physical fitness.

2. Hanging on the bar. Patients were held on the bar for as long as possible, which allowed for assessing the grip strength and endurance of the upper body muscles. The results were recorded in seconds and served as an indicator of overall physical endurance.

3. Pushing a medicine ball (9 kg). In this test, patients pushed a medical ball weighing 9 kg for a maximum distance. It helps to assess both upper body strength and power, as well as coordination of movements.

4. Compression of the wrist expander. Patients used a wrist expander for 60 seconds to assess the endurance of the arm muscles. This test is an effective way to measure grip strength and overall functional ability in the upper extremities.

The testing was carried out under the careful clinical supervision of a neurologist and two assistants, which ensured a high level of safety and professionalism in the study. The neurologist monitored the participants' condition, controlling their physical response to the exercise and providing the necessary medical care in case of any unforeseen situations. The assistants actively helped in organising the testing, including preparing the equipment and instructing the participants before the start of the exercises. They also recorded the results and ensured compliance with test standards. This multidisciplinary interaction helped create a comfortable and safe environment for the participants, which was particularly important for obtaining reliable study results.

The study was conducted in accordance with Commission Directive No. 2005/28/EC [16] and the Helsinki Declaration [17]. All clinical trial participants provided written consent to participate in the study. They were familiarised with the objectives, methods, and procedures of the study. Participants were informed about how the information they provided would be used, that there were no risks involved, and that their anonymity would be ensured. Permission was obtained from the Ethics Committee of the Kyiv Regional Centre for Mental Health that the study complied with ethical standards and did not harm patients.

The results of each stage of testing were recorded in spreadsheets for further analysis. After completion of all tests, a comparative analysis of the data was carried out to identify changes in physical strength indicators. The study employed a paired t-test for matched samples and an F-test to assess variation between conditions, to ascertain the statistical significance of alterations in physical performance. These methodologies were chosen because of the within-subjects design, facilitating accurate assessment of individual changes pre- and post-intervention. The data were analysed and processed using statistical methods and Microsoft Excel and Statistica 6.0 software with significance established at $p < 0.05$. This method facilitated the evaluation of both average performance disparities and the consistency of repeated measures.

Results and Discussion

Traumatic brain injuries remain one of the most common injuries sustained by military personnel during combat, training, or accidents. These injuries can be closed (e.g., concussion, diffuse axonal injury) or open (gunshot and perforation wounds). Blast injuries resulting from the blast wave, as well as combined injuries involving multiple factors of injury, are also common outcomes. Traumatic brain injuries can cause severe cognitive and motor disorders, as well as complications such as infections and epilepsy, which significantly impair the quality of life of victims.

Traumatic brain injury can cause many complications, including malocclusion, temporomandibular joint disorders, traumatic cervical syndrome, and cervicogenic headaches. These disorders can manifest themselves not only in the form of neck pain and headaches but also in movement disorders, psycho-emotional and nervous dysfunction, as well as deterioration of the neck and jaw muscles. Comprehensive treatment of such consequences includes manual therapy, physical exercises, use of orthodontic appliances, and, in some cases, surgical interventions aimed at restoring the structure of the cervical spine, normalising muscle tone, and improving joint mobility. An important aspect of rehabilitation is strengthening the neck muscles, which helps to reduce pain, improve blood circulation, and accelerate recovery from injuries.

One of the most promising methods of rehabilitation for servicemen and women who have suffered from injuries and stress is the use of orthodontic and boxing mouthguards to improve cerebral circulation [18]. This method affects the temporomandibular joint, chewing, and neck muscles, which helps to improve blood flow by correcting the position of the jaw, relaxing muscles and reducing vascular compression. The mouthguards also help to normalise posture by reducing pressure on the cervical arteries and improving cerebral blood flow. The use of orthodontic mouthguards helps to change the occlusion, which in turn affects the position of the cervical vertebrae. This leads to a decrease in muscle tension around the vessels of the neck and a change in the angle of entry of the artery into the vertebra. As a result, the trajectory of the cervical artery is levelled, which significantly improves blood circulation in the carotid basin, one of the main sources of blood supply to the brain [19]. In addition, they stimulate nerve endings, which has a positive effect on cognitive function and reduces the frequency of headaches.

While working with patients suffering from malocclusion, it was noticed that such patients often have other complaints associated with cervical spine dysfunction, such as headaches, back pain, dizziness, visual impairment and memory loss. Additional examinations have shown that bite correction has a positive effect not only on the condition of the dentition but also on the general condition of the musculoskeletal system, in particular on the position of the cervical vertebrae. Given the ideas of A.T. Still [15], the founder of osteopathic treatment, as well as ortho-posthodontics and numerous cases of improved health in orthodontic patients, it was suggested that a change in bite position could affect the position of the vertebral artery and improve blood supply. This assumption became the ideological basis for improving blood supply to the brain with the help of orthodontic and boxing mouthguards.

The vertebral artery is the main vessel that supplies blood to the back of the brain, including the cerebellum, brain stem and occipital lobe. The vertebral arteries rise

upwards, passing through the transverse foramen of the cervical vertebrae and merging to form a single basilar artery, which continues to the circle of Willis and the cerebral arteries. Dysfunctions of the vertebral artery include various pathological conditions, such as intracranial dissection, in which damage to the artery wall leads to impaired blood flow and the risk of stroke, stenosis caused by atherosclerosis, degenerative disc disease or congenital anomalies, and vertebrobasilar insufficiency associated with insufficient blood supply to the posterior regions of the brain. Extravascular compression of the vessel by osteophytes or muscle spasms, fibromuscular dysplasia – congenital narrowing of the artery, and thrombosis that occurs in the setting of trauma, dissection, or atherosclerotic changes are also common. Doppler ultrasound, magnetic resonance imaging, computed tomography angiography, and classical angiography are used for the diagnosis of vertebral artery pathologies, including stenosis, dissection, thrombosis, and other vascular complications associated with traumatic cervical injuries.

The vertebral artery is crucial for maintaining the normal functioning of the brain, and any damage, such as narrowing or compression, can lead to serious consequences, including stroke. Correction of the position of the vertebral artery includes various techniques aimed at improving blood circulation and relieving tension in the neck. The use of manual techniques, such as mobilisation of the cervical spine, posture correction and work with muscle tone, helps to eliminate vascular compression and restore normal blood flow.

Dysfunction of the vertebral artery caused by its stenosis can significantly disrupt the blood supply to the posterior parts of the brain, leading to the development of neurological symptoms, including dizziness, coordination disorders and transient ischaemic attacks. The progression of stenosis increases the risk of ischaemic stroke, especially if there is insufficient compensation for blood flow through collateral pathways. Treatment includes drug therapy aimed at improving blood flow and controlling risk factors, and in more severe cases, endovascular or surgical correction methods to restore the artery lumen and prevent ischaemic complications. Vertebral artery stenosis and intracranial dissection differ in nature, mechanism of development and clinical manifestations. Stenosis is a chronic narrowing of the artery caused by atherosclerosis, external compression, congenital anomalies or inflammation, which leads to a gradual decrease in blood flow. Vertebral artery dissection is acute damage to the vessel wall accompanied by the formation of an intramural haematoma or intimal flap, which sharply disrupts blood flow. Stenosis develops as a result of chronic processes, such as osteochondrosis, while vertebral artery dissection occurs suddenly, often after trauma or due to weakness of the vessel wall. Clinically, stenosis is manifested by dizziness and ischaemic episodes, and vertebral artery dissection is manifested by acute neurological symptoms or stroke. Treatment of stenosis is aimed at improving blood flow and includes stenting in severe cases, while in the case of vertebral artery dissection, anticoagulants and thrombolytics are used to prevent complications. Given the close anatomical relationship between the cervical spine, vertebral arteries and the cerebral vasculature, it can be assumed that improvement of cervical hypolordosis contributes to an increase in collateral hemodynamics of the cerebral arteries and improved blood flow.

Recent research has investigated the possible impact of orthodontic devices, particularly mouthguards, on cerebral circulation. Similarly, an observational study by D.P. Garner [20] examined the effect of the mandible's physiological rest position on cerebral blood flow and physical balance. The study observed changes in cerebral blood flow during activities such as clenching, tooth tapping, and mandibular rest position. The results highlighted significant variations in cerebral blood flow during clenching compared to other tasks, suggesting a potential link between mandibular positioning and cerebral circulation.

The results of the study showed that the use of orthodontic mouthguards during exercise demonstrated an increase in physical performance. Participants performed pull-ups, deadlifts, wrist extensions, and throws of 9 kg gymnastic balls. Table 1 shows the participants' achievements in pull-ups with and without orthodontic mouthguards. In the first test, participants were able to perform an average of 7.3 pull-ups, with maximum results ranging from 5 to 12 pull-ups. This demonstrates the diversity of fitness levels among the participants. In the second test, where orthodontic mouthguards were used, the average result was 10.7 pull-ups, with a maximum of 15 pull-ups, confirming the high efficiency of the mouthguards in improving performance. The average difference between the two tests was +3.4 pull-ups (46.58%), which highlights the positive impact of orthodontic mouthguards on the upper part of the body strength development.

Table 1. Pull-up results of study participants without and with the use of orthodontic mouthguards

Testing method	Study participants										Average value (times)	Average growth/ decrease, %
Pull-ups (times)	1	2	3	4	5	6	7	8	9	10		
Without the use of orthodontic mouthguards	5	6	7	8	12	10	6	6	7	6	7.3	
Using orthodontic mouthguards	10	8	10	11	15	11	12	10	10	10	10.7	46.58
Difference +/–	+5	+2	+3	+3	+3	+1	+6	+4	+3	+4	+3.4	

Source: compiled by the authors

Table 2 shows the participants' achievements in hanging from the bar without and with orthodontic mouthguards. In the first test, participants averaged 54.3 seconds on the bar, with maximum results ranging from 50 to 60 seconds. In the second test, where the orthodontic mouthguards were used, the average time increased to 76.4 seconds, with maximum values reaching 85 seconds. This confirms the effectiveness of using the mouthguards to improve performance and increase the time spent on the bar. The average difference between the two tests was +22.1 seconds (40.7%).

Table 2. The results of hanging on the bar without and with orthodontic mouthguards

Testing method	Study participants										Average value (seconds)	Average growth/ decrease, %
Hanging on the crossbar (seconds)	1	2	3	4	5	6	7	8	9	10		
Without the use of orthodontic mouthguards	52	52	52	60	55	60	55	52	55	50	54.3	40.7
Using orthodontic mouthguards	62	70	80	75	82	85	70	80	85	75	76.4	
Difference +/-	+10	+18	+28	+15	+27	+25	+15	+28	+30	+25	+22.1	

Source: compiled by the authors

Table 3 shows the results of the 9 kg medical ball pushing test obtained by the participants both without and with orthodontic mouthguards. In the first test, the participants were able to push the ball an average of 4.63 metres, with maximum results ranging from 4 to 5.5 metres. In the second test, where the orthodontic mouthguards were used, the average increased to 5.45 metres, with maximum results reaching 6.2 metres. This shows a significant improvement in the results due to the use of the mouthguards, which confirms their effectiveness in improving strength and coordination. The average difference between the two tests was +0.82 metres (17.73%).

Table 3. Results of pushing a medical ball 9 kg/m without and with orthodontic mouthguards

Testing method	Study participants										Average value (meters)	Average growth/ decrease, %
Medicine ball push 9 kg/m	1	2	3	4	5	6	7	8	9	10		
Without the use of orthodontic mouthguards	4.2	4.9	4	5.5	5	4.5	4.5	4.2	5	4.5	4.63	17.73
Using orthodontic mouthguards	4.8	5.5	4.5	6	5.5	6	5	6	6.2	5	5.45	
Difference +/-	+0.6	+0.6	+0.5	+0.5	+0.5	+1.5	+0.5	+1.8	+1.2	+0.5	0.82	

Source: compiled by the authors

Table 4 shows the participants' wrist extensor grip performance without and with orthodontic mouthguards. In the first test, the participants were able to perform an average of 128.9 compressions in 60 seconds, with maximum results ranging from 84 to 164 compressions. In the second test, where the Orthodontic mouthguards were used, the average increased to 152.1 compressions, with maximum results reaching 197 compressions. This confirms the effectiveness of the mouthguards in improving performance, which also reflects the positive impact on upper limb strength and endurance. The average difference between the two tests was +23.2 compressions (18.04%), which highlights the significant improvement in performance with orthodontic mouthguards.

Table 4. Results of wrist extensor compression without and with orthodontic mouthguards

Testing method	Study participants										Average value (times)	Average growth/ decrease, %
Wrist expander squeeze in 60 seconds (times)	1	2	3	4	5	6	7	8	9	10		
Without the use of orthodontic mouthguards	84	148	150	150	131	164	90	150	132	90	128.9	18.04
Using orthodontic mouthguards	107	170	162	185	151	197	110	192	141	106	152.1	
Difference +/-	+23	+22	+12	+35	+20	+33	+20	+42	+9	+16	23.2	

Source: compiled by the authors

The paired t-test results indicated statistically significant enhancements in physical performance across all four assessments, with pull-up performance rising by 46.58% ($t = 7.52$, $p < 0.001$), bar hang improving by 40.7% ($t = 10.49$, $p < 0.001$), medicine ball push exhibiting a 17.73% increase ($t = 7.08$, $p < 0.001$), and a 23.2% increase in the average number of compressions ($t = 6.99$, $p < 0.001$). Moreover, the F-test for variance revealed no significant variations in performance variability between circumstances for any of the tasks. In the pull-up test, the F-ratio was 0.71 ($p = 0.31$); in the hanging on the bar test, the F-ratio was 0.87 ($p = 0.44$); in the medicine ball push, the F-ratio was 1.17 ($p = 0.66$); and the compressions F-test indicated no significant difference in variability between the two conditions ($F = 1.40$, $p = 0.31$).

The statistical analysis indicates that the use of orthodontic mouthguards resulted in substantial enhancements in physical performance across all evaluated activities. The paired t-tests revealed statistically significant enhancements in pull-up performance, bar hanging, medicine ball push, and wrist expander compression, with improvements between 17.73% and 46.58%. However, the F-tests showed that these improvements did not cause more differences in how consistent the performance was, as there were no significant changes in performance consistency between the groups before and after the intervention. This indicates that the orthodontic mouthguards significantly improved physical performance while ensuring uniform outcomes across subjects.

Thus, the study used various methods to assess the strength and endurance of the participants. These tests provided a comprehensive approach to analysing physical fitness, allowing identifying the impact of orthodontic mouthguards on performance. The results showed that the use of orthotics during exercise led to an increase in physical performance by an average of 30%. In particular, the pull-up test showed a significant improvement, with the average result increasing from 7.3 to 10.7 pull-ups. Similarly, the time spent holding onto the bar increased from 54.3 to 76.4 seconds, confirming the effectiveness of the mouthguard in improving endurance. In addition, the results of the medicine ball push showed an increase in distance from 4.63 to 5.45 metres, indicating an increase in strength and coordination. The wrist expander squeeze also showed positive changes, with the average number of squeezes increasing from 128.9 to 152.1 per 60 seconds. These data underline the significant improvement in results when using orthodontic mouthguards in all tests. Thus, the results of the study confirm the effectiveness of orthodontic mouthguards as a means of increasing physical activity and overall functional capacity of participants.

The cervical spine is the most vulnerable to external negative influences. Mechanical stress on the cervical spine can cause biomechanical disorders that manifest as vertebral artery syndrome, which includes cerebral, vascular and autonomic symptoms. The results of a study by T. Sakaguchi *et al.* [21] showed that rehabilitation of the cervical spine after injury plays a key role in restoring physical function, improving the ability to perform daily tasks and improving quality of life. The multifaceted approach includes restoring mobility, strengthening muscles and improving spinal balance, which is often overlooked. Strengthening the deep neck and trapezius muscles is particularly important, as their weakness is associated with axial pain. Rehabilitation should begin with light exercises, gradually moving on to isometric and strength exercises, which promote muscle hypertrophy, improve blood circulation, and reduce swelling and pain sensitivity. The cervical muscles play a key role in supporting and orientating the head, as well as providing breathing, phonation and swallowing functions, providing important physical support to the cervical spine. Their dysfunction can occur as a result of injuries, inflammation and nervous disorders, which negatively affects muscle function and increases pain. For a successful recovery, it is recommended to start rehabilitation exercises as early as possible, avoiding increased pain, and gradually restoring muscle function.

A study involving 24 students aged 18 to 23 years showed that the use of physiotherapy in patients with functional compression syndrome of the vertebral arteries helps to reduce the clinical manifestations of the disease, restore proper spinal biomechanics and improve blood flow in the vertebral arteries [22]. This is in line with the results of the study, which showed that the use of physiotherapy methods in the treatment of functional compression syndrome of the vertebral arteries is highly effective, contributing to the restoration of spinal biomechanics and improving blood supply to the brain. The study results also confirm the additional benefits of using orthodontic mouthguards in the rehabilitation of patients with traumatic brain injuries and traumatic cervical syndrome.

The results of the study confirmed that the use of mouth guards that change the position of the jaw has a positive effect on physical performance due to biomechanical and neuromuscular effects. REHASPLINT orthodontic mouthguards not only correct the bite but also improve physical performance. It has been shown that jaw repositioning through the use of mouthguards has a positive effect on spinal alignment and muscle function. This was reflected in an increase in strength (pull-ups increased by 46.58%), endurance (holding on the bar increased by 40.7%), coordination and power (ball pushing improved by 17.73%). The results of the study are consistent with the findings of D.L. Golem & S.M. Arent [23], who note the positive effect of bite correction on posture and proprioception, which in turn improves sports and physical performance. Thus, the results of the study confirm the effectiveness of Orthodontic mouthguards as a means of improving the biomechanics of movement, strength and endurance, which is especially important for the rehabilitation of patients with traumatic brain injuries and traumatic cervical syndrome.

The results of the study confirmed that there is a link between the masticatory and musculoskeletal systems, where jaw closure has a positive effect on physical performance through the potentiation of simultaneous activation. The amount of jaw compression is critical for the formation of neuromuscular effects that provide a powerful occlusion. The use of bite alignment mouth guards improves the symmetry of the masticatory muscles and the even distribution of occlusal loads. The realignment of the jaw position and the vertical size of the occlusion helps to improve neuromuscular balance. Thus, the correct use of orthodontic mouthguards can significantly enhance the effect of potentiating simultaneous activation and improve overall physical performance. While some studies have attributed the ergogenic effects of simultaneous activation potentiation solely to jaw clenching, others have demonstrated an increase in these effects when using oral devices such as custom mouthguards [24]. A study involving

eight elite swimmers of the Spanish national team showed that the use of custom mouth guards for bite alignment has an ergogenic effect, improving jump and pull performance [25]. Although there was no significant effect on the starting reaction time and the 15-metre freestyle distance, such mouthguards can be useful for increasing athletic potential in powerful movements and the overall quality of the training process. However, in a study involving 12 professional male handball players, there was no apparent effect of improved motor performance or increased muscle activity when wearing orthodontic mouthguards [26]. However, there was a more balanced activity of the cervical and back muscles in dynamic conditions.

The results of the study by A. Yasuda *et al.* [27], conducted with the participation of thirteen athletes with cerebral palsy (men, n = 12; mean age 27.3 ± 8.96 years) and ten healthy men from the control group (mean age 28.5 ± 1.35 years), showed that the use of mouth guards can change the nature of masticatory muscle activity in athletes with cerebral palsy and help improve balance during static exercises. Another study involving 23 professional basketball players (mean age 25.8 ± 8.6 years) demonstrated that wearing individual orthodontic mouthguards for eight weeks affected balancing, although no significant changes in body alignment were found [28]. However, a more detailed univariate analysis revealed improvements in pelvic torsion and kyphotic angle after both acute and re-treatment. Pelvic torsion, which characterises the anteroposterior displacement of the right and left parts of the pelvis, is an important indicator, as its deviation from the normal range (0°) may indicate potential abnormalities in the musculoskeletal system. The study showed a significant reduction in the pelvic torsion angle of the participants, indicating an improvement in pelvic balance. These results emphasise the potential role of mouthguards in correcting postural parameters and strengthening the biomechanical stability of athletes. The study's results indicate the need to determine further the effects of mouthguards on functional muscle activity and balance in different groups of athletes and under various conditions.

The results of the study confirm the effectiveness of REHASPLINT orthodontic mouthguards in improving the functional state of the jaw system and its interaction with the musculoskeletal system. The use of occlusion-correcting mouthguards can help improve blood circulation and neuromuscular activity, which in general affects the overall physical condition. The results of the study open up significant opportunities for rehabilitation after traumatic brain injuries and strokes, as well as for the treatment of speech and motor disorders resulting from contusions and accu barotrauma. The use of this method can significantly speed up the recovery process, which helps reduce rehabilitation costs and potentially reduces the costs of insurance companies.

Conclusions

The study confirmed that the use of REHASPLINT orthodontic mouthguards contributes to a significant improvement in the physical performance of the participants. As a result of the use of the orthodontic mouthguards, an increase in strength, endurance, and coordination of movements was observed, which was manifested in the growth of such indicators as pull-ups, holding on the crossbar, pushing a medicine ball and squeezing a wrist expander.

It was found that the mouthguards have a positive effect on neuromuscular balance, ensuring symmetry of muscle function and optimising biomechanics. This is associated with improved jaw position and reduced load on the temporomandibular joint, which has a positive effect on the overall condition of the musculoskeletal system. The results confirm that the correction of occlusion with mouth guards improves physical performance and stabilises the spine and activating the neck muscles.

The study found that the use of orthodontic mouthguards during exercise contributes to a significant improvement in physical performance. When performing pull-ups, the average result increased by 46.58% (from 7.3 to 10.7 pull-ups), which indicates an increase in upper body strength. The time spent holding the bar increased by 40.7% (from 54.3 to 76.4 seconds), demonstrating improved endurance and muscle control. When pushing a 9 kg medicine ball, the average distance increased by 17.73% (from 4.63 to 5.45 metres), indicating an increase in strength and coordination. The wrist expander compression showed an increase of 18.04% (from 128.9 to 152.1 compression in 60 seconds), reflecting an improvement in upper limb strength and endurance. The greatest effect of the use of mouthguards is observed in exercises that require coordination and stability, such as holding on to the bar and pushing the ball.

