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Dynamics of bone remodeling markers under osteoplastic materials in experiment

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Abstract. Molecular regulation of the balance between bone resorption and formation is primarily mediated by the RANKL/RANK/OPG signaling pathway and the Wnt-mediated pathway, the key inhibitor of which is sclerostin. A comprehensive assessment of these regulatory markers allows elucidation of the mechanisms underlying the observed changes in bone resorption and formation during the application of osteoplastic materials. The aim of the study was to investigate the dynamics of serum concentrations of RANKL, OPG and sclerostin, as well as the RANKL/OPG ratio, on days 5, 14, 30 and 60 of experimental femoral bone defect healing under the application of collagen-free, collagen-containing osteoplastic materials and demineralized bone matrix (DBM) compared with an untreated defect. The study was performed on 170 Wistar rats. Serum RANKL and OPG concentrations were determined by sandwich ELISA (Thermo Fisher Scientific); sclerostin was measured by ELISA using commercial kits. Statistical analysis was performed using STATISTICA 10.0 (StatSoft). In the untreated defect group on day 5, RANKL exceeded the control level by 163.6 %, OPG decreased by 28.5 %, and sclerostin increased by 100.4 %. In the DBM group, a pro-osteogenic profile was already evident from day 5, with OPG exceeding the control by 25.6 %, and from day 14 RANKL fell below the control level. The RANKL/OPG ratio in the DBM group remained below the control throughout the observation period. A gradient of regulatory efficacy of the materials was identified (DBM > collagen-containing implant > collagen-free implant > untreated defect), which is consistent with the data on resorption and formation markers and confirms the realization of the osteoreparative effect through modulation of the RANKL/RANK/OPG signaling pathway and suppression of sclerostin-mediated blockade of Wnt signaling. The obtained results substantiate the preferential use of demineralized bone matrix for accelerating reparative osteogenesis at the molecular regulatory level.

Keywords: osteoplastic materials; RANKL; osteoprotegerin; sclerostin; bone remodeling; demineralized bone matrix; reparative osteogenesis.

Introduction

The molecular balance between resorption and formation of bone tissue is ensured by the coordinated action of regulatory signaling systems, the key among which is the RANKL/RANK/OPG axis. Receptor activator of nuclear factor κ B ligand (RANKL) is expressed on the surface of osteoblasts, osteocytes and bone marrow stromal cells and, upon binding to the RANK receptor on osteoclast precursors, initiates

their differentiation, activation and prolongs the survival of mature osteoclasts [1]. Osteoprotegerin (OPG) is a soluble decoy receptor of the TNF family that competitively binds RANKL and prevents its interaction with RANK, thereby inhibiting osteoclastogenesis [1, 2]. The RANKL/OPG ratio is a recognized integral indicator of the bone remodeling balance: its increase indicates a shift toward resorption, while a decrease indicates predominance of formation [1, 3].

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In parallel with the RANKL/RANK/OPG axis, bone formation is regulated by the Wnt/ β -catenin signaling pathway, the key physiological inhibitor of which is sclerostin – a glycoprotein secreted by osteocytes that binds to the LRP5/6 co-receptors, blocking the Wnt cascade and suppressing osteoblastic differentiation and activity [4]. Since RANKL, OPG and sclerostin are produced predominantly by cells of the osteoblastic lineage and osteocytes, they constitute a single regulatory network that links the processes of bone resorption and formation within one remodeling cycle [5].

The dynamics of this regulatory triad have been studied in models of physiological remodeling and under osteoporotic changes [3, 5]; however, data on its behavior under implantation of osteoplastic materials of different composition – collagen-free, collagen-containing and demineralized bone matrix – remain limited. This complicates the molecular interpretation of the observed differences in the dynamics of bone resorption and formation markers.

The aim of the study: to investigate the dynamics of serum concentrations of the regulatory markers of bone remodeling RANKL, OPG and sclerostin, as well as the RANKL/OPG ratio, on days 5, 14, 30 and 60 of experimental healing of a femoral bone defect under the application of collagen-free, collagen-containing implantation materials and demineralized bone matrix compared with intact control and untreated defect.

Materials and Methods

The study was performed at the Departments of Functional and Laboratory Diagnostics, Pathological Anatomy with Sectional Course and Forensic Medicine, and at the Interdepartmental Educational and Research Laboratory Center of I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine, in compliance with Directive 2010/63/EU of the European Parliament and of the Council, the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 18.03.1986) and the Resolution of the First National Congress on Bioethics (Kyiv, 2001), and was approved by the University Bioethics Commission.

The study was conducted on 170 linear white Wistar rats weighing 180–210 g, divided into five groups: Group I – intact animals without defect modeling (control); Group II – animals with a modeled femoral bone defect without correction; Group III – animals with implantation of a bone regeneration material without collagen; Group IV – animals with implantation of a bone regeneration material containing collagen; Group V – animals with application of demineralized bone matrix. The materials were obtained from ABM Technology LLC.

Animals of Groups II–V under sodium thiopental anesthesia (40 mg/kg body weight intraperitoneally) underwent osteoperforation of the femur with a bur under aseptic conditions, forming a standard defect 3 mm in diameter. After introduction of the tested material, the defect was covered with an ActiveBone collagen membrane, and the wound was sutured layer by layer. Animals were withdrawn from the experiment, and blood for biochemical analysis was collected on days 5, 14, 30 and 60 after surgery.

RANKL concentration was determined by the enzyme-linked immunosorbent assay using sandwich ELISA with monoclonal antibodies specific for soluble RANKL (Thermo Fisher Scientific) according to the manufacturer's instructions; the result was expressed in ng/mL. OPG concentration was determined by sandwich ELISA: monoclonal capture antibodies against OPG were pre-coated on the plate wells; after binding of the analyte from the test sample, detector antibodies conjugated with horseradish peroxidase were added; the optical density of the colored reaction product was measured at 450 nm (Thermo Fisher Scientific kits); the result was expressed in ng/mL. Sclerostin concentration was determined by the enzyme-linked immunosorbent assay using commercial test systems according to the manufacturer's instructions; the result was expressed in ng/mL.

Statistical processing of the results was performed using the Statistica 10.0 package (StatSoft Inc.). Data are presented as mean $\pm$ standard error of the mean ($M \pm m$). Normality of distribution was checked by the Shapiro-Wilk test. One-way analysis of variance (ANOVA) followed by pairwise comparison using Student's t-test was applied to compare indicators between groups and observation periods; differences were considered statistically significant at $p < 0.05$.

Results

Control (baseline) values in the intact group were: RANKL – (0.22 ± 0.04) ng/mL, OPG – (89.7 ± 4.3) ng/mL, sclerostin – (0.483 ± 0.028) ng/mL (Table).

On day 5 in the untreated defect group, the most pronounced shifts were recorded: RANKL exceeded the control by 163.6 %, OPG decreased by 28.5 %, and sclerostin increased by 100.4 %, reflecting simultaneous hyperactivation of pro-resorptive signaling and suppression of osteoblastogenesis. Application of implantation materials was accompanied by a dose-dependent attenuation of this imbalance: in the collagen-free group RANKL +136.4 %, OPG -20.7 %, sclerostin +62.3 % relative to control; in the collagen-containing group – RANKL +59.1 %, OPG -5.6 %, sclerostin +35.4 %. The least pronounced shifts were observed in the DBM group: RANKL exceeded the control by only 9.1 %, while OPG already on day 5 exceeded the control level by 25.6 %, and sclerostin by 27.9 %.

Table. Markers of bone regeneration regulation in the serum of animals with a perforating femoral bone defect under the application of different osteoplastic materials

Indicator / Term	RANKL, ng/mL	OPG, ng/mL	Sclerostin, ng/mL
Intact control, n=10	0.22±0.04	89.7±4.3	0.483±0.028
Untreated defect			
Day 5, n=10	0.58±0.07*	64.1±3.6*	0.968±0.048*
Day 14, n=10	0.41±0.06*	68.3±4.8*	0.831±0.036*
Day 30, n=10	0.39±0.05*	72.3±6.5*	0.655±0.034*
Day 60, n=10	0.27±0.06	78.4±7.1	0.561±0.025
Collagen-free implant			
Day 5, n=10	0.52±0.05*	71.1±6.7*	0.784±0.042**
Day 14, n=10	0.35±0.03*	76.4±6.3	0.726±0.038*
Day 30, n=10	0.27±0.04	75.6±7.1	0.621±0.046*
Day 60, n=10	0.24±0.05	81.3±7.8	0.543±0.031
Collagen-containing implant			
Day 5, n=10	0.35±0.02**^	84.7±7.3	0.654±0.042**^
Day 14, n=10	0.31±0.02	87.2±8.3	0.566±0.039#^
Day 30, n=10	0.28±0.03	93.6±9.2	0.529±0.033#
Day 60, n=10	0.20±0.01	97.5±8.8	0.492±0.030
Demineralized bone matrix			
Day 5, n=10	0.24±0.02**^&	112.7±9.1**^&	0.618±0.036**^
Day 14, n=10	0.16±0.01**^&	126.2±10.4**^&	0.514±0.028#^
Day 30, n=10	0.14±0.01**^&	118.9±9.7**^	0.495±0.031#
Day 60, n=10	0.19±0.02	99.3±8.8	0.476±0.024#