The results confirm that REHASPLINT orthodontic mouthguards improve muscle function and overall physical performance by optimising bite biomechanics. The effectiveness of the mouthguards in the rehabilitation of patients with traumatic brain injuries and traumatic cervical syndrome has been confirmed, which allows recommending them to improve the physical capabilities of military personnel and patients during rehabilitation. The effectiveness of REHASPLINT mouthguards opens up prospects for their implementation both in sports practice to improve performance and in the rehabilitation of patients with traumatic brain injury and traumatic cervical syndrome. The findings emphasise the need for further research to better understand the mechanisms of action of the mouthguard and its potential in clinical practice.

Acknowledgements

None.

Funding

None.

Conflict of Interest

None.

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Покращення фізичних показників при використанні ортодонтичних апаратів REHASPLINT

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Анотація. Корекція прикусу з використанням ортодонтичних апаратів сприяє покращенню кровообігу за рахунок впливу на положення хребетної артерії, нормалізації м'язового тонусу, зниженню больових відчуттів та відновленню рухливості суглобів. Дане дослідження було присвячене вивченню впливу ортодонтичних апаратів REHASPLINT на фізичні показники пацієнтів із черепно-мозковими травмами та травматичним шийним синдромом. В рамках дослідження було проведено клінічний експеримент за участю 10 пацієнтів віком від 25 до 38 років. Оцінка фізичної сили включала підтягування, вис на перекладині, штовхання медичного м'яча (9 кг) та стиснення кистьового еспандера. Тестування проводилося у два етапи: без використання ортодонтичних кап та з їх використанням. Результати дослідження підтверджують, що використання кап сприяє покращенню м'язової функції та загальних фізичних показників за рахунок оптимізації біомеханіки прикусу. Проведене дослідження показало, що використання ортодонтичних кап під час фізичних вправ сприяє значному покращенню фізичних показників учасників. Під час виконання підтягувань середній результат збільшився з 7,3 до 10,7 підтягувань, що свідчить про зростання сили верхньої частини тіла на 46,58 %. Час утримання на перекладині зріс з 54,3 до 76,4 секунд, що демонструє поліпшення витривалості та м'язового контролю на 40,7 %. При штовханні медичного м'яча вагою 9 кг середня відстань збільшилася з 4,63 до 5,45 метра, що вказує на підвищення сили та координації рухів на 17,73 %. Стиснення кистьового еспандера показало зростання середнього результату зі 128,9 до 152,1 стиснення за 60 секунд, збільшивши силу та витривалість рук на 18,04 %. Вплив ортодонтичних кап найбільш помітний у вправах, що потребують координації та стійкості, таких як утримання на перекладині та штовхання м'яча. Отримані дані підкреслюють ефективність ортодонтичних кап у реабілітації пацієнтів із черепно-мозковими травмами та травматичним шийним синдромом. Використання кап може бути рекомендовано для покращення фізичних можливостей військовослужбовців та пацієнтів у період реабілітації

Ключові слова: черепно-мозкова травма; травматичний шийний синдром; хребетна артерія; мозковий кровотік; ортодонтичні капи; фізичні показники; фізична реабілітація

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616.831-005.4:612.82:611.395:577.152.1:569.323.4
DOI: 10.63341/ijmmr/1.2025.78

Article's History:
Received: 17.09.2024; Revised: 03.02.2025; Accepted: 27.05.2025

Effect of mesenchymal stromal cell transplantation on nitric oxide metabolism in rat cortex during ischemia-reperfusion

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Abstract. One of the causes of stroke is acute impairment of cerebral blood flow, which initiates with the formation of acute neuronal energy deficiency, activation of the "ischaemic cascade", and nitrosative stress. Reactive nitrogen species, namely nitric oxide and peroxynitrite, play a central role in tissue damage. The search for new therapeutic strategies to address these processes remains relevant. The objective of this study was to evaluate the effect of transplantation of mesenchymal stromal cells of various origins, their lysates, and citicoline on nitric oxide metabolism in the somatosensory cortex of the eyes using an ischaemia-reperfusion model. An experimental model was established using 126 rats, with bilateral 20-minute occlusion of the internal carotid arteries followed by reperfusion. The animals were divided into groups according to the substances administered: mesenchymal stromal cells extracted from Wharton's jelly of the human umbilical cord, human and rat adipose tissue, rat fetal fibroblasts, lysates of mesenchymal stromal cells from Wharton's jelly, and citicoline. On days 7 and 14 after treatment, indicators of nitric oxide metabolism in the somatosensory cortex following ischaemia-reperfusion were analysed. The results demonstrated that transplantation of mesenchymal stromal cells from Wharton's jelly of the human umbilical cord and rat fetal fibroblasts, as well as administration of citicoline, significantly altered total nitric oxide synthase activity during the observed periods. It was found that mesenchymal stromal cells derived from human Wharton's jelly, particularly when combined with citicoline, reduced nitrosative stress. Thus, the ischaemia-reperfusion model induced an imbalance in the functioning of the nitric oxide system. The greatest protective effect was observed with transplantation of mesenchymal stromal cells from Wharton's jelly of the human umbilical cord, which effectively safeguarded neurons from nitrosative stress, in a manner comparable to citicoline

Keywords: cerebral ischaemia; Wharton's jelly; stromal cells; citicoline; NO synthase

Suggest Citation:
Konovalov S, Yoltukhivskyy M, Gadzhula N. Effect of mesenchymal stromal cell transplantation on nitric oxide metabolism in rat cortex during ischemia-reperfusion. Int J Med Med Res. 2025;11(1):78–84. DOI: 10.63341/ijmmr/1.2025.78

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Introduction

Stroke is the most prevalent vascular disease worldwide and one of the leading causes of disability and mortality. Among its various forms, ischaemic stroke is the most common, representing a major global health challenge due to its high incidence, complex pathogenesis, and limited treatment efficacy. The mechanisms of ischaemia-reperfusion (IR) injury, which significantly worsen the prognosis after stroke, have become a focus of intensive research aimed at improving therapeutic outcomes.

Ischaemic brain injury triggers a cascade of biochemical events in the affected brain regions, ultimately resulting in oxidative stress that causes irreversible neural tissue damage and cell death following reperfusion. A literature review by V. Chavda *et al.* [1] summarised the powerful molecular mechanisms underlying the development of oxidative stress and its detrimental impact on neural tissue during ischaemic stroke. In a study by S. Arfin *et al.* [2], it was found that after restoration of perfusion in an occluded artery, secondary reperfusion injury occurs in the brain. This is accompanied by increased production of reactive oxygen species (ROS), enhanced inflammation, and an intensified immune response, which disrupt the integrity of the blood-brain barrier (BBB) and eventually lead to cerebral oedema. In another study conducted by A. García-Sánchez *et al.* [3], it was shown that oxidative stress – driven by excessive ROS production from microglia and astrocytes, along with reactive nitrogen species – disrupts synaptic transmission and neuron-glia interactions during ischaemic and reperfusion injuries. Under conditions of elevated ROS production, nitro-oxidative stress arises due to increased nitric oxide (NO) synthesis. Nitric oxide, predominantly produced by enzymatic reactions involving L-arginine and oxygen, is catalysed by three isoforms of nitric oxide synthase (NOS): neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). Among these, activated nNOS and iNOS are implicated in NO overproduction, which exacerbates damage to the ischaemic brain. During reperfusion, oxygen preferentially reacts with NO to form a potent oxidant, peroxynitrite ($ONOO^-$), which possesses a much stronger oxidising capacity than either NO or oxygen alone. The findings of L. Wu *et al.* [4] indicate that the cytotoxic effect of NO is primarily associated with peroxynitrite, formed through a diffusion-limited reaction between NO and another free radical, the superoxide anion. Data obtained by L. Piacenza *et al.* [5] demonstrated that peroxynitrite interacts with proteins, lipids, and DNA through direct oxidative reactions or indirectly via radical-mediated mechanisms, resulting in significant oxidative damage that leads to either apoptosis or necrosis of cells.

Therefore, there is an urgent need to develop safer and novel therapeutic options for the treatment of IR injury. The management of ischaemic stroke frequently involves a combination of strategies aimed at restoring neurological function. Reviews by C. Li *et al.* [6] and F. Shehjar *et al.* [7] noted that traditional treatment methods based on antithrombotic and neuroprotective therapies are significantly limited due to their low safety profile and limited treatment efficacy. However, ongoing research is focused on developing improved therapeutic strategies to reduce stroke-induced damage and maximise recovery of lost neurological function in patients with acute ischaemic stroke. The therapeutic focus has shifted towards stem cell therapy as one of the most promising approaches for treating a wide range of neurodegenerative diseases. T. Li and G.H. Zhu [8] emphasised that stem cell therapy not only has the potential to promote neuroregeneration, but also to suppress neuroinflammation, enhance angiogenesis, and improve the microenvironment in the ischaemic brain, thereby contributing to functional recovery in patients with ischaemic stroke. M. Chan and Y. Nalapko [9] underlined the potential of regenerative medicine approaches, including stem cell therapy, in restoring neurological functions in stroke patients. Among many types of stem cells, mesenchymal stromal cells (MSCs) are considered the most suitable option for the treatment of ischaemic stroke due to their regenerative and immunomodulatory properties [10-12]. W. Li *et al.* [10] reviewed recent preclinical and clinical data confirming the efficacy of MSCs in modulating post-stroke inflammation and promoting angiogenesis and neurogenesis. Similarly, E.H. Ntege *et al.* [11] highlighted that MSC-based therapies can reduce ROS levels, stabilise the blood-brain barrier, and promote neural repair. X. Wu *et al.* [12] further explained that the therapeutic effects of MSCs are largely mediated by their secretome, which contains anti-apoptotic, trophic, and immunoregulatory factors.

One of the key mechanisms underlying the protective action of modern neuroprotective agents is their modulatory effect on NO metabolism, particularly with respect to the development of nitrosative stress in brain tissues. In light of this, it was appropriate to investigate the modulatory effects of MSCs of different origins, cell lysates from human umbilical cord Wharton's jelly-derived MSCs, and citicoline on the dynamics of NOS activity in the rat somatosensory cortex during experimental IR, as a potential mechanism underlying their cytoprotective properties.

Materials and Methods

The study involved 126 sexually mature male Wistar rats, each weighing between 160 and 190 g. The animals underwent 20-minute bilateral ischaemia of the internal carotid arteries (ICAs) under propofol anaesthesia (Propofol-Novo, LLC "Novofarm-Biosynthesis", Ukraine; 60 mg/kg, intraperitoneally). This investigation is a continuation of previous work assessing the therapeutic effects of mesenchymal stromal cells (MSCs) of various origins on biochemical processes in the somatosensory cortex of rats subjected to induced IR injury [13, 14]. The chosen IR model effectively mimics the clinical presentation of cerebral infarction and serves as an optimal platform for evaluating potential neuroprotective agents. The rats were bred and housed in the vivarium of the National Pirogov Memorial Medical University, Vinnytsya (NPMMU), under standard

laboratory conditions with free access to food and water. The study was conducted in full compliance with international bioethical standards, including the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes [15], and the Law of Ukraine No. 344-IV [16]. MSCs and MSC lysate were obtained from the Institute of Molecular Biology and Genetics (IMBG) of the National Academy of Sciences of Ukraine (NAS), as part of an official scientific cooperation agreement between IMBG NAS and NPMMU. Rats were chosen as experimental subjects due to the morphological and angioarchitectural similarities between their cerebral cortex and that of humans.

For the experiment, the animals were randomly assigned to nine groups, each comprising 14 rats. The first group consisted of intact (untreated) animals. The second group included sham-operated rats, which underwent anaesthesia, skin incision, and vessel preparation, but without placement of silk ligatures on the ICAs, to control for procedural trauma. The third group (pathology control) underwent 20-minute IR of the ICAs followed by a single intravenous injection of 0.9% saline solution (2 ml/kg). The fourth group received a transplantation of 10^6 human Wharton's jelly-derived MSCs (hWJ-MSCs) per animal. The fifth group received 10^6 rat embryonic fibroblasts (REFs) per animal. The sixth group was administered 10^6 human adipose tissue-derived MSCs (AT-MSCs), and the seventh group received 10^6 rat AT-MSCs per animal. The eighth group was given 0.2 ml of lysate derived from hWJ-MSCs. The ninth group received a single dose of the reference drug citicoline ("Neuroxon", Arterium Corporation, Ukraine) at 250 mg/kg. As early MSC transplantation has been shown to promote greater neurological recovery, reduce infarct volume, and require fewer donor cells (1×10^6) to achieve therapeutic effects, intravenous administration of all tested substances was performed immediately after IR [17]. On the 7th and 14th days following treatment, the animals were humanely euthanised by decapitation under propofol anaesthesia (Propofol-Novo, Novofarm-Biosynthesis LLC, Ukraine; 60 mg/kg, intraperitoneally), and the brains were promptly extracted. Biochemical parameters of nitrosative balance in the rat somatosensory cortex were assessed under IR conditions and in the context of therapeutic correction.

Biochemical studies were conducted in the scientific research and clinical diagnostic laboratory of NPMMU, certified by the Ministry of Health of Ukraine. Brains were extracted from decapitated animals, and tissues of the somatosensory cortex were rinsed with cold 1.15% KCl solution before being homogenised at 3,000 rpm (Teflon-glass) in 1.15% KCl (1:3, w/v). The postnuclear fraction was obtained from the homogenates by centrifugation (30 minutes, 600 × g, at -4°C) and stored at -20°C until further analysis. The total activity of NOS was assessed by measuring the concentration of nitrite anion (NO_2^-) following incubation of the postnuclear supernatant for 60 minutes in a reaction medium. Each 1 ml of reaction mixture contained 50 mM KH_2PO_4–NaOH buffer (pH 7.0), 1 mM $MgCl_2$, 2 mM $CaCl_2$, 1 mM NADPH, and 2.2 mM L-arginine (NADPH from Sigma, USA) [18]. Total NOS activity was determined using a spectrophotometric method. Optical density measurements were performed with an APEL PD-303 spectrophotometer (Japan). This method is based on the stereospecific reduction of NADPH during the formation of NO from L-arginine. The decrease in NADPH, which is equimolar to the amount of NO formed, was recorded spectrophotometrically at a wavelength of 340 nm. Total protein content in the postnuclear fraction was determined using the Lowry method [19]. Statistical analysis of the obtained data was conducted using Microsoft Excel 2015 and Statistica 14.0 software. Differences between the studied parameters were evaluated using the non-parametric Mann-Whitney U test, with statistical significance set at $p < 0.05$.

Results and Discussion

No differences were observed in the total NOS activity within the somatosensory cortex between intact and sham-operated animals. Consequently, the sham-operated rats were used as the control group. In this study, nitrosative stress was found to develop in rats on days 7 and 14 following cerebral ischaemia-reperfusion (IR), as evidenced by increased NOS activity. Specifically, the study established that cerebral IR in rats resulted in an average increase in total NOS activity in the somatosensory cortex by 82.4%, 22.0%, 38.5%, 66.5%, 71.0%, 80.7%, and 11.1% ($p < 0.05$) on day 7, and by 72.0%, 19.5%, 33.0%, 55.9%, 59.4%, 62.5%, and 10.0% ($p < 0.05$) on day 14, in comparison to sham-operated animals (Table 1). This increase in NOS activity is likely attributed to the iNOS, whose expression is known to rise during inflammatory responses.

Table 1. Parameters of nitrosative stress in the somatosensory cortex of rats under conditions of cerebral IR and following therapeutic intervention (M ± m, n = 7)

Experimental conditions / Biochemical parameter		Groups of animals								
		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9
		Intact	Sham-operated	IR (control pathology)	IR + hWJ-MSCs	IR + REF	IR + human AT-MSCs	IR + rat AT-MSCs	IR + MSC lysate	IR + citicoline
NOS, pmol/min·mg protein	7th day	119.3 ± 3.93	122.6 ± 4.66	223.6 ± 9.18* (+82.4%)	149.6 ± 5.11*#$ (+22.0%) [-33.1%]	169.7 ± 3.91*#$ (+38.5%) [-24.1%]	204.1 ± 4.91*$ (+66.5%)	209.6 ± 7.91*$ (+71.0%)	221.4 ± 7.17*$ (+80.7%)	136.1 ± 3.10*# (+11.1%) [-39.1%]

Continued Table 1

Experimental conditions / Biochemical parameter		Groups of animals								
		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9
		Intact	Sham-operated	IR (control pathology)	IR + hWJ-MSCs	IR + REF	IR + human AT-MSCs	IR + rat AT-MSCs	IR + MSC lysate	IR + citicoline
NOS, pmol/min·mg protein	14th day	116.6 ± 2.36	121.3 ± 3.90	208.6 ± 8.70* (+72.0%)	145.0 ± 3.21*#$ (+19.5%) [-30.5%]	161.3 ± 5.79*#$ (+33.0%) [-22.7%]	189.1 ± 6.18*$ (+55.9%)	193.3 ± 10.54*$ (+59.4%)	197.1 ± 8.06*$ (+62.5%)	133.4 ± 4.35*# (+10.0%) [-36.0%]

Notes: * – $p < 0.05$ in comparison to the corresponding time group of sham-operated animals; # – $p < 0.05$ in comparison to the corresponding time group of animals with control pathology; $ – $p < 0.05$ in comparison to the corresponding time group of citicoline-treated animals. In round brackets – changes of the parameter compared to its level in sham-operated animals; in square brackets – changes relative to the parameter of the control pathology group
Source: created by the authors

The therapeutic interventions applied for IR brain injury in rats during the subacute and recovery phases of acute cerebrovascular insufficiency exerted a positive modulatory effect on the NO cycle, leading to a statistically significant reduction in total NOS activity. The most pronounced decrease in total NOS activity was observed with citicoline treatment, followed by transplantation of hWJ-MSCs, and to a lesser extent with REFs. Specifically, during the experimental period, NOS activity in the somatosensory cortex decreased progressively, averaging 39.1%, 33.1%, and 24.1% by day 7 of follow-up compared to the control group. By day 14, the reductions were 36.0%, 30.5%, and 22.7%, respectively ($p < 0.05$).

Thus, the subacute phase of stroke is characterised by an imbalance in the functioning of the nitric oxide system in the somatosensory cortex of the rat brain, associated with a 1.8-fold increase in total NOS activity ($p < 0.05$). Similar changes were observed during the recovery phase of acute cerebral ischaemia. Among the tested treatments, hWJ-MSCs – more so than other MSCs and MSC lysates – along with the reference drug citicoline, contributed most effectively to restoring normal NO cycle functioning in the ischaemic brain during both subacute and recovery phases of stroke. It was also demonstrated that, in terms of modulating total NOS expression, REFs were somewhat inferior to hWJ-MSCs, indicating a higher cerebroprotective potential of xenotransplantation. This effect of hWJ-MSCs may be one of the key mechanisms underlying their protective action in ischaemic and reperfusion injury in the context of cerebral IR in rats.

An important objective of the present study was to elucidate the biochemical mechanisms underlying the cerebroprotective effects of MSCs of different cytological origins, particularly through their influence on nitro-oxidative stress during IR injury in the somatosensory cortex. Numerous studies have highlighted the critical involvement of reactive nitrogen species (RNS) in various pathological processes occurring during reperfusion following ischaemia. Nitric oxide and peroxynitrite are the principal RNS involved in IR injury and are major contributors to nitrosative stress. For example, the study by K. Yatsenko *et al.* [20] demonstrated glial cell activation during ischaemic stroke. In another study, Q. Liu and S.K. Sorooshyari [21] established that microglia become activated within the first hours following ischaemia and act as major sources of cytokine release after stroke. Y. Chen *et al.* [17] showed that microglia and astrocytes are the primary producers of ROS and RNS, which together influence synaptic transmission and play a critical role in neuron-glia communication, contributing to secondary neural damage during IR injury.

A number of experimental studies have also demonstrated the effectiveness of using mesenchymal stromal cells (MSCs) to normalise the functioning of the NO system in the brains of animals with ischaemic stroke. For instance, D. Lapi *et al.* [22] found that bone marrow-derived MSCs increased endothelial NOS (eNOS) expression in rats following transient middle cerebral artery occlusion. S.S. Wang *et al.* [23] demonstrated that extracellular vesicles derived from MSCs exert therapeutic effects in various neurological disorders, including ischaemic stroke and hypoxic-ischaemic brain injury, by suppressing iNOS expression. B. Soria *et al.* [24], using a model of radiation-induced neurological complications, showed that intranasal delivery of human MSCs reduced iNOS expression and oxidative stress biomarkers, ultimately promoting neuronal survival and improving cognitive function in mice. Y. Li *et al.* [25] also reported that MSC transplantation therapy can reduce the number of activated microglia and suppress the expression of pro-inflammatory cytokines, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Thus, MSCs may modulate microglial activation, reducing neuroinflammation and secondary brain injury following ischaemic stroke. Furthermore, Y. Wang *et al.* [26] found that transplantation of hWJ-MSCs increased NO levels and enhanced nNOS activity in a mouse model of Alzheimer's disease. These findings suggest that the antinitrosative effects of MSCs are likely disease-dependent and may vary based on the pathological context.

A distinctive feature of the present study was the use of intravenous transplantation of MSCs of different origins, along with intravenous administration of factors isolated from Wharton's jelly-derived MSCs (WJ-MSCs) and citicoline. An increase in total NOS activity in the brains of experimental animals may indicate NO hyperproduction. At

this stage of cerebral IR, brain injury is primarily associated with excessive NO formation, predominantly due to activation of Ca^{2+}-dependent NOS, which aligns with findings in the literature [1]. These studies support the existence of a temporal pattern in the expression of different NOS isoforms during ischaemic brain injury. During the recovery phase following ischaemia, NO overproduction is mainly driven by iNOS activation.

Thus, the data from this research confirm the therapeutic potential of hWJ-MSC transplantation. It was found that intravenous administration at a dose of 10^6 cells per animal resulted in more pronounced suppression of total NOS expression compared to other types of MSCs and their lysates. Moreover, Wharton's jelly-derived MSCs were not inferior to citicoline (250 mg/kg) in restoring normal functioning of the nitric oxide cycle in the somatosensory cortex. The therapeutic effect of prenatal stem cell transplantation in rats with brain IR injury exceeded that of adult adipose tissue-derived stem cells, as evidenced by a more significant suppression of total NOS expression. These findings expand current knowledge on the therapeutic potential of MSCs for the treatment of IR injury and open new perspectives for the development of effective cell therapy approaches to correct nitric oxide metabolism disorders.