Notes: 1. * – statistically significant difference compared with animals without bone defect modeling;
 2. ^ – statistically significant difference compared with animals with bone defect without correction;
 3. # – statistically significant difference compared with animals with bone defect and correction without collagen;
 4. & – statistically significant difference compared with animals with bone defect and correction with collagen.

On day 14 in the DBM group, the RANKL level fell below the control by 27.3 %, while OPG reached its peak value ((126.2±10.4) ng/mL; +40.7 % relative to control). In the collagen-containing group, OPG practically normalized on this term (-2.8 % relative to control). In the untreated group the imbalance persisted: RANKL +86.4 %, OPG -23.9 %, sclerostin +72.0 % relative to control. By day 30 in the DBM group, RANKL reached its minimum (-36.4 % relative to control), while OPG remained elevated by 32.6 %.

By day 60, the indicators in all groups approached the control values while retaining the intergroup gradient: in the untreated group RANKL remained elevated by 22.7 %, OPG was decreased by 12.6 %, and sclerostin by 16.1 %; in the DBM group RANKL was lower than control by 13.6 %, OPG was higher by 10.7 %, and sclerostin practically reached the baseline level (-1.4 %) (Fig. 1).

The integral indicator of osteoclastogenic potential is the RANKL/OPG ratio (Fig. 2). In the untreated

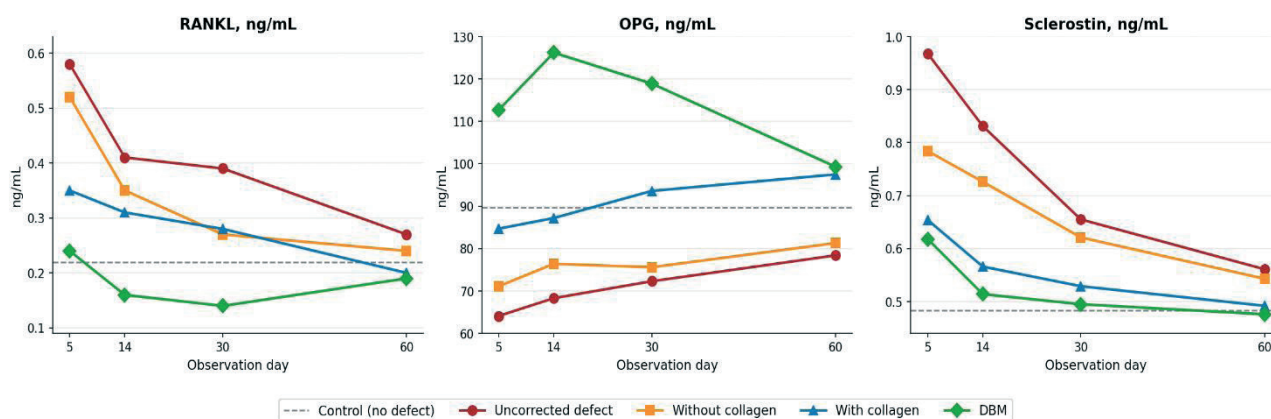


Fig. 1. Dynamics of serum concentrations of RANKL, OPG and sclerostin in the study groups on days 5, 14, 30 and 60 of observation.