Conclusions

The 20-minute modelled IR of the ICAs induced an imbalance in the functioning of the NO system in the somatosensory cortex of rats, characterised by an increase in total NOS activity. This finding confirms the key role of nitrosative stress in the pathogenesis of ischaemic brain injury and its progression during the reperfusion phase. Therapeutic correction of ischaemic and reperfusion injury in the somatosensory cortex under IR conditions using hWJ-MSCs proved superior to other tested MSCs and MSC lysate, demonstrating a positive modulatory effect on nitrosative stress. Among all options studied, hWJ-MSCs exhibited neuroprotective effects comparable to those of the reference drug citicoline, indicating their potential as an alternative or adjunctive treatment. Specifically, both citicoline (250 mg/kg, i.v.) and hWJ-MSCs (10^6 cells/animal, i.v.) significantly contributed to the normalisation of total NOS activity in the affected brain regions during both the subacute and recovery phases. In contrast, REFs demonstrated lower efficacy, highlighting the advantages of xenogeneic cell therapy with hWJ-MSCs. Despite these promising results, one limitation of the study is the use of a single dose and administration schedule, which may not reflect the optimal therapeutic regimen. Future research should address dose-response relationships, long-term outcomes, and additional mechanisms of action. In conclusion, this study experimentally substantiates the therapeutic potential of hWJ-MSCs in managing IR injury and provides a scientific foundation for the development of an injectable, cell-based pharmaceutical product. These findings support the need for further translational research and clinical trials to evaluate the safety and efficacy of hWJ-MSCs in patients with acute ischaemic stroke.

Acknowledgements

None.

Funding

None.

Conflict of Interest

None.

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Вплив трансплантації мезенхімальних стромальних клітин на обмін монооксиду азоту в соматосенсорній корі щурів при ішемії-реперфузії

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Анотація. Однією з причин інсульту є гостре порушення мозкового кровообігу, яке починається з утворення гострого дефіциту енергії нейронів, активації «ішемічного каскаду» та нітрозативного стресу. Реактивні форми азоту, зокрема оксид азоту та пероксинітрит, відіграють центральну роль у пошкодженні тканин. Пошук нових терапевтичних стратегій для боротьби з цими процесами залишається актуальним. Метою цього дослідження було оцінити вплив трансплантації мезенхімальних стромальних клітин різного походження, їх лізатів та цитиколіну на метаболізм оксиду азоту в соматосенсорній корі очей за допомогою моделі ішемії-реперфузії. Експериментальна модель була створена з використанням 126 щурів, яким проводилась двостороння 20-хвилинна оклюзія внутрішніх сонних артерій з подальшою реперфузією. Тварин було розділено на групи відповідно до введених речовин: мезенхімальні стромальні клітини, отримані з Вартонових драглів пуповини людини, жирової тканини людини та щура, ембріональні фібробласти щура, лізат мезенхімальних стромальних клітин Вартонових драглів, цитиколін. На 7-й і 14-й день після лікування було проаналізовано показники метаболізму оксиду азоту в соматосенсорній корі головного мозку після ішемії-реперфузії. Результати продемонстрували, що трансплантація мезенхімальних стромальних клітин з Вартонових драглі людської пуповини та фетальних фібробластів щурів, а також введення цитиколіну значно змінили загальну активність оксиду азоту синтетази протягом спостережуваних періодів. Було виявлено, що мезенхімальні стромальні клітини, отримані з Вартонових драглів людини, особливо в поєднанні з цитиколіном, зменшували нітрозативний стрес. Таким чином, модель ішемії-реперфузії викликала дисбаланс у функціонуванні системи оксиду азоту. Найбільший захисний ефект спостерігався при трансплантації мезенхімальних стромальних клітин з Вартонових драглів з пуповини людини, які ефективно захищали нейрони від нітрозативного стресу, подібно до цитиколіну

Ключові слова: церебральна ішемія; Вартонові драглі; лізат; цитиколін; NO-синтаза

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616-053.31-056.7:575.1
DOI: 10.63341/ijmmr/1.2025.85

Article's History:
Received: 20.11.2024; Revised: 06.03.2025; Accepted: 27.05.2025

From neonatal signs to developmental delay: An infant with Wolf-Hirschhorn syndrome – a case study

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Abstract. Wolf-Hirschhorn syndrome (WHS) is a rare genetic disorder with significant developmental, metabolic and craniofacial manifestations, highlighting the importance of continued research due to these challenges. This case report presents an 8-month-old female infant, born at term but classified as small for gestational age, who exhibited developmental delays, metabolic abnormalities and craniofacial dysmorphology characteristic of WHS. This report aimed to emphasise the clinical progression and diagnostic difficulties encountered in cases of WHS. Comprehensive genetic analyses and clinical evaluations were conducted, confirming the diagnosis. Key findings included recurrent respiratory distress with multiple failed weaning attempts, severe failure to thrive, seizures, sensorineural hearing loss, central hypotonia and feeding difficulties. Early neonatal complications and a prolonged, challenging stay in the neonatal intensive care unit were also noted, following which the infant was lost to follow-up until re-presenting at 8 months of age. This report underscores the necessity of early genetic screening and continuous follow-up for infants with congenital anomalies such as WHS. The findings may support paediatricians and neonatologists in the early identification and management of similar cases, thereby improving long-term outcomes

Keywords: 4p16.3 deletion; microcephaly; hypotonia; seizures; failure to thrive; Greek warrior helmet syndrome

Suggest Citation:
Jayakrishnan VY, Parthasarathy G, Dwivedi A, Vineeth VP. From neonatal signs to developmental delay: An infant with Wolf-Hirschhorn syndrome – a case study. Int J Med Med Res. 2025;11(1):85–94. DOI: 10.63341/ijmmr/1.2025.85

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Introduction

Wolf-Hirschhorn Syndrome (WHS) is a rare congenital disorder that presents significant challenges in paediatric healthcare due to its diverse clinical manifestations and the complexity of diagnosis and management. The condition is caused by a deletion of genetic material at the 4p16.3 region and is associated with a spectrum of systemic complications, including neurodevelopmental delays, epilepsy, craniofacial anomalies, cardiac defects and metabolic disturbances. Despite advancements in medical genetics and diagnostic methodologies, WHS remains under-recognised in neonatal and early paediatric care, leading to delays in intervention and the formulation of comprehensive care plans. Given its substantial impact on affected individuals and their families, early genetic screening, multidisciplinary management, and ongoing research are critical to improving clinical outcomes and supporting the development of individualised care strategies.

Seizures are a predominant feature of WHS, often manifesting in early infancy. J. Paprocka *et al.* [1] highlighted that epilepsy in WHS is frequently refractory to conventional antiepileptic drugs, necessitating personalised therapeutic approaches. T. Corrêa *et al.* [2] analysed epileptogenic mechanisms in WHS and demonstrated that multiple genes within the 4p16.3 region contribute to seizure susceptibility. Their findings emphasise the importance of genetic testing in the prediction and management of epilepsy in patients with WHS. Seizures in WHS tend to follow a complex course, often requiring a combination of antiepileptic medications to achieve partial control.

Phenotypic variability in WHS remains a major challenge in clinical diagnosis. E.C. Gavril *et al.* [3] studied seven newly diagnosed cases of WHS, highlighting craniofacial anomalies such as a broad nasal bridge, high forehead and wide-set eyes as the most consistent clinical indicators. A. Mills *et al.* [4] provided insights into the genetic basis of these craniofacial anomalies, demonstrating that neural crest defects play a significant role in the syndrome's characteristic dysmorphology. Their research reinforces the need for early clinical assessment to enable timely diagnosis. Abnormalities in neural crest migration during embryogenesis contribute not only to craniofacial dysmorphisms but also to the congenital heart defects and urogenital anomalies observed in WHS.

Despite advances in medical care, individuals with WHS continue to experience significant morbidity. N.L. Shannon *et al.* [5] examined life expectancy and mortality patterns in WHS, reporting that proactive management strategies are essential for addressing complications such as feeding difficulties, recurrent infections and metabolic disturbances. Feeding difficulties remain a major concern, with many infants requiring nasogastric or gastrostomy tube placement to ensure adequate nutrition. Studies have shown that early nutritional interventions, including specialised feeding strategies, significantly improve growth outcomes and reduce hospitalisations due to failure to thrive.

Cognitive outcomes in WHS vary widely, although intellectual disability is almost universal. A. Battaglia & J.C. Carey [6] emphasised the importance of early intervention using specialised educational programmes and speech therapy, which have been shown to enhance communication skills and overall quality of life. Their study reflects growing interest in targeted educational interventions, including sensory integration techniques and alternative communication methods such as sign language or augmentative communication devices. The psychosocial burden on families caring for individuals with WHS is substantial. S. Berrocoso *et al.* [7] assessed the quality of life and psychosocial features of family caregivers, finding that robust social support networks and effective coping strategies are vital for caregiver well-being. Many families experience considerable stress due to the complex medical needs of children with WHS, necessitating structured caregiver support programmes and access to mental health resources.

This study aimed to document a case of Wolf-Hirschhorn syndrome in an 8-month-old female patient, highlighting the clinical challenges and emphasising the importance of genetic screening and multidisciplinary management in addressing this rare and complex disorder.

Materials and Methods

This case report concerns a patient managed at the Institute of Naval Medicine and Army Hospital (Research & Referral), part of the Hospitals of the Armed Forces Medical Services, India, between February 2021 and June 2023. The patient was monitored and treated over several months, with follow-up assessments conducted during the same period. This report focuses on an 8-month-old female patient diagnosed with Wolf-Hirschhorn syndrome (WHS). Upon admission, the patient underwent a series of clinical evaluations, including a comprehensive physical examination that revealed craniofacial dysmorphisms and developmental delays. Diagnostic investigations included tandem mass spectrometry (TMS) for inborn errors of metabolism, two-dimensional (2D) echocardiography, and brainstem evoked response audiometry (BERA). A high-resolution CT scan of the temporal bones and a magnetic resonance imaging (MRI) of the brain were also performed. To confirm the diagnosis of WHS, clinical exome sequencing was carried out, followed by multiplex ligation-dependent probe amplification (MLPA) to detect a heterozygous deletion of 4p16.3. Both tests were conducted using kits from MRC Holland (Amsterdam, the Netherlands), following the manufacturer's recommendations. The patient was enrolled in early intervention programmes, including physiotherapy, occupational therapy and speech and language therapy. Seizure management involves a combination of antiepileptic drugs (AEDs), including levetiracetam, sodium valproate and clobazam. Nutritional intake was closely monitored, and appropriate measures were implemented to support growth and development. Informed consent was obtained from the patient's legal guardians prior to

all evaluations, treatments and genetic testing. All clinical procedures conformed to the guidelines set out in the Declaration of Helsinki [8]. Written informed consent was also obtained from the patient's parents for the publication of this case report, including the use of clinical photographs. All identifying information has been anonymised to protect the patient's privacy per ethical guidelines and institutional protocols.

Results and Discussion

The case involves a female, the second child of non-consanguineous parents, delivered at full term with a birth weight (Wt) of 2,100 g, length (Lt) of 48 cm, and classified as small for gestational age with asymmetrical intrauterine growth restriction (IUGR) (Ponderal Index: 1.9; weight-for-length: −4.1 Z-score based on WHO chart) [9]. She was initially started on Paladai feeds from day one and remained otherwise asymptomatic alongside her mother until 48 hours post-birth. Subsequently, she developed progressively worsening tachypnoea without significant desaturation. The initial sepsis screen was negative, and chest radiography was unremarkable. Respiratory distress worsened necessitating continuous positive airway pressure (CPAP) management in the neonatal intensive care unit. She experienced a complicated early neonatal course beginning after 48 hours, with difficulty weaning off CPAP. There was no history of rashes, rhinitis, oedema, jaundice, organomegaly, or gross dysmorphisms noted at birth. A detailed antenatal history revealed no febrile illness, bleeding or spotting per vagina, or reduced fetal movements. It was a spontaneous conception; the mother was immunised and had no history of diabetes mellitus or hypertension. TORCH screening was negative, and there was no significant family history. The infant was started on empirical intravenous antibiotics according to the local neonatal intensive care unit protocol, which was discontinued after five days when culture reports returned negative. Multiple attempts at weaning were made, and she was successfully weaned off CPAP after eight days. During this period, she was fed via a nasogastric tube. Following weaning, feeding difficulties emerged in the form of poor oral intake, necessitating a combination of tube feeding and expressed breast milk. This later progressed to partially expressed milk and direct breastfeeding. She experienced weight loss post-CPAP but gradually began to gain weight with direct breastfeeding supplemented by expressed breast milk via Paladai.

Newborn screening with tandem mass spectrometry (TMS) for inborn errors of metabolism was negative. Screening 2D echocardiography revealed a small ostium secundum atrial septal defect, and otoacoustic emissions (OAE) screening showed bilateral "refer" findings at discharge. She was discharged on day 20 with recommendations for follow-up. At discharge, her Wt was 2,200 g (−4 Zscore), Lt was 49 cm (−1 to −2 Z-score), and occipitofrontal circumference (OFC) was 32 cm (−2 to −3 Z-score). She was discharged on direct breastfeeds, and birth-dose vaccines were administered as per the national immunisation schedule. After discharge, she was taken to her maternal home in a rural area in another state and was subsequently lost to follow-up.

Subsequently, the infant experienced recurrent, refractory generalised tonic-clonic seizures beginning at four months of age. A review of the medical records available at that time indicated a weight of 3,600 g (−4.7 Z-score), length of 55.5 cm (at −3 Z-score), and OFC of 36 cm (−3.6 Z-score). She was commenced on antiepileptic drugs (AEDs) – levetiracetam, followed by sodium valproate, which achieved seizure control. At eight months of age, she returned for follow-up with global developmental delay – no neck control, severe failure to thrive, and feeding difficulties (Wt: 4,300 g (−5.2 Z-score), Lt: 60 cm (−3.7 Z-score), OFC: 39.5 cm (−3 Z-score)) – alongside persistent generalised tonic-clonic epilepsy. Seizure semiology revealed that most seizures were triggered by short febrile viral illnesses, typically within the first 24-48 hours of fever onset. Episodes began with a cry, followed by sudden cessation of crying, upward deviation of the eyes, and jerky movements of all four limbs, lasting 2-3 minutes. Minimal frothing at the mouth was noted. Seizure activity either resolved spontaneously or ceased following medication, and was followed by a period of postictal drowsiness. This pattern remained consistent over time.

At the eight-month follow-up, detailed physical examination revealed craniofacial dysmorphism, including a broad nasal bridge extending to the forehead, high anterior hairline with a prominent glabella, highly arched eyebrows, widely spaced eyes, epicanthus, short philtrum, downturned corners of the mouth, microcephaly, and angulated ears (Fig. 1). Haematological and biochemical parameters, as well as metabolic screening, were within normal limits.

Figure 1. Photograph at eight months of age showing dysmorphic features associated with WHS
Source: authors' photo

She exhibited central hypotonia and bilateral severe-to-profound sensorineural hearing loss, confirmed by brainstem evoked response audiometry, which showed no consistent waveforms (Fig. 2).

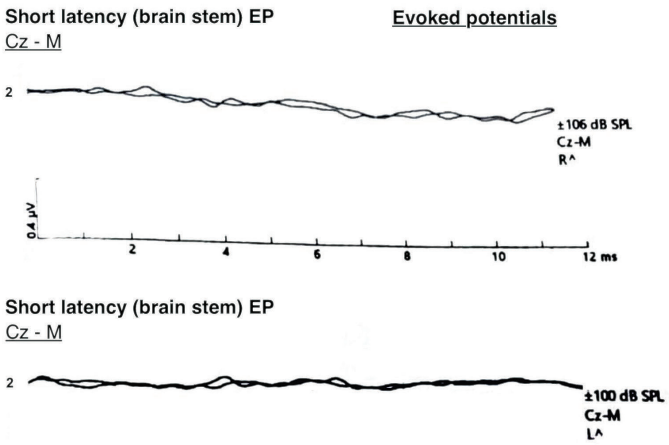

Figure 2. Brainstem evoked response auditory (BERA) showing absence of consistent waveforms
Source: authors' photo

A high-resolution CT scan of the temporal bones revealed no significant abnormalities. In addition, an electroencephalogram (EEG) showed epileptiform discharges in the right parieto-temporal region. Magnetic resonance imaging (MRI) of the brain performed at six months of age showed diffuse thinning of the corpus callosum and a subtle T2 hyperintense signal without diffusion restriction in the inferior aspect of the right cerebellar hemisphere (Fig. 3).

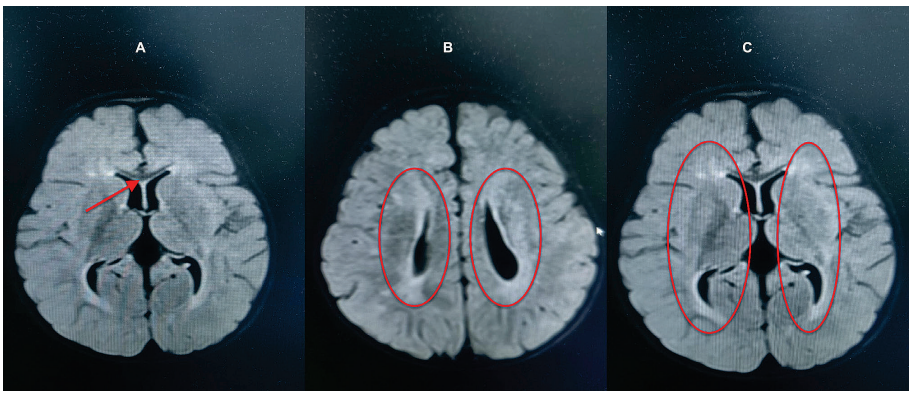

Figure 3. Axial view of brain magnetic resonance imaging
Notes: A – thinned corpus callosum (red arrow); B and C – symmetrical periventricular hyperdensity (red circle)
Source: authors' photo

No significant ocular abnormalities were detected on clinical or ophthalmological examination. The visual evoked potential was normal, indicating preserved cortical response to visual stimuli and intact visual processing pathways. Repeat 2D echocardiography and electrocardiography were conducted to assess cardiac function. Both investigations showed no significant abnormalities, and the previously noted atrial septal defect (ASD) had spontaneously closed, eliminating the need for further cardiac intervention (Fig. 4). A screening ultrasound of the abdomen, kidneys, ureters, and bladder revealed normal findings and chest radiography was also unremarkable.

The patient was lost to follow-up for an extended period, during which her clinical condition underwent significant changes. In view of the dysmorphic features and multisystem involvement, an underlying genetic aetiology was suspected. Consequently, clinical exome sequencing, along with mitochondrial genome sequencing, was performed. Clinical exome sequencing revealed a likely pathogenic copy number variant – a contiguous deletion of 6.2 Mb on Chromosome 4. As the sensitivity and specificity of next-generation sequencing for detecting large deletions and duplications are limited, an alternative method, such as MLPA or chromosomal microarray, was recommended to confirm the deletion. Her craniofacial dysmorphology was suggestive of the Greek warrior helmet appearance. The overall phenotype indicated a possible diagnosis of Wolf-Hirschhorn syndrome. To validate the nextgeneration sequencing findings, MLPA was performed according to the manufacturer's instructions (MRC Holland, Amsterdam, the Netherlands), which confirmed the presence of a heterozygous deletion at 4p16.3 (Fig. 5). The parents were offered karyotyping to rule out a balanced translocation, but they declined further investigation.

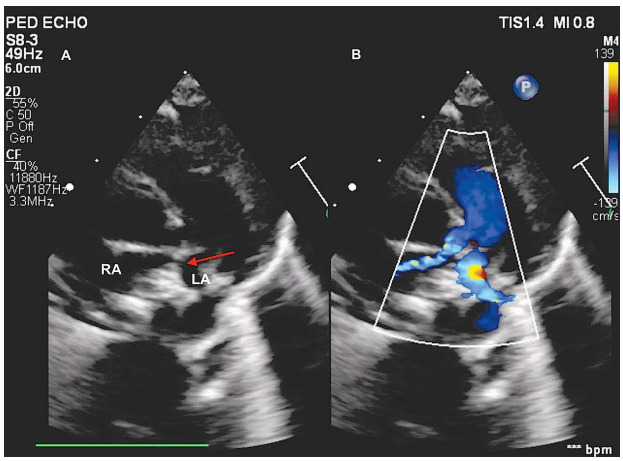

Figure 4. Apical four-chamber view on 2D echocardiography highlighting a small ASD identified during the neonatal period, which resolved spontaneously
Notes: A – ASD depicted by red arrow; B – doppler demonstrating blood flow across the interatrial septum
Source: authors' photo

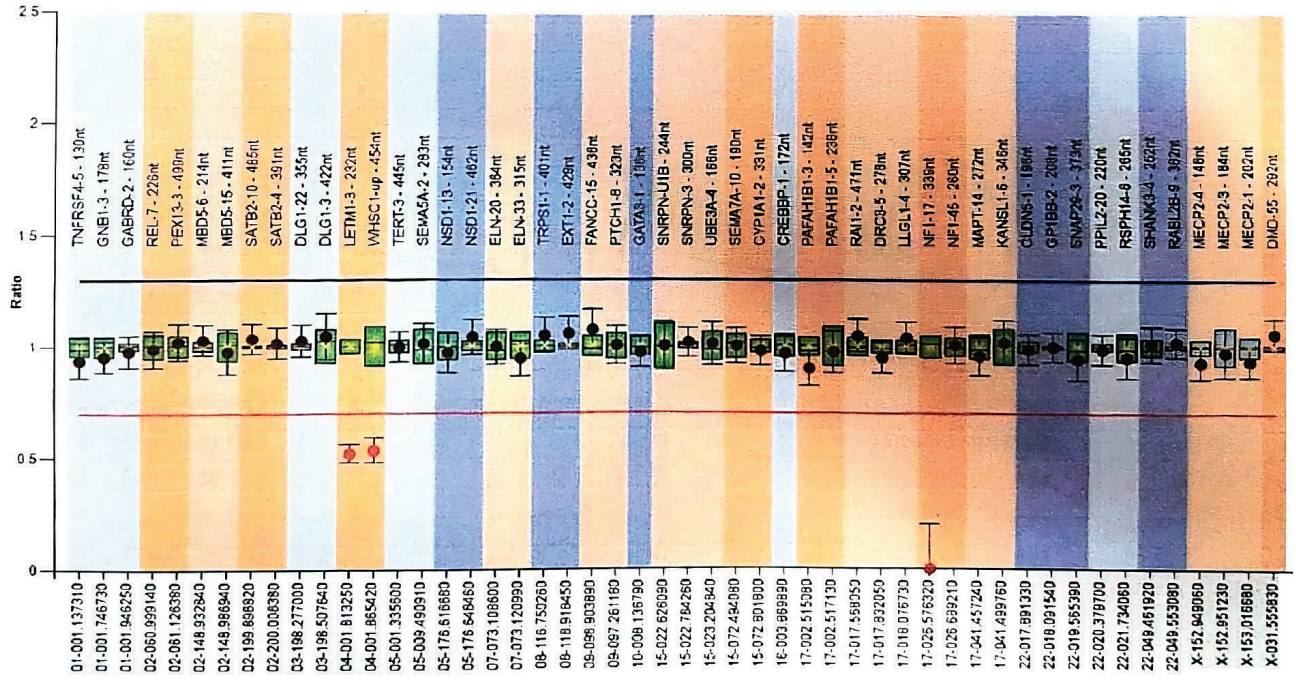

Figure 5. Multiplex ligation-dependent probe amplification (MLPA) analysis
Source: authors' material

She was enrolled in early intervention programmes, including physiotherapy, occupational therapy, and speech and language therapy. She was fully immunised for her age in accordance with the Indian national immunisation schedule. She is currently on three AEDs – levetiracetam, sodium valproate, and clobazam – for seizure control, and continues to exhibit severe global developmental delay. As of July 2024, she is two years and six months old and continues to experience profound developmental delays. Despite intensive rehabilitation, she remains unable to sit independently or achieve other age-appropriate motor milestones. However, her nutritional status has shown notable improvement with tailored dietary interventions, contributing positively to her overall health and growth. Nonetheless, she continues to experience breakthrough seizures, typically triggered by intercurrent illnesses such as viral infections or febrile episodes. These events remain a significant challenge in her management, requiring ongoing adjustments to her antiepileptic regimen. Follow-up EEGs have consistently demonstrated generalised epileptiform discharges, highlighting the persistent seizure activity that complicates her clinical course (Fig. 6). These findings reinforce the need for vigilant monitoring and a flexible, multidisciplinary approach to effectively manage her condition.

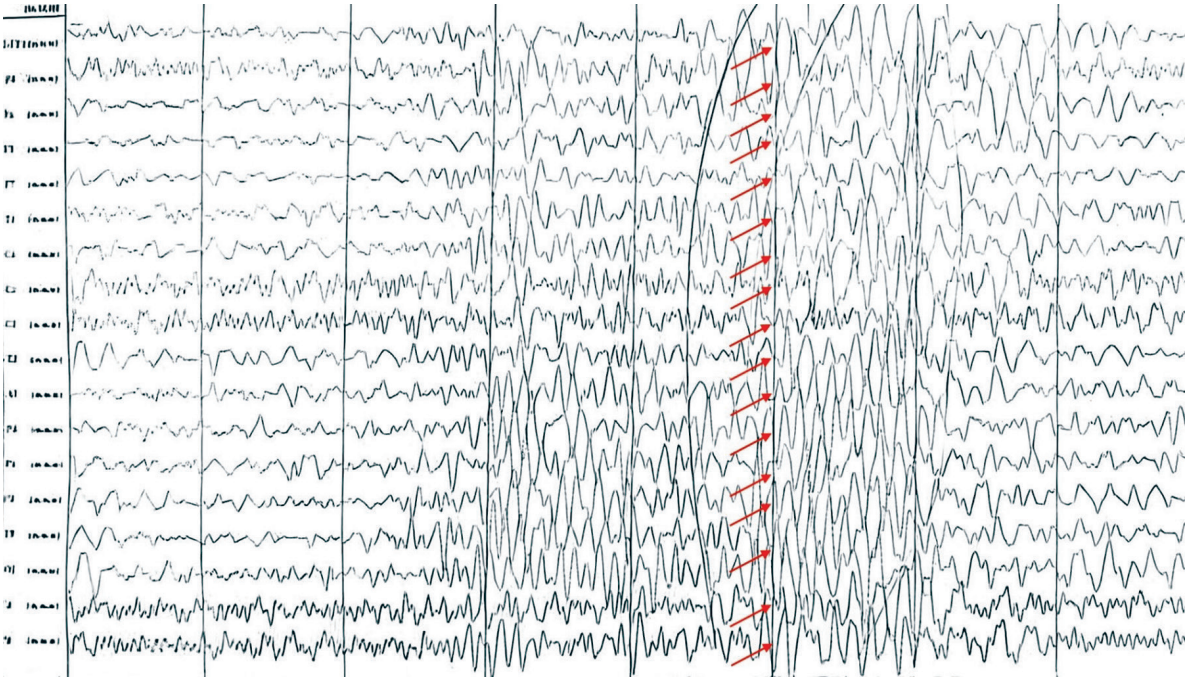

Figure 6. EEG demonstrating generalised epileptiform discharges (red arrow)
Source: authors' material

The management of WHS, as illustrated by this complex presentation, necessitates a multifaceted and highly individualised approach. This case underscores the importance of a comprehensive diagnostic strategy, beginning with the recognition of key phenotypic indicators and extending to advanced genetic investigations. WHS is associated with a wide spectrum of clinical manifestations that vary in severity and presentation depending on the extent of the chromosomal deletion. It is characterised by distinctive craniofacial features, often described as resembling a "Greek warrior helmet" [10]. These features include a broad, flat nasal bridge extending to the forehead, hypertelorism (widely spaced eyes), a high forehead, prominent glabella, and downturned corners of the mouth [11-13]. Other features may include micrognathia, cleft lip, and cleft palate. Such morphological characteristics are essential for the early recognition and diagnosis of WHS.

A study by R. Blanco-Lago *et al.* [14] reported that the mean age of patients in the group was 6.94 ± 6.37 years, while the mean age at diagnosis was 14.34 months. Delayed intrauterine growth was observed in 92.6% of pregnancies. Case management was particularly challenging due to severe developmental delays and the early onset of life-threatening conditions such as refractory epilepsy and profound hearing loss. Epilepsy, a significant concern in WHS, is often well-controlled with appropriate treatment. Generalised tonic-clonic seizures were initially observed, with recurrent episodes occurring despite monotherapy and dual therapy. Eventually, seizure control was achieved with a combination of three AEDs. The seizure type and semiology remained consistent throughout the course of treatment. The selected AEDs – levetiracetam, valproate, and clobazam – were chosen for their efficacy and safety profiles in infants.

A study by A. Battaglia *et al.* [15], involving 87 patients with WHS, revealed that epilepsy occurred in 81 of 87 patients (93%) within the first three years of life. Generalised tonic-clonic seizures accounted for 74%, tonic spasms – 18%, complex partial seizures – 12%, and clonic seizures – 7%. Seizures were often fever-triggered, as observed in many neurological conditions. They frequently occurred in clusters and included status epilepticus in half of the cases. Atypical absences developed in 33% of patients between the ages of one and six years, often with myoclonic components. The EEG showed distinctive abnormalities in 90% of patients, including high-amplitude spike-wave complexes and slow background activity. Epilepsy was well controlled in 81% of cases, primarily with valproate and phenobarbital. Seizure frequency often decreased with age, and many patients became seizure-free. In the present case, seizures were controlled with a combination of levetiracetam, valproate, and clobazam, selected for their established safety and efficacy in infants.

A study by K.S. Ho *et al.* [16], which examined caregiver-reported seizure presentations and treatment outcomes in WHS, highlights several significant findings. Levetiracetam, a broad-spectrum anticonvulsant known to be effective in WHS, demonstrated markedly better outcomes than medications in the carboxamide group. Additionally, both clobazam and levetiracetam showed the highest efficacy and retention rates, making them promising treatment options. These two agents operate via distinct mechanisms of action, providing viable alternatives if a change in therapy becomes necessary. In contrast, carbamazepine,

oxcarbazepine, and phenytoin were associated with the poorest seizure control and the highest incidence of adverse effects [17].

Otolaryngological manifestations of WHS include sensorineural hearing loss, dysplastic ears, deafness, recurrent respiratory tract infections, otitis media, and otitis media with effusion, as described by M.M. Lesperance *et al.* [18]. The patient had profound sensorineural hearing loss; however, due to the severity of the hearing loss and delayed presentation in infancy, it was determined that neither cochlear implantation nor hearing aids would provide meaningful benefit. Although she had no documented evidence of otitis media or related complications, ongoing surveillance during episodes of acute febrile illness is recommended to monitor for such potential issues.

Visual impairments are relatively uncommon in WHS, although some patients experience strabismus, refractive errors, or occasional structural anomalies of the eye. Ocular hypertelorism, ectopia lentis, and iris coloboma are also frequently observed. M.J. Ali & F. Paulsen [19] reported a case of congenital nasolacrimal duct obstruction in WHS, which remains a rare finding. Regular ophthalmological evaluations are essential for the early detection and management of these conditions to support better developmental outcomes. The initial ophthalmological assessment, including visual evoked potentials (VEP), did not reveal any significant abnormalities in this patient. Nevertheless, continued follow-up is necessary to monitor for refractive errors, lenticular abnormalities, and the development of strabismus.

Growth failure in WHS is multifactorial, resulting from feeding difficulties, metabolic abnormalities, and the underlying genetic factors that affect growth. Loss-of-function variants in the WHSC1 gene are associated with developmental delays, autism, and congenital heart conditions, indicating that such variants may lead to a milder phenotype of WHS. Disruptions in WHSC1 contribute to the developmental delays, craniofacial dysmorphisms, and short stature observed in affected individuals. Recent case reports suggest that early nutritional interventions and growth hormone therapy may significantly improve growth parameters in these children. Furthermore, studies by N.J. Boczek *et al.* [20] have demonstrated that consistent monitoring of growth indicators and dietary intake is crucial for timely and effective intervention. Significant growth failure was observed in the present case, primarily due to feeding difficulties that began during the neonatal period and persisted throughout infancy. Recurrent aspiration, often noted in such cases, may result in microaspiration, potentially leading to pneumonia and impaired pulmonary function.

Children with WHS commonly experience nutritional challenges owing to feeding difficulties, which may result in deficiencies of essential vitamins and minerals. A multidisciplinary approach, including input from a dietitian, is essential for devising individualised nutrition plans to address these deficiencies and to promote optimal growth and development. Tailored dietary interventions have been shown to improve weight gain and linear growth in similar cases. A study by T. Antonius *et al.* [21] revealed that all children with WHS exhibited marked intrauterine growth restriction. Despite adequate nutritional support, none demonstrated catch-up growth, and all remained short-statured with profound microcephaly. Given the immunological vulnerabilities often noted in children with WHS, it is essential to maintain an up-to-date vaccination schedule. Specific recommendations include additional vaccines against influenza and pneumococcal infections, as affected individuals may be more susceptible to respiratory complications. Coordination with healthcare providers is vital to ensure compliance with immunisation protocols and to minimise the risk of preventable infections.

A multidisciplinary team – comprising a paediatric neurologist, clinical geneticist, dietitian, and speech and language therapist – was integral to addressing the complex clinical needs of the patient, ranging from seizure control to nutritional support and communication therapy, given the presence of hearing impairment. The paediatric neurologist plays a critical role in diagnosing and managing neurological conditions such as epilepsy**,** which are common in genetic syndromes. The clinical geneticist is responsible for identifying the genetic basis of the condition, clarifying the chromosomal abnormalities, anticipating potential complications, and providing genetic counselling for the family. The dietitian addresses nutritional challenges, often arising from growth retardation, feeding difficulties, or metabolic disturbances, by developing individualised dietary plans to ensure adequate intake. The speech and language therapist focuses on communication difficulties**,** particularly in children with intellectual disabilities or hearing loss. They may introduce alternative communication strategies, including sign language or augmentative and alternative communication devices, to help the child communicate and engage effectively with others. Ongoing research into WHS suggests the potential for targeted therapies to mitigate the effects of gene expression deficits associated with the 4p deletion. Emerging advances in gene therapy and molecular medicine offer hope for more effective treatments that address the underlying genetic mechanisms of WHS. Upon the patient's re-evaluation at eight months of age, a prompt genetic assessment led to the definitive diagnosis of Wolf-Hirschhorn syndrome. Parental counselling was initiated soon after, and a comprehensive multidisciplinary care plan was implemented, incorporating physiotherapy, occupational therapy, speech and language therapy, and an antiepileptic treatment regimen. However, the approach was not without its limitations. The diagnosis was delayed due to a prolonged gap in follow-up following neonatal discharge, and the initial newborn screening was restricted to inborn errors of metabolism, excluding broader genetic testing despite the presence of early clinical warning signs.

Conclusions

This case of Wolf-Hirschhorn syndrome underscores the challenges associated with diagnosing and managing this

rare genetic disorder, which is characterised by multisystem involvement. The findings underscore the importance of early genetic screening, particularly in infants presenting with developmental delays, craniofacial dysmorphisms, or unexplained seizures. The diagnostic process, which included clinical exome sequencing and confirmatory multiplex ligation-dependent probe amplification, identified a 6.2 Mb deletion in the 4p16.3 region. This case demonstrates the utility of advanced genetic testing in confirming complex diagnoses and in guiding clinical management strategies. The management of WHS requires a multidisciplinary approach, given its diverse clinical manifestations, including profound sensorineural hearing loss, severe failure to thrive, and refractory epilepsy. This case illustrates how individualised treatment plans – including the use of antiepileptic drugs such as levetiracetam, valproate, and clobazam – can achieve partial seizure control, despite the inherent complexities of the condition. Early therapeutic interventions, such as physiotherapy and speech and language therapy, proved pivotal in addressing global developmental delays and in improving overall quality of life. Additionally, the case highlights the importance of ongoing follow-up to monitor growth parameters, developmental progress, and the potential for complications such as aspiration pneumonia. The findings emphasise the need for tailored nutritional plans and updated immunisation schedules to reduce the risks associated with immune and metabolic vulnerabilities in patients with WHS. This report contributes to the limited body of literature on this rare condition and provides valuable insights into its clinical course and multidisciplinary management. Future research into targeted therapies and geneediting technologies holds promise for addressing the underlying genetic abnormalities, with the potential to improve long-term outcomes for individuals affected by WHS and related disorders.

Acknowledgements
The authors express their sincere appreciation to the patient's family for their cooperation and consent to share this case.

Funding
None.

Conflict of Interest
None.

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Від неонатальних ознак до затримки розвитку: немовля з синдромом Вольфа-Гіршхорна – клінічний випадок

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Анотація. Синдром Вольфа-Гіршгорна (WHS) – це рідкісне генетичне захворювання, що супроводжується значними порушеннями розвитку, обміну речовин та черепно-лицевими проявами, що підкреслює важливість продовження досліджень з огляду на ці виклики. У цьому клінічному випадку представлено 8-місячну дівчинку, народжену в строк, але класифіковану як малу для гестаційного віку, яка мала затримку розвитку, порушення обміну речовин та черепно-лицьову дисморфію, характерні для WHS. Цей звіт мав на меті підкреслити клінічний перебіг та діагностичні труднощі, що виникають у випадках WHS. Були проведені комплексні генетичні аналізи та клінічне оцінювання які підтвердили діагноз. Основні ознаки включали рецидивуючу дихальну недостатність з численними невдалими спробами відлучення від грудного вигодовування, затримку росту, судоми, сенсоневральну приглухуватість, центральну гіпотонію та труднощі з годуванням. Також були відзначені ранні неонатальні ускладнення та тривале, складне перебування в відділенні інтенсивної терапії новонароджених, після чого дитина зникла з поля зору лікарів, поки не з'явилася знову у віці 8 місяців. Цей звіт підкреслює необхідність раннього генетичного скринінгу та постійного спостереження за немовлятами з вродженими аномаліями, такими як WHS. Результати можуть допомогти педіатрам та неонатологам у ранній діагностиці та веденні подібних випадків, тим самим покращуючи довгострокові результати

Ключові слова: делеція 4p16.3; мікроцефалія; гіпотонія; судоми; затримка росту; Greek warrior helmet syndrome

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616.441-06:611.018.4
DOI: 10.63341/ijmmr/1.2025.95

Article's History:
Received: 08.08.2024; Revised: 30.01.2025; Accepted: 27.05.2025

Cytological features of the diagnosis of recurrent nodular hyperplasia of thyroid gland

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Abstract. The study aimed to improve diagnostic approaches to the assessment of recurrent nodal tumours in the remaining thyroid tissue after surgical treatment, incorporating morphological, ultrasound and clinical and anamnestic features. The methodology included the examination of 69 patients with recurrent lesions classified as *Bethesda* categories *III* and *IV*, who underwent fine-needle aspiration core biopsy under ultrasound imaging, Doppler ultrasound with blood flow assessment, histological verification, and immunocytochemical staining. The results showed that in the *Bethesda III* group, the presence of malignant tumours was confirmed in 37% of cases, while in *Bethesda IV* only 24%, which casts doubt on the traditional notions of the risk of neoplasia in these categories. The *Bethesda III* was dominated by signs associated with malignancy: hypoechogenicity (57%), vertical orientation of the nodule (43%), intranodular blood flow (57%), and indistinct or irregular contours (25%). In group *IV*, follicular adenomas with benign echostructural features were more common (38%). Three morphotypes were identified: proliferative (69.6%), pseudo-recurrent inflammatory fibrous (14.5%) and true neoplastic (13%), with severe cellular atypia recorded in 2.9% of cases. A low correspondence between cytological and histological results (12-16%) was found, which justifies the need for a comprehensive diagnosis. The study determined that the presence of three or more independent risk factors significantly increases the probability of neoplastic transformation. The practical significance of the study is the formation of a multifactorial stratification system that can increase the accuracy of preoperative diagnosis, justify the choice of surgical tactics and reduce the frequency of misdiagnosis in clinical practice

Keywords: cellular atypia; hypoechoic structure; fibrous transformation; risk stratification; neoplastic transformation

Introduction

Recurrent nodular hyperplasia of the thyroid gland is an urgent problem of modern endocrinology and clinical pathology. Their significance is determined by the prevalence of thyroid diseases and the difficulty of diagnosing recurrent nodules in the tissue left after surgery. The differentiation between benign and malignant processes is complicated by the similarity of clinical and ultrasound signs. The discrepancy between cytology and histology results increases the risk of incorrect diagnostic decisions, which can lead to unnecessary surgery or delayed cancer detection. In this context, it is important to improve diagnostic algorithms, including the development of a multifactorial risk stratification system based on morphological, ultrasound, and clinical and anamnestic data. In the study, the term "neoplasia" is used to refer to the process of uncontrolled cell growth regardless of their nature, and "neoplastic transformation" to the transition of tissue to autonomous reproduction with the risk of malignant evolution.

One of the key diagnostic problems is the ambiguity of cytological findings in *Bethesda III-IV* cases. The presence of atypical follicular cells or follicular neoplasia makes it difficult to exclude malignancy. Yu.V. Buldygina *et al.* [1] noted that in these categories, there are often contradictions between cytological and histological findings, which

Suggest Citation:
Antoniv V. Cytological features of the diagnosis of recurrent nodular hyperplasia of thyroid gland. Int J Med Med Res. 2025;11(1):95–104. DOI: 10.63341/ijmmr/1.2025.95

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limits the effectiveness of fine needle aspiration biopsy. Even with a typical cellular structure, the risk of malignant transformation remains significant, which emphasises the need to expand the diagnostic criteria.

Hypoechogenicity of nodes as a sign of malignancy is interpreted ambiguously. Some authors regard it secondary, but A. Pasko & V. Skrypko [2] found that the combination of hypoechogenicity, intraductal blood flow and vertical orientation significantly increases the risk of neoplasia. The detection of three or more of these signs justifies the need for surgical treatment even in the presence of questionable cytological findings. Intranodular blood flow is considered an important diagnostic marker. V. Hoperia *et al.* [3] proved that high vascularisation is characteristic of malignant neoplasms, but its prognostic value increases only in combination with other echographic features.

The problem of pseudo-recurrence also creates significant diagnostic difficulties. D. Sgró *et al.* [4] noted that inflammatory fibrotic changes can mimic proliferative lesions and lead to false suspicions of malignancy. In this case, a comprehensive approach to nodal evaluation is required. Immunocytochemical markers are proposed as a method to increase the specificity of diagnosis. H.S. Ahn *et al.* [5] demonstrated that the use of markers such as galectin-3 and HBME-1 increases the specificity of cytological analysis, although positive staining is not absolute proof of malignancy without histological confirmation.

The frequency of follicular adenomas among recurrent nodules calls into question the feasibility of repeated operations. J. Chen *et al.* [6] found that most adenomas have a typical echostructure without aggressive features. He proposed a model of dynamic surveillance with repeated biopsy only when the characteristics of the node change, which reduces the number of unnecessary operations. The role of clinical and anamnestic factors (age, gender, family history, duration of the disease) was previously underestimated. G. Grani *et al.* [7] proved that their combination has a greater prognostic value than individual echographic or cytological features. Morphotyping of recurrent tumours is becoming increasingly important in risk stratification. N.P. Ohori & N. Nishino [8] proposed a classification of nodes according to the degree of proliferation and the nature of the atypia, distinguishing nodes with minimal changes, active benign proliferation, and suspected neoplasia. This approach reflects the variety of histological variants, although it has limitations for differentiating between reactive and neoplastic processes after surgery.

Thus, the diagnosis of recurrent thyroid nodules is a complex multifactorial process that requires the integration of morphological, echographic, clinical and anamnestic data. The study aimed to improve the cytological diagnosis of recurrent nodal hyperplasia by incorporating ultrasound, morphological and clinical characteristics.

Materials and Methods

The study was conducted in the period from 1998 to 2023 at the Medbud Medical Centre (MC) and the Department of Endocrine Surgery of the Kyiv City Clinical Hospital No. 3, a municipal non-profit enterprise (MNE) in Kyiv, Ukraine. Kyiv, Ukraine, with the involvement of the Laboratory of Pathological Anatomy and the Department of Ultrasound Diagnostics. The study included patients with nodular formations in the thyroid residue, detected by routine clinical and instrumental monitoring after subtotal resection or hemiresection.