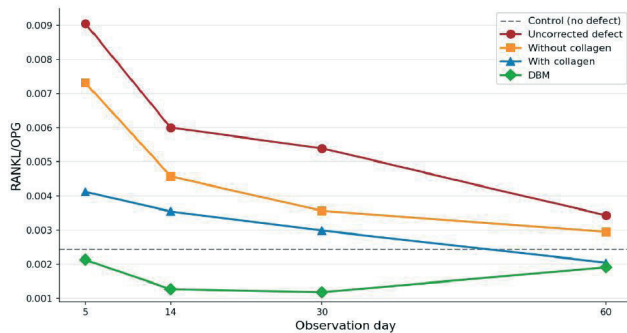


Fig. 2. Dynamics of the RANKL/OPG ratio in the study groups.

group it exceeded the control value 3.7-fold on day 5 and remained elevated even on day 60 (1.4-fold). In the collagen-containing group the ratio fell below the control level already on day 60 (0.84-fold), while in the DBM group it remained below the control throughout the entire observation period (from 0.87 on day 5 to 0.48 on day 30).

Discussion

The obtained results demonstrate that osteoplastic materials exert a regulatory effect at the molecular level, modulating the RANKL/OPG/sclerostin balance in a direction favorable for osteogenesis. The dynamics of RANKL and OPG in the untreated defect correspond to the pattern described in the literature: an increase in RANKL and a decrease in OPG in the acute phase of injury with subsequent activation of OPG in the bone formation phase, when osteoblasts acquire a dominant influence on the local microenvironment [6]. Notably, in the DBM group this sequence was substantially accelerated – a pro-osteogenic profile (elevated OPG, reduced RANKL) was already registered on days 5–14, whereas in the untreated defect analogous changes were only beginning.

The identified gradient of regulatory efficacy of the materials (DBM > collagen-containing implant > collagen-free implant > untreated defect) fully agrees with previously established data on resorption markers (CTX-I, TRAP-5b) and formation markers (PINP, BALP, osteocalcin): suppression of RANKL and an increase in OPG correlate with a decrease in resorption markers and an increase in bone formation markers. This confirms the hypothesis that the organic component of the materials (collagen, demineralized matrix) realizes the osteoreparative effect through modulation of the RANKL/RANK/OPG signaling pathway, approaching the physiological balance already in the early stages of healing [1, 2].

The parallel decrease in sclerostin in the groups with material implantation, most pronounced in the DBM group, is consistent with the role of sclerostin as an inhibitor of Wnt/ β -catenin signaling, the removal of which is a necessary condition for activation of osteoblastic differentiation [4]. Thus, the applied materials probably realize a dual mechanism of action – suppression of osteoclastogenesis via the RANKL/RANK/OPG axis and unblocking of osteoblastogenesis via sclerostin inhibition, which together ensure a coordinated and accelerated course of reparative osteogenesis compared with natural healing of the defect without correction.

Conclusions

1. Modeling of a femoral bone defect is accompanied by an acute increase in RANKL and sclerostin and a decrease in OPG on day 5 with gradual normalization of the balance by day 60, which is slowest in the untreated defect group.

2. Application of osteoplastic materials is accompanied by a dose-dependent attenuation of the imbalance of regulatory markers, most pronounced in the demineralized bone matrix group, where a pro-osteogenic profile (elevated OPG, reduced RANKL) is registered already from days 5–14.

3. The RANKL/OPG ratio in the DBM group remains below the control throughout the entire observation period, indicating a stable shift of the remodeling balance toward osteogenesis.

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Conflict of interest

The authors declare no conflict of interest.

Information on the use of artificial intelligence

The authors of the manuscript confirm that no generative artificial intelligence tools were used to obtain scientific data, conduct the research, or analyze the results. During the preparation of this article, the authors used the artificial intelligence tool Claude (Anthropic) for creating charts and data visualization; all generated charts were re-checked by the authors. All scientific data, interpretation of results, and conclusions belong to the authors, who bear full responsibility for the content of the publication.

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Динаміка регуляторних маркерів кісткового ремоделювання за умов застосування остеопластичних матеріалів в експерименті