The inclusion criteria were thyroid surgery, presence of neoplasms in the thyroid residue according to ultrasound, technical feasibility of fine needle aspiration biopsy (FNAB), availability of complete clinical documentation, and informative cytological specimen. Exclusions were made in cases of unsatisfactory smear quality, inability to perform control histology, or lack of a complete ultrasound examination. All participants provided written informed consent to participate in the study following the principles of the WMA Declaration of Helsinki [9] and the rules of good clinical laboratory practice (GCLP) [10].

Ultrasound imaging was performed using a *MyLab™ ClassC* device (Esaote, Italy) with a linear transducer with a frequency of 7.5-10 MHz. The standard procedure included a preliminary assessment of the anatomy of the thyroid residue, detection of nodular masses, measurement of their size in three planes, assessment of echogenicity, internal structure, presence of hypo- or hyperechoic inclusions, contours, capsule, shape, and orientation of the mass relative to the transverse axis. Calcifications (micro- or macrocalcifications), cystic components, areas of fibrosis, and the presence of echolocation shadows were analysed. Doppler examination included assessment of intra- and perinodular blood flow in colour and energy Doppler modes with determination of spectral characteristics of vessels.

FNAB was performed under ultrasound guidance using 22G needles and a 10 ml syringe. In total, 122 FNAB procedures were performed, which resulted in the preparation of 366 cytological smears (three smears from each punctured node). One of the smears was fixed in 96% ethanol for further Papanicolaou staining, the second in the air for Romanowsky-Gimza staining, and the third was reserved for possible immunocytochemical analysis. The specimens were analysed by light microscopy with multiple magnifications up to ×1,000 with the involvement of at least two independent cytologists. Interpretation was performed according to The *Bethesda* System for Reporting Thyroid Cytopathology (TBSRTC) classification, which provides a standardised approach to risk stratification [11].

Surgical interventions were performed in 69 patients: resection of the remaining thyroid tissue was performed in 52 cases, and dissection of regional lymphatic collectors was performed in 15 cases with subsequent histological verification of the removed lymph nodes. Histological examination of recurrent nodal masses was performed in all 69 cases. The average age of the examined patients was 45.3 ± 12.6 years (range 19 to 72 years). The gender distribution included 47 women (68%) and 22 men (32%). The study of anamnestic data included a

mandatory analysis of the type of primary surgical intervention and morphological characteristics of the primary pathological process: Subtotal resection was performed in 45 patients and hemi-resection in 24 patients. Primary histological findings included nodular goitre (29 cases), follicular adenoma (25 cases), and papillary thyroid cancer (15 cases).

Laboratory preparation of biological material for histology included fixation in 10% neutral formalin, embedding in paraffin, making 4-5 μm thick sections on a microtome *HM 325* (Thermo Fisher Scientific, USA), followed by staining with haematoxylin and eosin. The standards of diagnostic morphological description followed the recommendations of the WHO Classification of Tumours [12]. The analysis of lymphatic collectors was performed by ultrasound evaluation of regional lymph node groups (central, lateral and supraclavicular zones) with subsequent morphological verification in cases of surgical removal. The number of affected groups and morphological features of the lymphoid tissue were covered to objectify the degree of prevalence of the pathological process and predict the risk of neoplastic transformation.

Results

The analysis of anamnestic data formulated a generalised characteristic of patients with recurrent thyroid nodular formations. Primary surgical interventions included subtotal resection in 45 patients and hemi-resection in 24 patients. According to the results of a morphological examination of the initially removed thyroid tissue, nodular goitre (n = 29), follicular adenoma (n = 25) and papillary thyroid cancer (n = 15) were most often verified. Table 1 shows the distribution of primary operations and corresponding morphological diagnoses.

Table 1. Primary surgical interventions and morphological diagnoses in patients with recurrent thyroid tumours

Type of primary transaction	Primary cytological diagnosis	Nature of subsequent recurrence (benign/malignant)
Subtotal resection	Nodular goitre (n = 18)	Benign
Subtotal resection	Follicular adenoma (n = 14)	Benign
Subtotal resection	Papillary cancer (n = 13)	Malignant
Hemiresection	Nodular goitre (n = 11)	Benign
Hemiresection	Follicular adenoma (n = 11)	Benign
Hemiresection	Papillary cancer (n = 2)	Malignant

Notes: cases of malignant recurrence were evaluated separately according to postoperative histology
Source: compiled by the author

As can be seen from Table 1, most primary interventions were performed for benign processes (nodular goitre or follicular adenoma). Malignant tumours were detected in 15 patients at the stage of primary treatment, which led to increased oncological alertness during follow-up. Accordingly, among the recurrences, malignant neoplasms were found only in patients with primary carcinoma. The analysis of cytological specimens obtained by FNAB in patients with recurrent thyroid masses identified three main morphological phenotypes: benign proliferative changes, pseudo-recurrent inflammatory fibrous transformations, and true recurrence of the neoplastic process. These changes required differentiation from highly differentiated forms of carcinoma (Table 2).

Table 2. Cytological characteristics of lesions in the remaining thyroid tissue

Cytomorphological type of formation	Number of cases	Share	Main cytological features
Benign proliferative changes	48	69.6%	Colloid, thyroid cells without atypia, dense clusters
Pseudo relapse (lymphoid aggression)	10	14.5%	Lymphocytes, plasma cells, fibroblasts, isolated thyroid cells
True recurrence (neoplasia)	9	13%	Epithelial proliferation, fibrosis, blood supply
Severe atypia	2	2.9%	Anisocytosis, mitosis, chromatin structure disorders

Notes: a true recurrence of the neoplastic process was the re-formation of tumour tissue after surgical treatment. A pronounced atypia was not considered cancer without morphological confirmation
Source: compiled by the author

The cytological examination of the remaining thyroid tissue in the postoperative period determined a clear morphological and functional stratification of the detected focal lesions. The study of the points obtained by FNAB under the control of ultrasound Doppler revealed the presence of four main cellular patterns: benign proliferative, lymphoid-inflammatory, fibrous-remodelling and malignant atypical. Each of them has unique microscopic features that determine the diagnostic and prognostic value. The most common variant (in 69.6% of cases) was a benign proliferative pattern characterised by the presence of thyroid follicular cells tightly grouped in compact microarchitectural structures. These cells had small, rounded nuclei with uniform chromatin, without nucleolar structures.

The cytoplasm was moderately basophilic, cell boundaries were clear, and there were no mitotic figures. Colloids in the form of amorphous or droplet-like masses were present in the background. Such a picture was indicative of a stable, reactive proliferative state, which is often found in the remaining thyroid tissue after hemiresection or limited resection. Clinically, these lesions demonstrate slow or no growth, low TSH levels, no lymphadenopathy, and do not require urgent surgical correction.

The second most frequent (14.5%) was the lymphoid-inflammatory pattern, which was accompanied by the presence of many mature and immature lymphoid elements. Of diagnostic difficulty were preparations with a predominance of young lymphocyte nuclei morphologically similar to blasts, as well as the detection of plasma cells, macrophages with phagocytosed colloid, and neutrophils. These components formed dense foci with a pronounced background, whereas the thyroid epithelium was presented in the form of individual cells or small groups with slight variability of nuclei. In 30% of these cases, the detection of fibroblasts and fibrocytes was diagnostically important, confirming the presence of an active immune or granulomatous process. In clinical practice, this is associated with pseudo-recurrences in the setting of chronic Hashimoto's thyroiditis or postoperative fibrosis with intense remodelling.

The third morphotype was the fibrotic-reactive variant, detected in 13% of patients. It combined proliferative thyroid cells with a dense stromal component. It was characterised by the presence of mature fibroblasts, collagen fibres, and increased microvascular density. The vessels had an elongated shape, sometimes with pronounced endothelial swelling, which is an indirect sign of neoangiogenesis. However, in most cases, the nuclear architecture of thyroid cells remained monotonous, without signs of carcinomatous atypia. This was indicative of a reactive dystrophic process, often associated with previous surgery, local ischaemic syndrome, or postbiopsy changes. This pattern is an example of pseudotumour transformation, which can potentially be interpreted as a suspected neoplasia.

The smallest but most clinically significant cytomorphological type of malignant cellular atypia was 2.9% of cases. These samples were dominated by cells with pronounced anisocytosis, hyperchromia, mitotic activity, and frequent pseudoinclusions in the nuclei. In a few cases, nuclear furrows characteristic of *papillary thyroid carcinoma* were observed. The usual architectural distribution was disturbed, the nuclei were arranged chaotically, and the cytoplasm was vacuolated, with foci of granulation. Preparations of this type were accompanied by active vascularisation and clinical signs of palpable lymph nodes and subfibrillation. Thus, the cytological differentiation of foci in the thyroid residue should be not only quantitative but also qualitative. A thorough analysis of the cellular composition identified not only the morphology but also the pathogenetic nature of the lesion, which significantly increases the accuracy of preoperative diagnosis and reduces the risk of erroneous clinical decisions.

In the study, which included patients with recurrent thyroid nodules after surgery, assessment of the diagnostic accuracy of the *Bethesda* cytological report was emphasised. A total of 69 patients with cytological findings of categories *III* and *IV* were analysed. In the *Bethesda III* group (n = 19), thyroid cancer (7 cases) and nodular goitre (5 cases) were most often detected, which indicates the difficulty of differential diagnosis with uncertain morphological criteria. In the *Bethesda IV* group (n = 50), the main diagnosis based on histological verification was follicular adenoma (19 cases), indicating a significant number of benign lesions among cases suspected of neoplasia (Table 3).

Table 3. Types of focal lesions in patients after surgery with uncertain cytological findings *Bethesda III* and *IV*

Type of focal formation	*Bethesda III* (n = 19)	Coincidence with cytology	*Bethesda IV* (n = 50)	Coincidence with cytology	Initial cytological diagnosis	Nature of the malignant process (recurrence/new)	Node sizes (for *Bethesda IV* only)
Thyroid cancer	7	2	12	0	Papillary cancer (history/new diagnosis)	*Bethesda III*: 4 relapses, 3 new cases; *Bethesda IV*: 2 relapses, 10 new cases	11 knots ≤10 mm / 20 knots >10 mm
Follicular adenoma	4	0	19	6	Follicular adenoma	N/A	N/A
Nodular goitre	5	3	10	1	Nodular non-toxic goiter	N/A	N/A
Autoimmune thyroiditis	3	2	9	2	Lymphoid thyroiditis (Hashimoto's)	N/A	N/A

Notes: number of verified cases of cancer after re-examination in patients with *Bethesda III* (n = 19) and *Bethesda IV* (n = 50), including both recurrences and new diagnoses of malignancies, are demonstrated. Therefore, the total number of cases of PCa in this table (n = 19) exceeds the number of newly diagnosed malignancies (n = 15) reported in Table 1. The columns "Coincidence with cytology" show the frequency of complete correspondence between cytological and histological diagnoses. The cytological diagnosis detected cancer in only 2 of 19 patients (10.5%), which indicates the limited sensitivity of the *Bethesda* system in the postoperative setting. The low percentage of matches is explained by the morphological overlap of reactive, hyperplastic and neoplastic changes, as well as background inflammatory and fibrous transformations that complicate cytological differentiation. The nature of the malignant process (recurrence or neoplasm) is indicated separately
Source: compiled by the author

An in-depth analysis of the results of histological verification of recurrent nodal masses in patients after thyroid surgery shows the ambiguity of the diagnostic value of the *Bethesda* cytological classification, in particular its *III* and *IV* categories. Despite the generally accepted notion of a higher risk of malignancy in *Bethesda IV* cases, the study results demonstrate a different trend: malignant tumours in the *Bethesda III* group were detected in 37% of patients, which is significantly higher than in the *Bethesda IV* group (24%). This result indicates the complexity of cytomorphological differentiation of focal processes in the remaining thyroid tissue, especially in the context of postoperative changes and reactive transformations.

This paradox is partly explained by the presence of a morphological overlap between reactive, hyperplastic, inflammatory and neoplastic changes. Patients with *Bethesda III* often show proliferative thyroid epithelial complexes, background colloid, destructive components, infiltrates of polymorphic lymphocytes, and single atypical cells with vague signs of malignancy. These cytograms can be interpreted as benign or questionable, although they hide the early stages of the neoplastic process. Furthermore, in this group, in 15.8% of cases, background autoimmune thyroiditis was recorded, which can mask the initial signs of malignancy and create a false impression of lymphoid aggression or pseudo-recurrence.

In contrast, the *Bethesda IV* category is characterised by a significant proportion of benign neoplasms, in particular follicular adenomas (38% in this group). Such adenomas, especially those with microfollicular architecture and the presence of Ashkinase-Gurthle cells, are often cytologically interpreted as follicular neoplasia or suspected follicular carcinoma. This leads to a tendency to surgical treatment without a real oncological threat. However, despite the lower overall incidence of malignancy, cases of papillary cancer have also been reported in *Bethesda IV* patients, especially in younger patients and with nodules up to 1 cm in size, which underscores the importance of a comprehensive approach to risk stratification.

The diagnostic consistency of cytological and histological findings remained low: only 12-16% of cases had a complete agreement. This level of consistency is insufficient to make categorical decisions about treatment tactics. False negatives in the *Bethesda III* category are particularly dangerous, as they can lead to a delay in adequate oncological intervention. These data confirm the need not only to improve the standards of cytological interpretation but also to introduce immunocytochemical markers (Galectin-3, HBME-1, CK19) that differentiate between reactive and neoplastic cell complexes.

Ultrasound and Doppler evaluation of nodules in the remaining thyroid tissue revealed several characteristic echostructural features that correlated with the cytological findings of *the Bethesda III* and *IV* categories. In patients of the *Bethesda III* group (n = 19), the features traditionally associated with an increased risk of malignancy prevailed: hypoechogenicity, fuzzy contours, irregular shape and vertical location of the lesion. These characteristics were more frequently found in the subgroup with suspected neoplasia than in cases of benign cytological findings (Table 4).

Table 4. Ultrasound and Doppler signs of focal lesions in the thyroid residue

Characteristic	*Bethesda III* benign (n = 12)	*Bethesda III* neoplasia (n = 7)	*Bethesda IV* benign (n = 38)	*Bethesda IV* neoplasia (n = 12)
Hypoechoic zone	4 (33%)	4 (57%)	20 (53%)	6 (50%)
Hyperchogenic zone	2 (17%)	2 (29%)	3 (8%)	3 (25%)
Fine calcification	2 (17%)	1 (14%)	2 (5%)	3 (25%)
Continuous calcification	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Fuzzy contours	1 (8%)	2 (29%)	1 (3%)	2 (17%)
Incorrect form	0 (0%)	1 (14%)	0 (0%)	2 (17%)
Vertical positioning	0 (0%)	3 (43%)	0 (0%)	0 (0%)
Cystic degeneration	6 (50%)	1 (14%)	10 (26%)	2 (17%)
Areas of fibrosis	3 (25%)	2 (29%)	7 (18%)	2 (17%)
Intranodular blood flow enhancement	2 (17%)	4 (57%)	7 (18%)	4 (33%)

Notes: shows the absolute number of cases of each sign within the respective subgroup; in parentheses, the proportion (%) of the total number of patients in this subgroup
Source: compiled by the author

The analysis of ultrasound and Doppler characteristics of focal lesions in the thyroid residue demonstrated a clear differentiation of echostructural parameters depending on the category of the *Bethesda* cytological report. In patients with suspected neoplasia, both groups showed an increased frequency of ultrasound features considered to be factors of increased risk of malignancy: hypoechogenicity, fuzzy or irregular contours, the vertical location of the lesion in the transverse scan, the presence of microcalcifications and intranodular blood flow.

In the *Bethesda III* category, which is traditionally regarded as a group of uncertain risk, the most informative echo signals of malignancy were hypoechoicity (recorded in 57% of cases), the presence of fuzzy contours (25%) and vertical orientation of the lesion in cross-section (43%). At the same time, intranodular enhancement of blood flow was observed in 57% of lesions with suspected neoplasia, which is significantly higher than in the subgroup of benign processes of the same category. Cystic degeneration, on the contrary, prevailed in the benign

subgroup (50%), indicating its relatively high specificity in excluding malignancy.

The *Bethesda IV* group was characterised by less clear distinctions between benign and suspicious lesions. Despite a slightly higher frequency of fine calcification (25%) and fibrous changes (50%) in cases of suspected neoplasia, these signs were also found in 5-18% of cases in the benign subgroup. Hyperechogenic areas, traditionally associated with benign processes, were detected in both the benign and suspicious subgroups (8% and 25%, respectively), which reduces diagnostic significance in the context of this category. Solid calcification was recorded in only one case and can be considered a rare but highly specific marker.

Notably, indistinct contours and irregular shape of the lesion were more common in suspicious neoplasia cases in both categories, but these features showed higher sensitivity in *Bethesda III* (43% vs. 17% in *Bethesda IV*). Thus, despite the formal interpretation of *Bethesda IV* as riskier, the ultrasound picture revealed a higher concentration of malignancy-associated features in patients with *Bethesda III*. This confirms the previous morphological findings of a high degree of neoplastic transformation within a category with a less clearly defined atypia.

The analysis of patients with recurrent thyroid nodules who underwent cytological diagnosis identified the main markers that influence the clinical decision to repeat surgery. These markers are conditionally divided into three blocks: morphological (cytological) features, sonographic (Doppler ultrasound) characteristics and clinical and anamnestic parameters. The most predictive morphological signs of malignancy include severe cellular atypia, anisocytosis, mitosis and polymorphism, especially in combination with a lymphoid and fibrous background. Significant ultrasound features were found to be hypoechogenicity, blurred contours, the vertical location of the nodule in the transverse section, intranodular enhancement of blood flow, and the presence of microcalcifications. From the clinical point of view, the growth of the left stump, the appearance of cervical lymphadenopathy, young age (under 30 years), and nodes up to 1 cm in size showing growth or vascularisation were of decisive importance. The complex combination of three or more of these factors in one clinical case indicates a high risk of neoplastic transformation and is an absolute indication for surgical intervention, incorporating the feasibility of lymph node dissection. Instead, single markers without clinical progression require dynamic follow-up with control cytological or immunocytochemical analysis (Table 5).

Table 5. Comprehensive assessment of risk factors for recurrent thyroid tumours

Category of factors	Specific features	Diagnostic significance
Cytological	Cellular atypia, mitosis, anisocytosis, polymorphism	High
	Fibrotic-lymphoid background with epithelial proliferation	Average
Doppler ultrasound	Hypoechoic, fuzzy contours, vertical orientation	High
	Microcalcifications, intranodular blood supply	High
	Cystic changes, hyperechogenicity	Low (indicates benignity)
Clinical	Age <30 years, stump growth, lymphadenopathy, nodule ≤1 cm	High
	No dynamics, no vascular signal	Low

Source: compiled by the author

The systematisation of clinical, ultrasound and cytomorphological data in patients with recurrent masses in the thyroid residue has revealed close correlations between the total number of risk factors and the final treatment strategy. Cases with an uncertain cytological conclusion of *Bethesda III* and *IV* categories, which are characterised by a "grey area" of diagnosis, are notable. For these categories, a multifactorial approach to risk assessment is most justified. The results of the study indicate that the presence of three or more high-risk factors (morphological, sonographic, or clinical) in a single case is a reliable predictor of malignant transformation. In particular, the combination of hypoechogenicity, blurred contours, intranodular blood flow with pronounced cellular atypia, a background of lymphoid aggression and clinical signs (e.g., enlargement of the node in patients under 30 years of age) significantly increases the probability of detecting thyroid carcinoma during follow-up histological examination. Such patients are subject to active surgical intervention with an extended scope (including prophylactic dissection of cervical lymph nodes).

In contrast, in the presence of single or isolated features (e.g., fibrosis alone or single microcalcification without clinical dynamics), a conservative approach with dynamic follow-up is acceptable. In these cases, it is advisable to repeat FNAB after 6 months, as well as the use of immunocytochemistry to differentiate between pseudoatypia and early manifestations of neoplasia. In *Bethesda III*, the results showed a more aggressive profile of ultrasound changes, as well as a higher percentage of verified malignancy compared to category *IV*, suggesting a potential underestimation of this group in existing protocols. This requires increased oncological alertness even in cases of shapeless morphology accompanied by severe sonographic pathology. In this context, the *Bethesda IV* category often demonstrated a high rate of benign lesions (especially follicular adenomas), albeit with clear echostructural risk markers (indistinct contours, calcifications, irregular shape). Thus, the derived risk assessment model based on comprehensive stratification avoids overdiagnosis, which leads to unnecessary reoperation, and underdiagnosis, which can lead to delayed detection of the cancer process. This approach facilitates

individualised clinical decision-making for each patient, covering the morphological, echographic and clinical profile within the framework of an integrated diagnostic model.

Discussion

The study conducted a comprehensive analysis of the diagnostic efficacy of the *Bethesda* classification in the context of recurrent thyroid nodules after surgery. One of the key findings was the detection of a higher level of malignancy among cases of the *Bethesda III* category compared to *Bethesda IV*, which contradicts the established ideas about the grading of oncological risk. This trend is consistent with the data of M. Kujdowicz *et al.* [13], which indicate that morphological uncertainty in the *Bethesda III* category often hides early forms of neoplastic transformations. At the same time, D. Suster *et al.* [14] argued that the *Bethesda IV* category has the highest prognostic unfavourability, but the results of this study indicate the need to revise such ideas incorporating the ultrasound and cytomorphological characteristics of the nodes.

The predominance of malignant processes in the *Bethesda III* group is partly explained by the cytomorphological overlap of reactive and neoplastic changes, especially in the setting of autoimmune thyroiditis. M. Melo *et al.* [15] addressed the difficulty of interpreting thyroid cells in chronic inflammation, which increases the risk of misdiagnosis. At the same time, according to M.T. Macvanin *et al.* [16], the impact of the autoimmune process is secondary, and the level of malignancy in the *Bethesda III* category is overestimated. However, the analysis revealed a significant frequency of hypoechogenicity, vertical nodule orientation, and concomitant cytological atypia, which indicates a real oncological risk in this category. Histological verification of the material showed a high percentage of benign follicular adenomas among the *Bethesda IV* nodes. This correlates with the findings of L. Giovanella *et al.* [17] and W. Chatchomchuan *et al.* [18], which indicate the redundancy of surgical interventions in such cases and the need to improve the criteria for cytological suspicion.

Of particular importance in the diagnosis are clear echographic markers of malignancy, among which hypoechogenicity, fuzzy contours, vertical orientation and intranodular enhancement of blood flow dominated. These characteristics, according to M. Ali *et al.* [19] and Z. Xu *et al.* [20], have high sensitivity in detecting malignancy and may in some cases exceed morphological criteria in diagnostic information content. At the same time, in the *Bethesda IV* category, echographic features had lower specificity, which is consistent with the results of E. Haaga *et al.* [21], noting that hyperechoic areas, calcifications, and fibrosis are not reliable markers of malignancy. Contradictory data were presented by P. Bhagwat & S. Pomplun [22], who emphasised the possible significance of calcifications, but in this study, they were more common in benign nodes, which reduced their predictive value.

The cytological analysis identified four main morphotypes of nodes. The most abundant was the benign proliferative type, which fully corresponds to the characteristics proposed by I. Kholová *et al.* [23]. The detection of a lymphoid-inflammatory pattern in 14.5% of cases confirms the hypothesis of V.J. Bernet & A.-M. Chindris [24] regarding the role of chronic thyroiditis in the formation of pseudo-recurrence, although L. Chouhan *et al.* [25] noted the risk of missed malignancy. The fibrotic remodelling type, found in 13% of patients, was interpreted mainly as reactive, according to Y. Ito *et al.* [26], who associated it with tissue restructuring after surgery. However, Y. Alwelaie *et al.* [27] suggested that this morphotype may be associated with the early stages of neoplastic processes. In this study, morphological signs of malignancy were not detected: structural orderliness of collagen fibres, absence of cellular atypia, mitotic activity and neoangiogenesis were observed, which can be used to interpret these lesions as pseudotumour fibro-dystrophic transformations that do not require aggressive surgical tactics.

The smallest, but most significant group was made up of cases with severe cytological atypia (2.9% of samples). The detected nuclear furrows, anisocytosis, and mitoses met the criteria described by A. Harahap & C. Jung [28] for papillary cancer. Verification by histological data confirmed the diagnosis of oncopathology, which coincides with the approach proposed by H. Rahmati-Holasoo *et al.* [29]. Comprehensive risk assessment revealed three main groups of predictors: morphological, sonographic and clinical factors. The presence of three or more factors significantly increased the risk of malignancy, which is consistent with the multivariate analysis model described by E.A. Hall *et al.* [30]. At the same time, the critique of Z. Tang *et al.* [31] regarding the complexity of such models does not address the specifics of the postoperative transformation of thyroid tissue.

The age group of patients under 30 years, where an increased incidence of papillary cancer was observed even with small nodule sizes, was emphasised. This pattern is consistent with the data of M. Kumar *et al.* [32], highlighting the increased oncogenetic vulnerability of young people due to the activation of the *MAPK* and *PI3K/AKT* signalling pathways. The observations of J. Townsend & M. Perez-Machado [33] regarding the significance of nodule size were partially confirmed, as it was found that a combination of small diameter and high vascularisation as a sign of neoangiogenesis is more important. Improving diagnostic accuracy can be achieved by using immunocytochemical markers. In particular, the use of *Galectin-3*, *HBME-1*, and *CK19* verified the initial stages of neoplastic transformations, as described by M.-H. Wu *et al.* [34]. This is especially relevant for the *Bethesda III* category, where background inflammatory changes can mask true neoplasia. Thus, the results of the study justify the need to revise the risk stratification in the *Bethesda III* and *Bethesda IV* categories. Increased oncological alertness should primarily concern the Bethesda *III* category, while *Bethesda IV* requires a cautious assessment given the predominantly benign nature of the changes. The proposed multifactorial model can be used to optimise treatment tactics,

minimising the risks of over- and underdiagnosis in patients with recurrent thyroid nodules.

Conclusions

The *Bethesda III* and *IV* cytological classification has limited prognostic value in the diagnosis of recurrent thyroid nodules. A higher incidence of malignancy in the *Bethesda III* category (37%) compared to *Bethesda IV* (24%) indicates an underestimation of cancer risk in cases of uncertain cytomorphology. The morphological overlap of reactive, hyperplastic, inflammatory and neoplastic changes makes it difficult to reliably differentiate nodular lesions. Autoimmune thyroiditis masks early signs of malignancy, which affects the accuracy of cytological analysis. Echostructural features (hypoechogenicity, fuzzy contours, vertical location) were found to be important predictors of malignancy in the *Bethesda III* category. The presence of intranodular blood flow enhancement on Doppler increases the reliability of sonographic risk assessment. Four main cytological patterns were identified, which clarify the nature of recurrent nodal lesions. The benign proliferative type is the most common cytological variant among recurrent nodules. Cases of malignant atypia were detected in 2.9% of samples, which confirms the critical need for careful morphological analysis. A multifactorial approach (ultrasound + cytology + clinical dynamics) is optimal for risk stratification and selection of treatment tactics. Limitations of the study include a small sample (69 patients) and the lack of multicentre confirmation of the results, as well as limited study of metastasis to surrounding organs and tissues. The integration of genetic, immunohistochemical and molecular markers to improve the diagnosis of recurrent nodal tumours is a promising area.

Acknowledgements

None.

Funding

None.

Conflict of Interest

None.

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Цитологічні особливості діагностики рецидивних вузлових гіперплазій щитоподібної залози

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Анотація. Метою дослідження було вдосконалення діагностичних підходів до оцінки рецидивних вузлових утворень у залишеній тканині щитоподібної залози після хірургічного лікування, з урахуванням морфологічних, ультразвукових та клініко-анамнестичних ознак. Методологія включала обстеження 69 пацієнтів із рецидивними утвореннями, класифікованими за категоріями *III* та *IV* системи *Bethesda*, яким виконували тонкоголкову аспіраційну пункційну біопсію під контролем ультразвукової візуалізації, допплерографічне дослідження з оцінкою кровотоку, гістологічну верифікацію та імуноцитохімічне фарбування. Результати показали, що у групі *Bethesda III* наявність злоякісних пухлин підтверджено у 37 % випадків, тоді як у *Bethesda IV* – лише у 24 %, що ставить під сумнів традиційні уявлення про ризик неоплазії у цих категоріях. У *Bethesda III* домінували ознаки, асоційовані з малігнізацією: гіпоехогенність (57 %), вертикальна орієнтація вузла (43 %), інтранодулярний кровотік (57 %), нечіткі або нерівні контури (25 %). У групі IV частіше спостерігались фолікулярні аденоми (38 %) з доброякісними ехоструктурними ознаками. Виділено три морфотипи: проліферативний (69,6 %), псевдорецидивний запально-фіброзний (14,5 %) і справжній неопластичний (13 %), причому виражена клітинна атипія зафіксована у 2,9 % випадків. Встановлено низьку відповідність між цитологічними та гістологічними результатами (12-16 %), що обґрунтовує потребу в комплексній діагностиці. Виявлено, що наявність трьох або більше незалежних факторів ризику суттєво підвищує ймовірність неопластичної трансформації. Практичне значення дослідження полягає у формуванні багатофакторної системи стратифікації, яка дозволяє підвищити точність передопераційної діагностики, обґрунтувати вибір хірургічної тактики та знизити частоту хибнодіагностичних рішень у клінічній практиці

Ключові слова: клітинна атипія; гіпоехогенна структур; фіброзна трансформація; стратифікація ризику; неопластична трансформація

International Journal of Medicine and Medical Research

Journal homepage: https://ijmr.com.ua/
Volume 11, No. 1. 2025

UDC 616.71:615.822:615.832.6
DOI: 10.63341/ijmmr/1.2025.105

Article's History:
Received: 19.02.2025; Revised: 25.04.2025; Accepted: 27.05.2025

Review of modern approaches to the treatment of patients with musculoskeletal disorders and diseases using traditional Chinese medicine (TCM) – acupuncture

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Abstract. The relevance of the study is due to the substantial spread of diseases of the musculoskeletal system and the need for effective non-drug treatment methods. Its purpose was to analyse scientific data on clinical efficacy, physiological mechanisms of action, and innovative approaches to the use of acupuncture in the treatment of musculoskeletal pathologies. The study was a literature review of scientific publications of 2019-2025 using a comprehensive three-stage methodological approach, which included the analysis of published data on the clinical effectiveness of acupuncture on standardised scales and questionnaires, generalisation of research on neurophysiological mechanisms of action, and systematisation of modern innovative protocols presented in the scientific literature. An analysis of clinical studies showed that the effectiveness of acupuncture varies depending on techniques and nosological forms, with the highest level of evidence for chronic lower back pain and osteoarthritis. After a course of acupuncture (2-3 sessions per week, with a total duration of 4-8 weeks), a decrease in pain intensity on the visual-analogue scale was recorded by 2.87-4.1 points and an improvement in functional indicators by 9.5-20.3%. Based on the generalisation of the data, two theoretical models were formulated: a triune concept of therapeutic action of acupuncture, which covers physiological (reduction of pain symptoms), functional (restoration of motor activity), and psychoemotional (normalisation of psychological state) components and an integrative model of effectiveness in chronic pain, which includes short-term anaesthesia through neuromodulation, improvement of local microcirculation, and functional restoration of muscle-fascial structures. The examination of neurophysiological mechanisms demonstrated that the therapeutic effect of acupuncture is mediated by activation of the endogenous opioid system, modulation of inflammatory cytokines, and neuroplastic changes in brain networks, which is confirmed by neuroimaging methods. The study also systematised current innovations in acupuncture practice, including optimisation of treatment protocols, group forms of therapy, and telemedicine models. Integrative approaches that combined acupuncture with traditional treatments showed better results in 83% of the analysed studies compared to monocomponent interventions. The results of the study confirm the clinical effectiveness of various acupuncture techniques in diseases of the musculoskeletal system, which is justified by the complex effect on the neurophysiological mechanisms of pain modulation and proves the feasibility of including the method in standard therapeutic protocols

Keywords: chronic pain; functional state; therapeutic effect; pain syndrome; integrative approach

Introduction

Due to the limitations of conservative and surgical methods of treatment of the musculoskeletal system and the associated risks and long-term recovery, interest in milder complex approaches is growing; acupuncture, as a key component of traditional Chinese medicine (TCM), activates natural recovery processes, considers the individual characteristics of the patient and the general condition of the body, so it becomes a popular means of modern rehabilitation and prevention. The World Health Organisation (WHO) estimates that about 1.71 billion people (more

Suggest Citation:
Mazur Ya. Review of modern approaches to the treatment of patients with musculoskeletal disorders and diseases using traditional Chinese medicine (TCM) – acupuncture. Int J Med Med Res. 2025;11(1):105–20. DOI: 10.63341/ijmmr/1.2025.105

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than 20% of the world's population) suffered from musculoskeletal disorders in 2020, with lower back pain, arthritis, and osteoarthritis being the most common [1]. In Ukraine, according to P.M. Skrypnykov *et al.* [2], the prevalence of childhood diseases, including musculoskeletal diseases, increased from 1,253.0 cases per 1,000 children in 1994 to 1,748.0 cases in 2017, which is 41% higher, and 7.82% of periodontitis exacerbations were detected in internally displaced persons after 2022.

A. Rademacher [3] considered the problem of severe symptoms that accompany cancer treatment, in particular pain, fatigue, depression, and nausea. The researcher evaluated the safety and effectiveness of acupuncture as an integrative therapy in patients with cancer. The main focus was on symptoms that occur during treatment, especially in recipients of haematopoietic cell transplants. In conclusions of A. Rademacher, it is stressed that acupuncture is a safe method to reduce the burden of symptoms in this patient population. D. Akçalı *et al.* [4] raised the problem of treating various forms of headache, including migraines, which is a serious and common condition that often requires long-term medical treatment with potential side effects. The authors assessed the effectiveness of acupuncture as an adjunct or primary treatment for primary headaches. The conclusion of their study was the claim that acupuncture is a safe, cost-effective, and effective method in most cases of treating headaches.

The main problem in the study by P. Patel *et al.* [5] was a treatment for chronic pain that is often resistant to traditional pharmacotherapy. The researchers analysed the effectiveness of acupuncture in reducing chronic pain, underlining the importance of this method in the context of long-term treatment of patients who do not receive sufficient relief with standard means. In their findings, the authors agreed that acupuncture, despite long-standing criticism and treatment as a pseudomedicine, provides substantial long-term relief of symptoms in patients with chronic pain. In addition, I. Urits *et al.* [6] explored the use of acupuncture to treat migraines in an attempt to address the side effects of traditional pharmacological treatments. They reviewed the literature and analysed clinical studies on the effectiveness of acupuncture in treating migraine pain. Their results showed that acupuncture is a safe and potentially effective method for reducing the frequency and intensity of migraine attacks, and also has fewer side effects compared to pharmacotherapy.

In their comprehensive review, S.E. Iskandarani & G. Deng [7] addressed the problem of insufficient symptom control in patients with haematological malignancies, finding that acupuncture effectively reduces pain and nausea, although the results for symptoms such as neuropathy, fatigue, or pruritus are less convincing. This alligns with the results of J. Halámková *et al.* [8], who reviewed the use of acupuncture to treat symptoms in cancer patients in accordance with the international guidelines of the National Comprehensive Cancer Network (NCCN). Their study confirmed a positive effect on pain, nausea, and vasomotor disorders, while emphasising the need for a clearer definition of indications and contraindications to ensure the safe use of the method.

J. Zhu *et al.* [9] analysed the history, current state, and mechanisms of action of acupuncture, dealing with the scientific justification of this traditional practice. Their work confirmed the presence of positive effects, but noted that additional molecular studies are needed to accurately explain the mechanisms of action. This scientific basis is crucial for the wider adoption of acupuncture in modern medical practice. In the study on technological innovations, G. Litscher [10] investigated the use of artificial intelligence (AI) in acupuncture practice, focusing on integrating modern technologies to improve diagnostic accuracy. The results of this publication demonstrate that AI has the potential to improve the methodology, but the researcher underscored the critical importance of preserving the human factor, empathy, and ethical standards in the treatment process. This opens up promising areas for modernising traditional acupuncture practices, while emphasising the need to preserve their fundamental therapeutic principles.

Previous studies have substantial limitations in differentiating the effectiveness of different acupuncture techniques in specific nosological forms of musculoskeletal diseases. There is insufficient integration of neuroimaging, molecular, and clinical data to form a holistic model of the therapeutic effects of acupuncture. Innovative models of acupuncture care also remain poorly understood, which limits their availability and integration into modern health systems. Although many scientific works are devoted to acupuncture, research focused specifically on modern approaches to the treatment of the musculoskeletal system using TCM-acupuncture was not enough, which led to the need for this systematic review of the literature.

This paper aimed to systematise modern approaches to the treatment of the musculoskeletal system using acupuncture in the framework of TCM. Study objectives: analyse the clinical effectiveness of various acupuncture techniques in the main diseases of the musculoskeletal system with determination of the level of evidence for each technique; systematise the neurophysiological mechanisms of acupuncture action based on experimental and neuroimaging studies; investigate modern innovations and adaptations of traditional acupuncture methods, including optimisation of treatment protocols and new models of acupuncture care.

Materials and Methods

The study was presented as a literature review of scientific publications and concentrated on three key aspects of the use of acupuncture in pathologies of the musculoskeletal system. The clinical effectiveness of various acupuncture techniques was chosen as the first fundamental aspect, as it provides an empirical basis for further theorising. As part of this aspect, data from published studies by other authors on the effect of acupuncture on pain intensity, functional indicators, and quality of life parameters of patients were

analysed using standardised international scales and questionnaires. The methodological approach included a critical analysis of literature data on the effectiveness of acupuncture in various nosological forms of musculoskeletal diseases-osteoarthritis of large joints, chronic lower back pain, myofascial pain syndrome, rheumatoid arthritis, and fibromyalgia. Quantitative performance indicators presented in peer-reviewed publications of other researchers were analysed, with a particular focus on studies with follow-up periods of 4 to 12 weeks and additional evaluation points after 6 and 12 months to determine long-term effects. The theoretical analysis considered the results of comparing the effectiveness of acupuncture in relation to various control interventions presented in primary studies.

The neurophysiological mechanisms of action of acupuncture were viewed as the second key aspect providing scientific justification for the observed clinical effects. This aspect was highlighted to establish a causal relationship between acupuncture and physiological processes, focusing on the central mechanisms of analgesia, modulation of inflammatory processes, and neuroplastic changes that occur under the influence of acupuncture. The methodological approach focused on the investigation of physiological mechanisms and neurobiological bases of acupuncture effectiveness. Publications covering the results of neuroimaging studies, in particular, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), which displayed changes in the activity of specific areas of the brain under the influence of acupuncture, were examined. Studies on the activity of structures such as the anterior cingulate gyrus, insula, thalamus, prefrontal cortex, and periaqueductal grey matter, which play a major role in the formation and modulation of pain, were analysed in detail. In parallel, the molecular cellular mechanisms of acupuncture action were examined: neurotransmitter systems (opioid, serotonergic, noradrenergic), gamma-aminobutyric acid (GABA)-ergic system, immunological parameters (pro- and anti-inflammatory cytokines), vasoactive substances, and tissue regeneration factors. A comprehensive analysis method was used to integrate data on local, segmental, and systemic effects of acupuncture stimulation.

Modern innovative adaptations of traditional methods were chosen as the third central aspect that reflects the evolution of the method in the context of modern evidence-based medicine and is critical for the practical application of theoretical knowledge. The methodological approach included the investigation of modern innovations and scientifically based adaptations of traditional acupuncture methods. Publications describing new treatment protocols, combined approaches (acupuncture in combination with physical therapy, pharmacological treatment, massage, and thermal acupuncture), personalised schemes, and innovative models of care (group acupuncture, telemedicine methods) were analysed. Current trends in optimising the parameters of acupuncture stimulation were reviewed: the frequency of sessions (from 1 to 5 times a week), the duration of the course (from 2 to 12 weeks), the choice of location of points (local, distal, microsystem) and stimulation techniques (manual, electro-, laser acupuncture).

The combination of these three aspects allowed forming an integrative theoretical model that connects empirical data on efficiency with a scientific understanding of the mechanisms of action and determines promising directions for the development of the method. When describing the clinical effectiveness of acupuncture, the provisions of Guideline 00393 [11] were accounted for, which defines acupuncture as a therapeutic method that can improve the results of general treatment. This integrated approach was chosen due to the lack of complete theoretical concepts in the modern literature that combine the clinical, physiological, and methodological aspects of acupuncture. A systematic approach was used to process and analyse information, enabling the comparison and integration of data from heterogeneous sources. Methods of critical analysis of scientific publications were used, regarding their methodological quality, sample size, availability of adequate control groups, and statistical reliability of the results obtained. For systematisation and visualisation of data, tables were used that reflected the comparative effectiveness of various acupuncture techniques in specific nosological forms and neurophysiological mechanisms of their action, with an appropriate level of scientific evidence.

Results and Discussion

Clinical effectiveness of acupuncture in various categories of diseases of the musculoskeletal system. An analysis of clinical trials (2019-2025) indicates the differentiated effectiveness of different acupuncture techniques in the treatment of chronic lower back pain. H. Tan *et al.* [12] conducted a randomised controlled trial comparing acupuncture using sensitised points and routine integrative acupuncture, demonstrating a decrease in Visual Analogue Scale (VAS) scores by 2.87 ± 1.52 points in the sensitised acupuncture group versus 2.32 ± 1.36 points in the routine acupuncture group ($p = 0.042$). The functional state of the Roland-Morris questionnaire improved by 4.71 ± 3.16 and 3.57 ± 2.74 points, respectively. Notably, the method of sensitised acupuncture, although it demonstrates higher effectiveness, requires a doctor to have a deeper knowledge of the anatomical and topographic features of the location of biologically active points, which is a certain challenge for the widespread introduction of the technique into everyday clinical practice in Ukraine.

Comparative analysis of the effectiveness of electroacupuncture and manual acupuncture, conducted by J. Comachio *et al.* [13] in a clinical study of 66 patients, demonstrated the equivalence of both methods in reducing pain intensity after 6 weeks of therapy: a decrease on the VAS scale by 3.14 ± 0.52 points and 3.03 ± 0.47 points, respectively (the difference did not reach statistical significance, $p = 0.238$). Disability according to the Oswestry questionnaire decreased by $9.5 \pm 2.1\%$ in the electroacupuncture group and $8.9 \pm 1.9\%$ in the manual acupuncture group, confirming the absence of clinically substantial advantages of electrical

stimulation over classical manual techniques. This conclusion is of great practical importance for Ukrainian medical institutions, as it allows the effective use of traditional manual acupuncture without the need to invest in expensive electronic equipment for electroacupuncture, which is especially important in conditions of limited funding.

A long-term comparison of the effectiveness of different methods is particularly important. M.J. Dastjerdi *et al.* [14] a 2024 randomised trial (n = 112) compared acupuncture, venesection, and physical therapy with a follow-up period of 12 months. Acupuncture showed a more sustained reduction in pain after 12 months (a decrease in VAS by 3.46 ± 0.51 points from baseline) compared to physical therapy (2.13 ± 0.48 points, $p < 0.01$), where there was a gradual weakening of the therapeutic effect after 6 months. Functional status on the Oswestry index was also better in the acupuncture group after 12 months (improvement of 15.7 ± 3.2%) compared to physical therapy (10.2 ± 2.9%, $p < 0.01$). The theoretical basis for the long-term effect of acupuncture, in contrast to physiotherapy, can be its complex effect on the central mechanisms of pain modulation, and not just on local tissue processes. This feature provides for considering acupuncture as the method of choice for patients who need long-term control of chronic pain, in particular, among participants in military operations and victims of military operations in Ukraine.

The frequency of stimulation during electroacupuncture turned out to be a less important factor of effectiveness than the very fact of the procedure, which demonstrates the priority importance of the basic mechanisms of acupuncture influence over the parameters of stimulation. S.F. Torres *et al.* [15], in a triple-blind placebo-controlled study of elderly patients, identified no statistically significant difference between the low-frequency (2 Hz) and high-frequency (100 Hz) electroacupuncture groups in pain reduction (VAS improvement of 2.93 ± 0.71 and 3.04 ± 0.67 points, respectively, $p = 0.542$). Both groups, however, substantially outperformed placebo acupuncture (1.12 ± 0.59 points, $p < 0.001$), which highlights the specificity of the therapeutic effect of acupuncture intervention. These data allow formulating an important theoretical postulate: the effectiveness of acupuncture is based on deep neurophysiological mechanisms of activation of endogenous pain control systems, and not on specific stimulation parameters. The practical value of this provision is to simplify the clinical protocols of electroacupuncture, which can be adapted to different clinical conditions without loss of effectiveness.