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Анотація. Молекулярна регуляція рівноваги між резорбцією та формуванням кісткової тканини переважно опосередковується сигнальним шляхом RANKL/RANK/OPG і Wnt-опосередкованим шляхом, ключовим інгібітором якого є склеростин. Комплексна оцінка цих регуляторних маркерів дає змогу з'ясувати механізми, що лежать в основі змін процесів резорбції та формування кісткової тканини під час застосування остеопластичних матеріалів. Метою дослідження було вивчення динаміки сироваткових концентрацій RANKL, OPG і склеростину, а також співвідношення RANKL/OPG на 5, 14, 30 та 60 доби загоєння експериментального дефекту стегнової кістки під впливом безколагенових і колагеновмісних остеопластичних матеріалів, а також демінералізованого кісткового матриксу (ДКМ) порівняно з нелікованим дефектом. Дослідження виконано на 170 щурах лінії Wistar. Концентрації RANKL та OPG у сироватці крові визначали за методом сендвіч-імуноферментного аналізу (Thermo Fisher Scientific); рівень склеростину – методом ІФА із використанням комерційних наборів. Статистичний аналіз проводили за допомогою програмного забезпечення Statistica 10.0 (StatSoft). У групі нелікованого дефекту на 5 добу рівень RANKL перевищував контрольне значення на 163,6 %, концентрація OPG знижувалася на 28,5 %, а рівень склеростину підвищувався на 100,4 %. У групі ДКМ уже на 5 добу виявляли прооостеогенний профіль: рівень OPG перевищував контрольне значення на 25,6 %, а починаючи з 14 доби, концентрація RANKL була нижчою за контрольний рівень. Співвідношення RANKL/OPG у групі ДКМ протягом усього періоду спостереження залишалося нижчим за контрольне значення. Встановлено градієнт регуляторної ефективності досліджуваних матеріалів: ДКМ > колагеновмісний імплантат > безколагеновий імплантат > нелікований дефект, що узгоджується з даними щодо маркерів резорбції та формування кісткової тканини і підтверджує реалізацію остеорепаративного ефекту шляхом модулювання сигнального шляху RANKL/RANK/OPG та пригнічення склеростин-опосередкованого блокування Wnt-сигналіну. Отримані результати обґрунтовують доцільність переважного застосування демінералізованого кісткового матриксу для пришвидшення репаративного остеогенезу на молекулярно-регуляторному рівні.

Ключові слова: остеопластичні матеріали; RANKL; остеопротегерин; склеростин; ремоделювання кісткової тканини; демінералізований кістковий матрикс; репаративний остеогенез.

Comparative analysis of higher nursing education in Ukraine and abroad

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Abstract. In the modern world, a nurse occupies a key place in the healthcare system, acting not only as not only a performer of medical orders but also as an independent professional who provides care, coordinates treatment, and engages in health education. Rising demands on the profession necessitate obtaining higher education. For Ukraine, which is currently undergoing medical sector reforms and facing a workforce deficit due to the war and migration, analyzing the global experience of nursing academicization is critical for building its own sustainable training system. The aim of the study – to conduct a comprehensive analysis of the higher nursing education system in Poland, Germany, the USA, and Ukraine, identify their common and distinct features, and substantiate the possibilities of utilizing this experience to modernize nursing education in Ukraine. The study established that modern higher nursing education at the bachelor's and master's levels is a multi-component structure that harmoniously integrates professional, research, managerial, and pedagogical components, enabling the training of specialists as clinical leaders and healthcare managers. Historical and theoretical analysis allowed for the examination of F. Nightingale's classical nursing models, which continue to form a solid scientific and philosophical foundation for the profession, defining care as an independent humanistic discipline. Within the comparative analysis, national training models and the legal status of nurses in four countries – Ukraine, Poland, Germany, and the USA – were analyzed in detail. As a result of the study, a comprehensive comparative analysis of higher nursing education models in Ukraine, Poland, Germany, and the USA was performed, which allowed for the substantiation of strategic directions for the development of this field. It has been proven that modern global nursing has definitively evolved into an independent scientific and clinical discipline, where the master's level serves as the foundation for forming the concept of advanced nursing practice.

Keywords: higher nursing education; nursing; advanced nursing practice; bachelor's level; master's level; clinical leadership; academicization of nursing.

Introduction

The current stage of the global healthcare system's development is characterised by a fundamental shift in the professional practice model for nurses. Nursing has evolved into an independent scientific

and clinical discipline with its own theoretical basis and areas of development [1]. The leading trend in this transformation has been the academisation of higher education on a global scale, which has paved the way for the practical implementation of

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the concept of advanced practice nursing [2]. In developed countries, professionals with a second master's degree are not merely viewed as experienced implementers of medical orders, but as autonomous clinicians capable of performing primary and differential diagnoses, conducting independent scientific research, and managing the treatment and care process directly based on evidence-based medicine [3]. For Ukraine, which is pursuing a path of European integration and implementing large-scale reforms to its national healthcare system, thoroughly studying and systematising international experience in organising higher nursing education is strategically important. There are significant internal contradictions between the high quality of academic training for domestic nurses at bachelor's and master's level, and their legally restricted status in clinical practice. This study is relevant because there is a functional gap between the higher education system, which effectively produces autonomous leaders, and the regulatory framework, which confines them within the boundaries of an outdated executive model.