A substantial contribution to understanding the long-term effectiveness of acupuncture was made by the pragmatic BackInAction study conducted by L.L. DeBar *et al.* [16] on elderly patients. The study showed that the addition of acupuncture to standard medical care improved the functional state of the back on the Roland-Morris scale at 6 months by 3.84 ± 0.47 points versus 2.11 ± 0.43 points in the control group ($p < 0.001$), and at 12 months the difference was 3.26 ± 0.51 versus 1.97 ± 0.49 ($p < 0.01$). This result is of particular clinical importance, as it demonstrates the stability of the therapeutic effect over time, which is critical for chronic conditions. Notably, the methodological quality of this study determines the high reliability of the results obtained, which creates good reasons for introducing acupuncture into the national protocols for the treatment of chronic pain in Ukraine as an additional method, which can substantially increase the effectiveness of standard therapy.

Researching innovative acupuncture techniques, T. Li *et al.* [17] evaluated the clinical efficacy of silver needle warm acupuncture in the treatment of acute pain due to lumbosacral disc herniation. This modified technique resulted in a 4.1 ± 0.7-point reduction in VAS pain compared to 3.2 ± 0.6 points in the conventional warm acupuncture group ($p < 0.01$). Functional improvement on the Oswestry index was also more pronounced in the experimental group (20.3 ± 4.1% vs. 14.7 ± 3.8%, $p < 0.01$), which indicates the potential of improved acupuncture techniques to increase clinical efficacy. Although silver needle warm acupuncture demonstrates higher efficiency, its implementation in Ukraine has certain limitations due to the higher cost of materials and the need for additional training of specialists. However, the method can be considered promising for specialised pain treatment centres and rehabilitation facilities, especially for patients with severe pain syndrome who are immune to standard therapy.

An important aspect of the effectiveness of acupuncture is the duration of its effect. X. Lv *et al.* [18], in a cross-randomised study including women with chronic non-specific lower back pain, established that although acupuncture greatly improved back muscle endurance (+29.4 ± 6.7 seconds in the Biering-Sorensen test, $p < 0.001$) and local blood microcirculation (increased perfusion by 35.7 ± 8.9%, $p < 0.01$), the duration of this effect was limited to 9 minutes after the session, indicating the need for regular repeated treatment to maintain results. This aspect highlights an important drawback of the method – the short duration of the direct physiological effect, which requires the development of optimal protocols for repeated interventions. Thereby, the determined increase in microcirculation is of substantial theoretical importance since it complements the neurophysiological mechanisms of acupuncture with a vascular component, which may be critical in the treatment of ischemic pathologies of the musculoskeletal system common among older Ukrainian patients.

Based on the analysis of the presented studies, an integrative theoretical model of the effectiveness of acupuncture in chronic lower back pain can be formulated. This model includes three key components: short-term anaesthesia through neuromodulation, improvement of local microcirculation, and functional restoration of musculofascial structures. The short-term effect is realised mainly through activation of endogenous opioid systems and inhibition of nociceptive transmission, as evidenced by a rapid but short-term reduction in pain scores in a study by X. Lv *et al.* [18]. Instead, the long-term effect, most pronounced in the papers of L.L. DeBar *et al.* [16] and M.J. Dastjerdi *et*

al. [14], is likely associated with cumulative effects on neuroplasticity and tissue remodelling. The proposed triune model expands the theoretical understanding of the mechanisms of action of acupuncture and explains its versatile therapeutic effects. Unlike the traditional Eastern concept of meridians and energy balance, this model is based on modern scientific ideas about neurophysiological, microcirculatory, and functional mechanisms, which makes it more acceptable for integration into the Western scientific paradigm and the Ukrainian healthcare system.

The analysis of these clinical data allows expanding the theoretical understanding of the effectiveness of acupuncture not only in the context of treating lower back pain, and also in relation to other diseases of the musculoskeletal system. The American College of Rheumatology and the Arthritis Foundation have included acupuncture in the clinical guidelines for the treatment of osteoarthritis, positioning it as one of the possible components of a comprehensive therapeutic strategy, which indicates the recognition of the method in the global medical community [19]. Network meta-analysis performed by R.-X. Zhu *et al.* [20] demonstrated the superiority of electroacupuncture and the combination of acupuncture with thermal acupuncture in gonarthrosis, which indicates the feasibility of using combined methods. These recommendations are of direct importance for clinical protocols, since osteoarthritis of the knee joint is one of the most common degenerative joint diseases in Ukraine. The introduction of acupuncture as a component of complex therapy for this condition can substantially improve treatment outcomes and reduce the need for pharmacological interventions, which is of particular importance for elderly patients with comorbid conditions and an increased risk of side effects from drug therapy.

Regarding rheumatoid arthritis, a systematic review of J. Li *et al.* [21] identified a limited evidence base, although some studies indicate the possibility of achieving symptomatic relief. In fibromyalgia, according to the meta-analysis, conducted by X.-C. Zhang *et al.* [22], acupuncture shows an advantage over placebo in short-term pain reduction and in myofascial pain syndrome, as shown by M.J. Navarro-Santana *et al.* [23], the dry needle technique is effective. Of particular interest to the Ukrainian healthcare system is the use of acupuncture for myofascial pain syndrome, the prevalence of which has substantially increased among military personnel and civilians as a result of military operations. The dry needle technique, as a less resource-intensive alternative to traditional acupuncture, can be implemented in the field and in mobile medical units.

Summarising, a comprehensive analysis of systematic reviews devoted to the use of acupuncture in chronic pain syndromes focuses on the existing gap between the accumulated scientific data and their implementation in real clinical practice [24]. Acupuncture, in various modifications, demonstrates clinically substantial efficacy in chronic lower back pain with the highest level of evidence for short-term pain reduction (mean reduction of VAS by 2.87-4.1 points) and improvement of functional performance (reduction of disability according to Oswestry by 9.5-20.3%). Repeated courses of treatment are necessary to achieve a lasting, long-term effect, which is confirmed by the results of studies with a long follow-up period. Based on the synthesis of data from relevant systematic reviews and meta-analyses, Table 1 is presented below, which summarises the comparative effectiveness of various acupuncture techniques and related methods in the treatment of common diseases of the musculoskeletal system.

Table 1. Comparative effectiveness of various acupuncture techniques in major diseases of the musculoskeletal system

Diseases of the musculoskeletal system	Traditional manual acupuncture	Electroacupuncture	Dry acupuncture	Laser acupuncture	Level of evidence (common to acupuncture in this condition)
Chronic lower back pain	++	+++	++	+	High
Osteoarthritis of the knee joint	++	+++	+	++	High
Pain in the cervical spine	++	++	+++	+	Medium/High
Fibromyalgia	+	++	+	+	Low/Medium
Rheumatoid arthritis	+	++	(+)	+	Low/Medium
Epicondylitis	++	+	+++	++	Medium
Myofascial pain syndrome	++	++	+++	+	Medium

Notes: + + + high relative efficiency or strong evidence; ++ medium efficiency or moderate evidence; + low efficiency or limited evidence; (+) the evidence is very limited or contradictory. The level of evidence refers to the overall effectiveness of acupuncture techniques for a given condition, not to comparisons between techniques
Source: compiled by the author based on R.-X. Zhu *et al.* [20] and L. Cavaggioni *et al.* [24]

Analysis of the presented data demonstrates the differential effectiveness of acupuncture techniques depending on the pathology. In particular, electroacupuncture is most effective in treating chronic lower back pain and knee osteoarthritis, which correlates with a high overall level of evidence for these conditions. This indicates the potential advantage of electrical stimulation in pathologies associated with degenerative-dystrophic processes. However, dry acupuncture shows the best results in the treatment of pain in the cervical spine, epicondylitis, and myofascial pain syndrome, which indicates the special effectiveness of this technique in pathologies associated with trigger points and local muscle dysfunction. This differentiation of techniques according to their effectiveness in various pathologies

allows developing a personalised approach to the appointment of acupuncture, accounting for the specific disease and its pathophysiological features. For the Ukrainian healthcare system, this means the possibility of optimising available resources by directing specific techniques to those pathologies where they demonstrate the highest efficiency.

Traditional manual acupuncture is characterised by moderate effectiveness in most diseases, which confirms its versatility as a basic therapeutic approach. Laser acupuncture, on the other hand, shows relatively lower effectiveness in most pathologies, with the exception of epicondylitis. Special attention should be paid to the insufficient level of evidence regarding the effectiveness of acupuncture techniques in rheumatoid arthritis, fibromyalgia, and plantar fasciitis, which indicates the need for further research in these areas. In the clinical context, these data substantiate a differentiated approach to the choice of acupuncture techniques depending on the nature of the pathology and the evidence base, arguing for the priority use of the most effective techniques for a specific disease of the musculoskeletal system.

Analysis of randomised controlled trials shows that the effectiveness of acupuncture substantially depends on the parameters of treatment protocols. Y.-J. Chen *et al.* [25], through a systematic analysis of clinical studies, determined that the optimal frequency is 2-3 sessions per week, and the total duration of the course – 4-8 weeks. Clinical efficacy reaches a plateau when these parameters are exceeded, which indicates the existence of a certain therapeutic saturation threshold. This phenomenon is confirmed by X.Zou *et al.* [26], demonstrating that increasing the number of sessions above the recommended number did not lead to a statistically significant improvement in results. This feature is associated with the two-phase activation of endogenous antinociceptive systems, when the initial phase is characterised by a progressive increase in the effect, and the second – by relative stabilisation of the response against the background of adaptation of neuroimmune mechanisms. The optimal parameters of acupuncture protocols are of critical importance for the introduction of the method into Ukrainian medical practice, as they allow maximising results with the rational use of limited resources of the healthcare system. Maintaining an optimal session frequency (2-3 per week) and course duration (4-8 weeks) can provide the best cost-effectiveness ratio, which is essential in wartime and economic constraints.

E. Ginnerup-Nielsen *et al.* [27], in a prospective cohort study, established that patients with rheumatic diseases who received acupuncture displayed a substantial improvement in quality of life on the EQ-5D-3L scale compared to the control group. Subgroup analysis indicated the highest efficacy in patients with fibromyalgia and rheumatoid arthritis. For osteoarthritis of the hip joint, S.C. Chan & J.P. Engkasan [28] found a substantial reduction in pain intensity in VAS and an improvement in functional performance in the Western Ontario and McMaster universities Osteoarthritis Index (WOMAC) after a course of acupuncture. These changes correlated with improved quality of life in SF-36, especially in the areas of physical functioning and social activity. The results of these studies point to an important aspect of the effectiveness of acupuncture – its impact on the overall quality of life, which goes beyond simple pain relief. For Ukrainian patients with chronic diseases of the musculoskeletal system, especially those affected by the hostilities, this complex impact on the quality of life can be of particular importance, contributing not only to physical but also to psychosocial recovery.

It is important to compare acupuncture with other treatments. In a randomised clinical trial, the Integrative Medicine Program for Advanced Cancer Treatment (IMPACT), acupuncture and massage were compared in reducing pain in patients with advanced cancer by A.S. Epstein *et al.* [29]. Both methods showed a statistically significant reduction in pain intensity, with no substantial difference between the two. Thereby, acupuncture has shown better results in reducing fatigue and improving sleep quality. K. Trinh *et al.* [30] established a differential effectiveness of acupuncture in different localisations of pain syndrome. For pain in the hands and wrists, the greatest effect was observed in rheumatoid arthritis and tenosynovitis, while in osteoarthritis of the small joints of the hand, the effect was less pronounced. The researchers also noted improvements in both functional status and overall quality of life in patients with foot and ankle pain syndromes, especially plantar fasciitis and Achilles tendinitis. Comparative analysis of the effectiveness of various non-pharmacological treatment methods is crucial for the formation of comprehensive rehabilitation programmes. In particular, the combination of acupuncture with massage and physical therapy can provide a synergistic effect in the treatment of patients with polymorphic pain syndromes and multiple injuries, which make up a considerable proportion of patients in rehabilitation centres.

The results obtained in real clinical practice are of special interest. M. Lu *et al.* [31], within the framework of the Alberta Complementary Health Integration Project, recorded that after a course of acupuncture, patients reported a substantial reduction in pain intensity (by 75.5%), improvement in sleep quality (by 53.1%), and overall quality of life (by 42.6%). It is important to emphasise that data obtained in real clinical practice often show higher rates of subjective improvement than the results of strictly controlled randomised trials. This phenomenon can be explained by psychological factors, positive expectations, and better individualisation of treatment. For the Ukrainian healthcare system, this fact means that the introduction of acupuncture in clinical practice can give even better results than predicted on the basis of experimental studies.

Systematic monitoring of the psychoemotional state of patients indicated additional therapeutic effects of acupuncture. C.-T. Tang *et al.* [32], in their clinical audit using the standardised PROMIS system, found that acupuncture substantially improves both physical performance and psychoemotional state, particularly the levels of anxiety and depression. The psychoemotional component of the

therapeutic effect of acupuncture is fundamental in the context of post-traumatic stress disorders and anxiety-depressive states, the prevalence of which has substantially increased in Ukraine as a result of military operations. The introduction of acupuncture in psychological rehabilitation programmes can provide a comprehensive approach to restoring the physical and mental health of victims.

Generalisation of the results of these studies allows formulating a triune concept of the therapeutic effect of acupuncture, covering physiological, functional, and psychoemotional components. The physiological component is implemented through a direct reduction in pain symptoms, the functional component provides restoration of motor activity, and the psychoemotional component contributes to the normalisation of the patient's psychological state. This conceptual model explains the complex effect of acupuncture on various aspects of the quality of life of patients with diseases of the musculoskeletal system and justifies the synergistic nature of the therapeutic effect. The proposed triune concept expands the traditional understanding of the mechanisms of action of acupuncture, integrating modern scientific data from various fields of medicine. This model can become a theoretical basis for the development of comprehensive rehabilitation programmes using acupuncture, aimed at the comprehensive recovery of patients. Available clinical data strongly demonstrate that acupuncture provides statistically and clinically substantial improvements in pain scores, functionality, and quality of life. Systematic application of the method in accordance with optimised protocols creates an opportunity to achieve sustainable positive results, thereby forming a reliable evidence base for wider implementation of acupuncture in clinical guidelines and protocols for the treatment of diseases of the musculoskeletal system.

Physiological mechanisms and neurobiological bases of acupuncture effectiveness. Studies conducted in 2019-2025 majorly expanded the understanding of the neurophysiological mechanisms by which acupuncture modulates pain perception and reduces inflammatory processes in the tissues of the musculoskeletal system. Data analysis allows identifying several key mechanisms of action. According to the studies by Z. Lyu *et al.* [33], central sensitivity of pain pathways is substantially reduced under the influence of acupuncture due to normalisation of neuroglial cross-communication and regulation of synaptic plasticity. Researchers have recorded a decrease in glutamate levels in the ascending excitatory pathways of pain with simultaneous activation of opioid systems, GABA-ergic, noradrenergic, and serotonergic mechanisms in the descending pain modulation system. An additional effect is inhibition of the production of pro-inflammatory cytokines (interleukin-1β, interleukin-6, tumour necrosis factor-α) against the background of increased levels of anti-inflammatory interleukin-10, which reduces both peripheral and central sensitisation. The integration of these data makes it possible to consider acupuncture as a method of multimodal neuromodulation, which simultaneously affects different parts of the pathological process. Special attention is paid to the mechanism of normalisation of neuroglial cross-communication, which indicates the profound effect of acupuncture not only on neuronal populations, but also on glial cells, which play a key role in maintaining chronic pain.

Electroacupuncture demonstrates additional mechanisms of action described by M. Zhou *et al.* [34]. The authors determined that this method activates serotonergic, noradrenergic, endocannabinoid, and purinergic pathways, forming a complex effect on the pain circuits of the central nervous system. Frequency-dependent analysis showed that 2-10 Hz stimulation effectively suppresses neuropathic pain through simultaneous activation of endogenous opioid and monoaminergic mechanisms. An optogenetic study by I.-H. Hsiao *et al.* [35] established a specific mechanism of action of acupuncture in inflammatory pain. Inhibition of somatosensory cortex and anterior cingulate cortex activity was observed due to reduced expression of the CaMKIIα signalling protein, which plays a critical role in the formation of pathological plasticity in central pain networks. These data support the ability of acupuncture to modulate the central mechanisms of pain at the cortical level by inhibiting the pathological excitation of neural ensembles. A comparative analysis of these studies reveals an important pattern – the existence of various mechanisms of anaesthesia, depending on the nature of the pathological process. In neuropathic pain, serotonergic and endocannabinoid mechanisms dominate, while in inflammatory pain, changes in CaMKIIα expression and decreased somatosensory cortex activity are of primary importance. This differentiation explains why acupuncture can be effective in different types of pain syndromes, acting through the most relevant mechanisms for a particular pathology.

The study by Y. Gao *et al.* [36] demonstrated activation of μ- and κ-opioid receptors in the spinal cord under the influence of acupuncture. This process is accompanied by inhibition of Toll-like microglial receptors responsible for initiating an inflammatory response, resulting in a decrease in central sensitisation. Furthermore, S.-S. Ding *et al.* [37] determined that acupuncture modulates a local inflammatory response by activating neutrophils that release endogenous opioid peptides involving the Motif Chemokine ligand 1/Motif Chemokine Receptor 2 (CXCL1/CXCR2) signalling pathway. The identified link between the immune and opioid systems is of particular theoretical interest, as it demonstrates the neuroimmune nature of the analgesic effect of acupuncture. This mechanism may explain the therapeutic effectiveness of acupuncture in autoimmune joint diseases, such as rheumatoid arthritis, where impaired immune regulation is the basis of the pathological process. Modulation of Toll-like microglial receptors via opioid pathways forms the molecular basis for reducing neurogenic inflammation, which is of primary importance in inflammatory arthropathies.

The integration of these scientific data allows forming a holistic view of multi-level neurophysiological modulation under the influence of acupuncture. The method

implements its analgesic and anti-inflammatory effects through a complex effect on endogenous opioid mechanisms, neurotransmitter systems, central sensitisation processes, and neuroimmune cross-communication. Such a multicomponent mechanism of action justifies the therapeutic effectiveness of acupuncture and opens up prospects for its integration into the complex treatment of chronic pain syndromes of the musculoskeletal system. The neurophysiological mechanisms underlying the analgesic effect of acupuncture in diseases of the musculoskeletal system are multifaceted and involve interactions at different levels of the nervous system. Based on the analysis of scientific data, the key mechanisms and the level of their scientific confirmation are summarised in Table 2.

Table 2. Neurophysiological mechanisms of action of acupuncture in modulating musculoskeletal pain

Mechanism of action	Neurophysiological pathways involved	Clinical effect	Level of scientific confirmation
Endogenous opioid system	Release of β-endorphins, enkephalins, activation of μ- and κ-opioid receptors	Analgesia, reduced perception of pain	High
Modulation of inflammatory mediators	Reduced levels of IL-1β, TNF-α, IL-6; increased levels of IL-10	Anti-inflammatory effect, reduction of oedema	Medium
Activation of downstream inhibitory pathways	Serotonergic (5-HT) and norepinephrine pathways	Inhibition of pain signal transmission	High
Effects on the autonomic nervous system	Balancing sympathetic and parasympathetic activity	Improvement of local blood circulation and tissue trophism	Medium
Neuroplastic changes	Inhibition of CaMKIIα-signalling in the somatosensory cortex and anterior cingulate gyrus	Long-term reduction of chronic pain	High
Local tissue reactions	Release of adenosine through activation of A1 receptors	Local tissue regeneration, pain reduction	Medium
Brain stem activation	Stimulation of the periaqueductal grey matter and the suture nucleus	Activation of internal analgesic mechanisms	High
GABA-ergic transmission modulation	Increased activity of GABA and its receptors	Reduced neuronal hypersensitivity	Medium

Source: compiled by the author based on I.-H. Hsiao *et al.* [35] and X. Ma *et al.* [38]

Grouping mechanisms by confirmation level indicates that the rapid analgesic effect in the acute period is more due to the activation of the opioid system and descending inhibitory circuits, while neuroplastic changes provide stable adaptations in the cerebral cortex. Less-researched pathways – autonomic modulation, local tissue responses, and GABA-ergic transmission – are likely supporting factors that enhance anti-inflammatory processes and promote trophic regulation. The comparison of central and peripheral links (from the regulation of cytokines and adenosine in tissues to changes in the conduction of pain signals) highlights the multi-level nature of acupuncture and indicates the need for further examination of the relationships between these systems, in particular in the context of the interaction of opioid and glutamatergic transmission. The existence of potential synergistic interactions between different mechanisms is notable. For example, activation of the opioid system not only directly reduces pain sensitivity but also helps reduce neurogenic inflammation, which in turn lowers nociceptor sensitisation. Similarly, inhibition of CaMKIIα signalling in the somatosensory cortex may increase the efficiency of GABAergic transmission by reducing the excitability of neural networks. This interaction of various mechanisms forms a complete system of neurophysiological response to acupuncture stimulation, which explains its complex therapeutic effect.

Neuroimaging techniques, including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have provided objective evidence for the central mechanisms of acupuncture's action. M. Qi *et al.* [39] performed a meta-analysis using the activation probability estimation (ALE) algorithm, covering 15 studies. The results showed a substantial increase in activity in the left side of the varolian bridge and posterior insula, and a decrease in activity in the cerebellum, temporal lobe, and right precentral gyrus compared to baseline. These changes suggest a complex, targeted neuromodulation of pain pathways and emotional processes that distinguishes true acupuncture from placebo effects. Of particular importance is the detected activation of the posterior insula, which is responsible for interoceptive awareness and processing of visceral sensations. This area of the brain combines somatosensory information with an emotional assessment of pain, forming a subjective experience of pain sensation. Changes in activity in this area under the influence of acupuncture can explain not only a decrease in the intensity of pain but also a decrease in its emotional component, which is critical in chronic pain syndromes, where the emotional component often increases pain.

Innovative approaches to integrated analysis of PET and fMRI data, presented in a paper by D.K. Saha *et al.* [40], demonstrated that acupuncture affects the functional and molecular connectomes of the brain. The Neuromark PET technique enables the assessment of holistic functional and molecular relationships in the brain, including sensorimotor, visual networks, and the brain's default mode system. This provides a deeper understanding of how acupuncture can affect not only local changes in activity but also the

integrated interregional interaction of brain networks. Analysis of molecular connectomes opens up a new dimension in understanding the mechanisms of action of acupuncture, moving research from the level of macroscopic changes in brain activity to the level of molecular interactions. Changes in the brain's default mode system, which is activated during rest and self-referential thinking, explain the effect of acupuncture on the cognitive and emotional aspects of pain perception. This complements the purely physiological model of acupuncture's action with a cognitive-behavioural component, which is important for understanding its therapeutic potential in complex pain syndromes. A substantial contribution to understanding neuroplastic changes under the influence of acupuncture was made by the meta-analysis by Q. Lv *et al.* [41], who demonstrated that in patients after stroke, acupuncture causes hyperactivation in the basal ganglia and insula, and normalisation of activity in the primary motor cortex (Brodmann area 4) and additional motor cortex (Brodmann area 6). These changes were directly correlated with improved motor function, which confirms the neuroplastic nature of the therapeutic effect of acupuncture.

A combined FDG-PET/fMRI study conducted by S.S. Madsen *et al.* [42] confirmed that acupuncture affects not only functional brain activity but also glucose metabolism in somatosensory and motor networks. Active brain regions after acupuncture stimulation are characterised by increased metabolic activity, which confirms the relationship between changes in hemodynamics and metabolism in response to therapeutic intervention. Although this study focuses on patients after stroke, its results are important for understanding the mechanisms of action of acupuncture in musculoskeletal disorders. Normalisation of activity in the motor cortex can contribute to the restoration of correct motor patterns in myofascial syndromes and arthropathies, where violation of motor stereotypes is often an important pathogenetic factor. Hyperactivation of the basal ganglia, which are responsible for automating movement, may explain the improvement in motor function after a course of acupuncture, even in chronic degenerative joint diseases. These results consolidate the understanding that acupuncture is not limited to local stimulation of peripheral receptors, but causes complex changes at the level of integrated brain networks, which provides a long-term modification of pain perception and supports the restoration of impaired musculoskeletal functions. The latest data also highlight the importance of standardised neuroimaging applications for verifying the therapeutic mechanisms of acupuncture in high-quality clinical trials.

In parallel with the central mechanisms, local tissue responses to acupuncture stimulation are important. Z. Liu *et al.* [43] demonstrated using mathematical modelling that under the influence of a magnetic field created by an acupuncture needle, interstitial blood flow and active oxygen transport are substantially enhanced. This helps restore mitochondrial metabolism and accelerate regenerative processes in muscle fibres. A notably pronounced effect is observed in tissues with increased permeability, such as oedematous areas. Thus, local tissue changes caused by acupuncture stimulation include improvements in tissue oxygenation, activation of neuro-immune mechanisms, stimulation of cell repair, and remodelling of the extracellular matrix.

Acupuncture stimulation also causes complex systemic effects by modulating neuro-immune-endocrine interactions. W.-L. Yu *et al.* [44], in a systematic review of experimental studies, demonstrated that acupuncture activates local immune cells, including neutrophils, macrophages, and mast cells. This is accompanied by an increase in the expression of chemo- and mechanosensitive molecules that trigger signalling cascades through the cholinergic, adrenal, and splenic nervous systems, integrating a local immune response with systemic neuro-immune regulation. J.A. Perdrizet *et al.* [45] established that stimulation of certain acupuncture points, such as the GV-14 point, leads to an increased humoral immune response, as evidenced by an increase in the level of neutralising antibodies after vaccination. This indicates the ability of acupuncture intervention to modulate the activity of the adaptive immune system by affecting Meridian networks. The ability of acupuncture to influence the adaptive immune response is important in the context of autoimmune diseases of the musculoskeletal system, such as rheumatoid arthritis and ankylosing spondylitis. Modulation of antibody production and T-cell activity can alter the course of immunopathological processes, reducing the destruction of joint tissue. However, the exact mechanisms of this effect require further investigation, especially regarding the specificity of immunomodulation and its long-term effects. This area of research opens up prospects for the development of targeted acupuncture protocols aimed at correcting immune disorders in specific pathologies.

A.Y. Fan [46] demonstrated that at the level of the autonomic nervous system, specific acupuncture stimulation, in particular, electroacupuncture, activates the vagus-adrenal axis. This leads to the release of catecholamines from the adrenal medulla and promotes an anti-inflammatory response. The mechanisms of action of acupuncture are not limited only to the activation of one pathway, but also cover multisystem modulation at various levels, including parasympathetic and sympathetic regulation, which provides for adapting immune responses according to the stage of the pathological process. Activation of cholinergic anti-inflammatory pathways, especially the vagus-adrenal axis, is one of the key mechanisms of systemic action of acupuncture. This mechanism explains why stimulation of distant points can affect local inflammatory processes in joints and muscles. The vagal nerve inhibits the production of pro-inflammatory cytokines by macrophages through activation of nicotinic acetylcholine receptors of the α7 subtype. It is noteworthy that this effect is realised without suppression of protective immune functions, which makes acupuncture a safe method of immunomodulation, unlike many pharmacological immunosuppressants. This

mechanism is particularly important for the treatment of systemic inflammatory diseases such as rheumatoid arthritis, where long-term anti-inflammatory therapy is required. Regarding the effect on the endocrine system, J. Halámková *et al.* [8] discovered that acupuncture can activate the hypothalamic-pituitary-adrenal axis by stimulating neural transmission in the spinal cord and midbrain. This leads to the regulation of the release of stress hormones and anti-inflammatory factors such as cortisol. The secretion of endogenous opioids is stimulated, which helps to reduce the perception of pain and improve the overall homeostasis of the body. Thus, the combination of neuroimaging, tissue, and systems studies forms a holistic view of the multi-level mechanisms of action of acupuncture. Integration of central neuroplastic changes, local tissue responses, and systemic neuro-immune-endocrine effects provides a comprehensive therapeutic effect of acupuncture in diseases of the musculoskeletal system, which is confirmed by objective research methods.

Modern innovations and scientifically based adaptations of traditional acupuncture methods. During 2019-2025, TCM techniques underwent a substantial transformation in their application to diseases of the musculoskeletal system. This evolution has covered several critical areas of development of treatment protocols, improvement of techniques, and models of service delivery. The study by Y.-C. Hwang *et al.* [47] analysed randomised controlled trials to pinpoint the most effective acupuncture points for pain control. Their results identified SP6, ST36, LI4, and LR3 as particularly effective points, while recognising state-dependent variations. For example, migraine treatment showed an optimal response to GB20, LR3, GV20, Taiyang, LI4, and TE5 points, while dysmenorrhea treatment benefited from the use of SP6, CV4, SP8, LR3, and BL32 points. This systematic analysis provided the basis for the development of structured therapeutic protocols. It is noteworthy that the identification of universal points such as LI4 and LR3, which demonstrate effectiveness in various pathological conditions, changes the paradigm of acupuncture treatment from a purely syndromic approach to a systematic methodology with elements of evidence-based medicine. Systematic mapping of the effectiveness of different points in specific pathologies allows rationalising therapeutic protocols, reducing the subjectivity of the choice of acupuncture points, which has conventionally been considered a limitation of the method.

A fundamental advance in the treatment strategy was the integration of regional and distal points within a single session. As demonstrated by L.L. DeBar *et al.* [16], this approach allows purposefully influencing both local and systemic pathological processes, giving better results compared to monofocal stimulation. The same team determined that including acupuncture in interdisciplinary rehabilitation programmes increases clinical efficacy, especially when point selection is based on assessments of muscle dysfunction and segmental movement disorders. Therapeutic regimens were further enhanced by the inclusion of microsystem acupuncture, in particular, scalp acupuncture, auricular therapy, and limb acupuncture. In post-stroke rehabilitation studies, Q. Lv *et al.* [41] demonstrated that stimulation of the motor zones of the scalp in combination with traditional channel points gives a pronounced effect through simultaneous peripheral and central neuromodulation.

The development of personalised treatment protocols was another substantial achievement. The study by I.-H. Hsiao *et al.* [35] and Y. Gao *et al.* [36] showed that the inclusion of biomarkers, such as inflammatory cytokine levels and indicators of autonomous regulation, in treatment planning allows for more precise individualisation of point selection and stimulation parameters. The evolution from subjective diagnosis to objective point selection based on biomarkers transforms acupuncture from an empirical art to a precision therapeutic tool. The implementation of laboratory and instrumental methods for evaluating effectiveness allows overcoming the historical barrier between TCM and the modern biomedical model, creating an integrative approach that combines thousands of years of empirical knowledge with precise methods of molecular medicine. The use of polymorphisms of opioid receptor genes and neurotransmitter systems to predict individual sensitivity to acupuncture opens a new era of pharmacogenomics of non-invasive interventions. Comparative studies of the effectiveness of specialised acupuncture techniques have provided important clinical results. J.J. Mao *et al.* [48] determined that electroacupuncture is more effective than auricular acupuncture in reducing chronic musculoskeletal pain among cancer patients, with therapeutic effects lasting up to 24 weeks. Further, studies by T. Bao *et al.* [49], involving women who survived breast cancer, confirmed that personalised electroacupuncture outperformed combat auricular acupuncture in terms of pain reduction.

Laser acupuncture has also shown promising results. Meta-analyses of Y.C. Hung *et al.* [50] indicate that this method substantially reduces pain levels, functional limitations, and disability in patients with musculoskeletal disorders, demonstrating a substantial effect compared to dummy treatment. Papers of J. Comachio *et al.* [13] and M.J. Dastjerdi *et al.* [14] also proved that personalisation of method selection optimises therapeutic outcomes while minimising side effects. The emergence of technologically advanced methods of acupuncture stimulation, such as laser acupuncture, electroacupuncture with controlled stimulation parameters, and magnetic acupuncture, substantially expands the therapeutic arsenal beyond classical acupuncture. Meanwhile, the difficulty of objectively comparing these methods lies in the different mechanisms of their action – if mechanical stimulation with a needle activates mainly mechanoreceptors and nociceptive fibres, then laser and magnetic acupuncture directly affect tissue metabolism through photobiomodulation and electromagnetic induction, respectively. Most comparative studies focus on clinical outcomes without a detailed analysis of differences in molecular mechanisms of action, which creates

methodological dissonance and makes it difficult to develop optimal combined protocols. Integrative treatment approaches have received substantial evidence-based support. S. Pugazhendi *et al.* [51] evaluated comprehensive protocols combining physical therapy, pharmacological interventions, and, if necessary, surgical care with acupuncture. Their large-scale study in India indicated that such comprehensive non-invasive physical therapy with acupuncture reduced the need for surgery and decreased pain levels. In postoperative rehabilitation, C.A. Dilaveri *et al.* [52] established that the combination of massage and acupuncture effectively reduces stress, pain, and anxiety levels.

A review of randomised controlled trials of D. Ha *et al.* [53] confirmed that integrative treatment that combines acupuncture with pharmacotherapy or physical therapy demonstrates higher efficacy compared to monocomponent interventions. In particular, 83% of the analysed studies showed improved results when using integrative methods, while maintaining a low risk of side effects. The synergy of integrative treatment protocols is manifested both in the arithmetic summation of therapeutic effects and the potentiation of the action of individual components. For example, acupuncture analgesia increases exercise tolerance during rehabilitation exercises, which in turn accelerates functional recovery. Pharmacological agents can modify the neurochemical environment, increasing the effectiveness of acupuncture neuromodulation. Another advantage of the integrative approach is the ability to reduce the dosage of pharmacological drugs, which lowers the risk of side effects and drug dependence, especially in the long-term treatment of chronic pain. Modern rehabilitation practice has seen innovations in models of acupuncture care. M.D. McKee *et al.* [54] investigated group treatment protocols and found that this approach allows multiple patients to be treated simultaneously without substantially reducing quality. Their study showed that group acupuncture is comparable to individual treatment in reducing chronic pain, thereby increasing accessibility for economically disadvantaged segments of the population.

Development of telemedicine models for self-guided acupuncture applications explored by S. Ribagin *et al.* [55] demonstrated that video consultations effectively teach patients the exact location of acupuncture points and correct self-stimulation techniques. This approach ensures continuous rehabilitation even in remote regions. Standardisation of treatment protocols through the development of point selection algorithms was investigated by Y.-B. Jiang *et al.* [56] showed effectiveness in balancing evidence-based approaches with personalised care. In spinal cord injury rehabilitation studies, combining standardised acupuncture with rehabilitation techniques resulted in substantial improvements in motor function and quality of life compared to traditional rehabilitation.

Diversifying the channels of acupuncture care addresses accessibility issues while contributing to the integration of this method into multidisciplinary treatment protocols, which is supported by the findings of S.L. Kolasinski *et al.* [19], L. Cavaggioni *et al.* [24], and G. Litscher [10]. The transformation of models for providing acupuncture services through the introduction of group sessions, telemedicine consultations, and self-help programmes is no less important an innovation than technological improvements to the method itself. The transition from the traditional "one patient – one doctor" model to flexible treatment formats ensures wide availability of acupuncture, despite the global shortage of qualified specialists. Paradoxically, the technologisation and standardisation of acupuncture, which originally developed as the art of individualised treatment, can lead to the loss of a personalised approach. Therefore, developing models that balance cost-effectiveness, accessibility, and maintaining individualisation of treatment is a critical challenge. The innovations introduced between 2019-2025 laid the foundation for the further development of acupuncture as a scientifically based, cost-effective, and clinically substantial component of modern rehabilitation programmes. Developments in the field of digitalisation and personalisation of acupuncture interventions using AI tools to predict individual therapeutic responses and optimise treatment protocols are especially promising. The integration of acupuncture into digital medicine is a natural evolutionary stage in the development of this ancient method of treatment. Machine learning algorithms that analyse data sets on the effectiveness of various acupuncture protocols allow identifying non-obvious correlations between the clinical characteristics of patients and their response to specific stimulation methods. Therewith, automated diagnostic systems that use computer vision to analyse patients' pulse and tongue in accordance with the principles of TCM can overcome the subjectivity of traditional diagnostics, ensuring reproducibility of assessment and point selection. Thus, the synthesis of the millennial tradition of acupuncture with modern technologies creates a new paradigm of personalised medicine, where empirical knowledge is enhanced by the capabilities of analytical data processing.

Practical recommendations for effective optimisation of acupuncture practice. Based on the analysis of modern studies on acupuncture in diseases of the musculoskeletal system, it is advisable to highlight the following recommendations for acupuncture practice. A necessary step in the development of acupuncture practice should be the introduction of standardised treatment protocols. It is advisable to develop and approve at the national level clinical protocols for the use of acupuncture in the most common diseases of the musculoskeletal system. Such protocols should include clear algorithms for selecting points according to the clinical picture, optimal stimulation parameters, and performance evaluation criteria that ensure consistency and reproducibility of therapeutic outcomes.

Substantial improvements in treatment outcomes can be achieved through the integration of acupuncture into multidisciplinary rehabilitation programmes. Acupuncture should become a mandatory component of rehabilitation programmes for patients with chronic pain and functional

disorders. Special attention should be paid to coordinating acupuncture interventions with physical therapy, kinesiotherapy, and psychological support to achieve a synergistic therapeutic effect. Increasing the availability of acupuncture services requires diversification of their delivery models. It is advisable to ensure the development of group forms of treatment and telemedicine consultations to expand the coverage of the population. An important element should be the introduction of patient training programmes for self-stimulation of simple acupuncture points, which will allow maintaining the therapeutic effect between sessions and reduce the burden on the medical system.

Technological improvement of acupuncture practice requires expanding the use of modern diagnostic methods, including analysis of biomarkers and heart rate variability, to objectify the choice of stimulation points and parameters. The introduction of electronic clinical decision support systems to optimise acupuncture protocols will improve the effectiveness and safety of procedures. High-quality training of specialists requires strengthening training and advanced training programmes. It is necessary to modernise the training for acupuncture specialists, focusing on integrating traditional knowledge with modern scientific data. The development of interdisciplinary educational initiatives for doctors of various specialities will help to expand understanding of the role of acupuncture in complex treatment and overcome professional barriers.

Further development of acupuncture requires prioritisation of scientific research. Research efforts should focus on investigating the molecular mechanisms of action of acupuncture, especially in pathologies with a low level of evidence, such as rheumatoid arthritis and fibromyalgia. Developing high-quality research projects to evaluate the long-term effectiveness and economic feasibility of various acupuncture techniques will help strengthen the evidence base of the method. The implementation of these recommendations will optimise the use of acupuncture in clinical practice, improve the quality of medical care for patients with diseases of the musculoskeletal system, and promote the integration of traditional and modern methods of treatment into a single healthcare system.

Conclusions

The study highlighted a high clinical efficacy of acupuncture in chronic lower back pain, knee osteoarthritis, and myofascial pain syndrome, which is confirmed by a decrease in pain intensity by 2.87-4.1 points on the visual-analogue scale and an improvement in functional indicators by 9.5-20.3%. Optimal therapy parameters included 2-3 sessions per week with a total course duration of 4-8 weeks, while the effectiveness varies depending on the nosology, with the advantage of electroacupuncture and dry acupuncture in certain pathologies. Data from clinical studies indicated a stable therapeutic effect of acupuncture, persisting for a long time after the end of treatment, which is especially valuable for patients with chronic conditions. The 2019-2025 papers deepened the understanding of the neurophysiological mechanisms of acupuncture, confirming the complex effects on the endogenous opioid system, modulation of inflammatory mediators, activation of downstream inhibitory pathways, and induction of neuroplastic changes in the central nervous system. Local tissue responses and systemic neuroimmune modulation were identified as important components of the therapeutic effect. Neuroimaging studies demonstrated substantial changes in activity in the left side of the varolian bridge, posterior insula, and other key brain structures under the influence of acupuncture, which correlates with clinical improvement in patients' condition. Modern innovative approaches, including group forms of treatment and telemedicine models, have expanded the possibilities of clinical application of the method, and integrative strategies combining acupuncture with traditional methods have shown better results in 83% of the analysed publications. Based on the research, recommendations were developed for the introduction of standardised treatment protocols, integration of acupuncture into multidisciplinary rehabilitation programmes, diversification of service delivery models, technological improvement of practice, and strengthening of scientific research.

Based on the results obtained, two theoretical models were developed: a triune concept of the therapeutic effect of acupuncture (physiological, functional, and psychoemotional components) and an integrative model of effectiveness in chronic pain (short-term anaesthesia, improvement of microcirculation, and functional tissue repair). These models enabled a better understanding of the multi-level nature of the therapeutic effects of acupuncture and justified an integrated approach to its application in clinical practice. A limitation of the study was the heterogeneity of primary clinical trials and the variety of methodological approaches, which complicated the direct comparison of the results of different studies. Prospects for further research include assessing the long-term effectiveness of acupuncture in less-known nosologies, optimising personalised biomarker-based protocols, and modernising traditional acupuncture practices through the use of AI and telerehabilitation.

Acknowledgements

None.

Funding

None.

Conflict of Interest

None.

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Огляд сучасних підходів до лікування пацієнтів із порушеннями та захворюваннями опорно-рухового апарату за допомогою традиційної китайської медицини (ТКМ) – голковколювання

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Анотація. Актуальність дослідження зумовлена значним поширенням захворювань опорно-рухового апарату та потребою в ефективних немедикаментозних методах лікування. Метою даної роботи був аналіз наукових даних щодо клінічної ефективності, фізіологічних механізмів дії та інноваційних підходів до застосування акупунктури при лікуванні патологій опорно-рухового апарату. Дослідження являє собою літературний огляд наукових публікацій 2019-2025 років з використанням комплексного триетапного методологічного підходу, що включав аналіз опублікованих даних щодо клінічної ефективності акупунктури за стандартизованими шкалами та опитувальниками, узагальнення досліджень нейрофізіологічних механізмів дії та систематизацію сучасних інноваційних протоколів, представлених у науковій літературі. Аналіз клінічних досліджень, виявив, що ефективність акупунктури варіюється залежно від технік і нозологічних форм, з найвищим рівнем доказовості для хронічного болю в нижній частині спини та остеоартриту. Після курсу акупунктури (2-3 сеанси на тиждень, загальною тривалістю 4-8 тижнів) зафіксовано зниження інтенсивності болю за візуально-аналоговою шкалою на 2,87-4,1 бала та покращення функціональних показників на 9,5-20,3 %. На основі узагальнення даних було сформульовано дві теоретичні моделі: триєдину концепцію терапевтичної дії акупунктури, що охоплює фізіологічний (зниження больової симптоматики), функціональний (відновлення рухової активності) та психоемоційний (нормалізація психологічного стану) компоненти, та інтегративну модель ефективності при хронічному болю, яка включає короткострокове знеболення через нейромодуляцію, покращення локальної мікроциркуляції та функціональне відновлення м'язово-фасціальних структур. Дослідження нейрофізіологічних механізмів продемонструвало, що терапевтичний ефект акупунктури опосередковується активацією ендогенної опіоїдної системи, модуляцією запальних цитокінів та нейропластичними змінами в мозкових мережах, що було підтверджено нейровізуалізаційними методами. У дослідженні також було систематизовано сучасні інновації акупунктурної практики, включаючи оптимізацію протоколів лікування, групові форми терапії та телемедичні моделі. Інтегративні підходи, що поєднували акупунктуру з традиційними методами лікування, продемонстрували кращі результати у 83 % проаналізованих досліджень порівняно з монокомпонентними втручаннями. Результати дослідження підтверджують клінічну ефективність різних технік акупунктури при захворюваннях опорно-рухового апарату, що обґрунтовано комплексним впливом на нейрофізіологічні механізми больової модуляції та доводить доцільність включення методу в стандартні терапевтичні протоколи

Ключові слова: хронічний біль; функціональний стан; терапевтичний ефект; больовий синдром; інтегративний підхід

INTERNATIONAL JOURNAL OF MEDICINE AND MEDICAL RESEARCH
Scientific-Practical Journal

Volume 11, No. 1
2025

Managing Editor:
T. Pyatkovskyy

Editing bibliographic lists:
T. Pyatkovskyy

Signed to the print 27.05.2025
Format 60*84/8
Conventional Printed Sheet 14.1
Circulation 100 copies

Publisher: I. Horbachevsky Ternopil National Medical University
46001, 1 Maidan Voli, Ternopil, Ukraine
Tel.: +380 352 524492
E-mail: info@ijmr.com.ua
https://ijmr.com.ua/