The aim of the study: to analyse the characteristics of higher nursing education systems in Ukraine, Poland, Germany and the United States, identify common trends, advantages and challenges, and explore opportunities for adapting these systems to improve nurse training in Ukraine.

Materials and Methods

The focus of this research is the professional training process for nursing specialists at the first (bachelor's) and second (master's) levels of higher education in Ukraine and countries with high levels of professional autonomy and successful integration into the international education system, such as Poland, Germany and the USA. The analysis focuses on structural-logical frameworks, educational and professional programme content, credit load distribution in accordance with the European ECTS system, and the legal autonomy of master's degree holders in clinical practice. The primary tools used to collect and systemise data were document and report analysis, and an audit of the curricula of selected higher education institutions, including Ivan Horbachevsky Ternopil National Medical University, the University of Warsaw, Jagiellonian University, the Charité Clinic in Berlin and Johns Hopkins University. The comparative-typological method was used to classify various models of professional training, the correlational method established a direct relationship between the level of academic training and the scope of professional authority, and the descriptive method provided a detailed description of the concept of advanced practice nursing.

Results

An analysis of leading international models has made it possible to identify various strategic approaches to higher education for nurses. The Bologna Process played an important role in standardising degree structures and introducing the European Credit Transfer and Accumulation System (ECTS). Poland has demonstrated success in rapidly adapting to European Union standards. There, the social status of the profession has been significantly elevated through the expansion of legal authority, particularly the right to write prescriptions. However, low pay levels have resulted in a significant shortage of personnel in the healthcare system [4, 5]. Germany emphasises impeccable clinical preparedness through its dual education system, in which practical training is integrated into the work of university hospitals. However, issues of staff overload and inconsistencies in practical education remain [6]. The United States remains a global benchmark for professional autonomy. There, the role of a nurse practitioner is functionally equivalent to that of a primary care physician. This is supported by a robust scientific foundation and the integration of advanced technologies into the care process [7, 8].

Over the past 70 years, the USA has shown steady growth in the level of academic training (from 15 % in 1950 to 72 % in 2025). This has been achieved through a multi-level nursing education system comprising the Bachelor of Science in Nursing (BSN), Master of Science in Nursing (MSN) and Nurse Practitioner (NP) qualifications, which define the roles of nurse practitioners and enhance the profession's autonomy, improving access to care. Poland experienced active growth during the period from 2000 to 2010. The rapid development of academic training (up to 98% by 2025) was the result of direct alignment with EU Directives. Germany has shown the most dynamic growth since 2020. Having maintained a low level of academic training (8–10 %) for a long time, Germany only transitioned to university-level education after adopting the *Pflegeberufegesetz* in 2020. The sharp increase to 35 % over the past five years indicates recognition that the old model was unable to meet the demands of modern intensive care (Fig. 1).

In the USA, a four-year bachelor's degree followed by a master's degree qualifies someone to become a nurse practitioner. This entitles nurse practitioners to see patients independently, make diagnoses and prescribe treatment, effectively placing them on a par with primary care physicians in terms of their role. Their level of autonomy is rated at 5 points. In Germany, despite a high level of practical training, autonomy remains moderate. Nurses are independent in matters of care and management, but limited in clinical decision-making, with a level of autonomy rated at

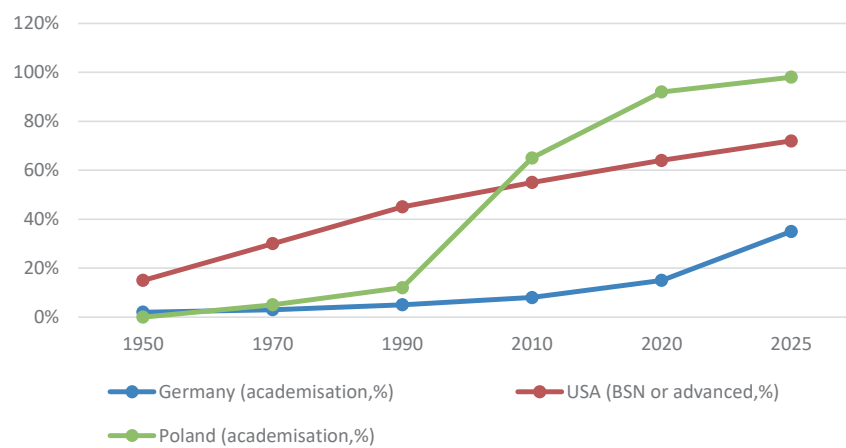


Fig. 1. Trends in the level of academic training in Nursing (1950–2025).

three points. In Poland, a nurse with a master's degree in nursing is authorised to write a limited number of prescriptions and order certain tests. However, the overall clinical strategy remains the responsibility of the physician, and the level of autonomy is set at two points (Fig. 2).

A comparative analysis of the domestic education system, using the example of the Ivan Horbachevsky Ternopil National Medical University shows that Ukraine has already achieved academic equivalence with global standards. In terms of credit load, duration of study and course content, Ukrainian bachelor's and master's programmes largely meet the highest international standards [9]. The current stage of development is characterised by the implementation of the principles of evidence-based nursing and in-depth clinical diagnostics. This ensures a high level of academic equivalence between Ukrainian education and international standards. However, legislative recognition of the professional autonomy of master's degree holders is also required. The introduction of

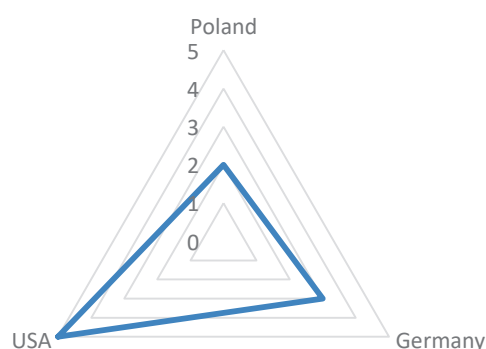


Fig. 2. Level of professional autonomy among nurses.

courses in clinical leadership and evidence-based nursing indicates that domestic education is developing in line with current global standards [10]. We compared the ratio of theoretical to practical components in bachelor's degree programmes in the USA, Germany, Poland and Ukraine (Fig. 3).

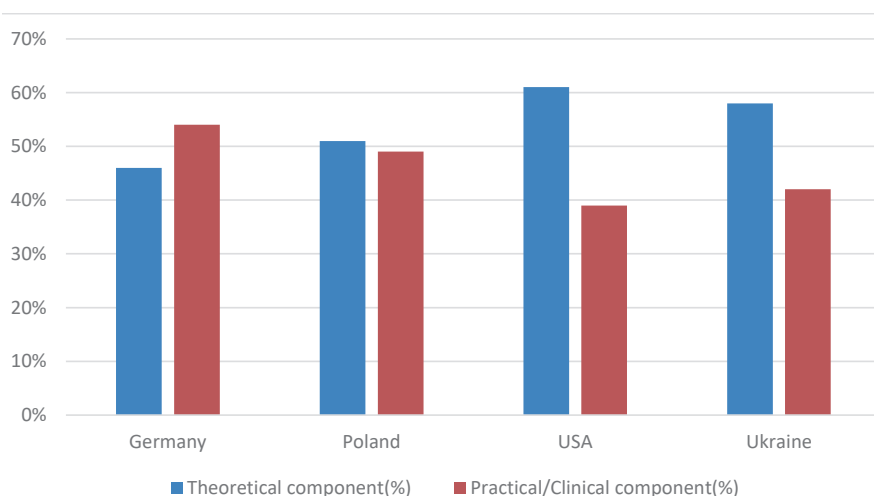


Fig. 3. Balance between theoretical and practical components in education.

Discussion

The fundamental difference in the way professional competencies are developed among nurses in the countries studied lies in their differing philosophical approaches to the profession. Germany has the most practical focus, with 54 % of the total programme (2,500 hours) devoted to this area, ensuring that graduates are fully prepared to provide direct patient care. Poland maintains a balance with 49 % (2,300 hours) of practical training, strictly adhering to EU directives. In contrast, the United States has the lowest percentage of practical training (39 %, or 1,800 hours), but this is offset by an exceptionally strong theoretical foundation (2,800 hours) and a well-developed simulation training system. In Ukraine, there is inconsistency in the provision of practical training. Educational programmes do not always meet international standards in terms of the number of clinical hours and the scientific content. At Ternopil National Medical University (TNMU), practical training (5 credits/150 hours) is integrated into each year of study to develop procedural skills.

Although Ukraine has implemented bachelor's, master's and PhD programmes in nursing, the adoption of international standards and simulation technologies appears necessary. A major challenge is the lack of a system for defining the roles of nurses with different levels of education in educational and healthcare institutions amid a staffing shortage.

Conclusions

1. An analysis of international experience has shown that the training models in Poland, Germany and the USA provide effective routes to developing professional autonomy via different mechanisms. The Polish model, in particular, demonstrates successful European integration by granting master's degree holders the

right to write prescriptions. The German model emphasises impeccable clinical preparedness through a dual education system, while the American model serves as a global benchmark where nurse practitioners function as full clinical decision-making partners with physicians.

2. A comparative analysis of structural-logical diagrams and training curricula in Ukraine, using the example of Ivan Horbachevsky Ternopil National Medical University, has demonstrated the full academic equivalence of the domestic model to international standards. In terms of ECTS credits and study duration, which includes a four-year bachelor's programme and a two-year master's programme, the Ukrainian system ensures that graduates are highly competitive and can integrate into the global medical community without a lengthy adaptation period.

3. However, the study revealed a critical functional gap: the mismatch between the high level of academic training of Ukrainian nurses with higher education and their extremely limited professional autonomy under national legislation. Unlike in developed countries, where educational level directly correlates with clinical authority, nurses with master's degrees in Ukraine remain legally restricted in their ability to make independent decisions, hindering the development of the field.

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Conflict of interest

The authors declare no conflict of interest.

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Порівняльний аналіз вищої медсестринської освіти в Україні та за кордоном

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Анотація. У сучасному світі медична(ий) сестра(брат) посідає(ють) ключове місце у системі охорони здоров'я, виступаючи не лише виконавцями призначень, а й самостійними фахівцями, які здійснюють догляд, координують лікування та займаються просвітницькою роботою. Зростання вимог до професії зумовлює необхідність отримання саме вищої освіти. Для України, яка перебуває у процесі реформування медичної галузі та стикається з кадровим дефіцитом через війну та міграцію, аналіз світового досвіду академізації медсестринства є критично важливим для розбудови власної стійкої системи підготовки кадрів. Метою дослідження було провести комплексний аналіз системи вищої медсестринської освіти у Польщі, Німеччині, США та в Україні, визначити їхні спільні та відмінні риси, а також обґрунтувати можливості використання цього досвіду для модернізації підготовки медичних сестер(братів) в Україні. У процесі дослідження встановлено, що сучасна вища медсестринська освіта бакалаврського і магістерського рівнів є багатокомпонентною структурою, яка гармонійно включає професійну, науково-дослідну, управлінську та педагогічну складові, що дозволяє готувати фахівців як клінічних лідерів та організаторів охорони здоров'я. Історико-теоретичний аналіз дозволив розглянути класичні моделі сестринства Ф. Найтінгейл, які до сьогодні формують надійний науковий і філософський фундамент професії, визначаючи догляд як самостійну гуманістичну дисципліну. В межах порівняльного аналізу було детально проаналізовано національні моделі підготовки та юридичний статус медичних сестер(братів) у чотирьох країнах: Україні, Польщі, Німеччині та США. У результаті проведеного дослідження здійснено комплексний порівняльний аналіз моделей вищої медсестринської освіти в Україні, Польщі, Німеччині та США, що дозволило обґрунтувати стратегічні напрямки у розвитку цієї галузі. Доведено, що сучасне світове медсестринство остаточно еволюціонує у самостійну науково-клінічну дисципліну, де магістерський рівень є базою для формування концепції розширеної медсестринської практики.

Ключові слова: вища медсестринська освіта; медсестринство; розширена медсестринська практика; бакалаврський рівень; магістерський рівень; клінічне лідерство; академізація медсестринства.



Microbiological characteristics of ulcerative lesions in t2dm with consideration of the Wagner classification model

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Abstract. According to monitoring studies, the number of patients with type 2 diabetes mellitus among the population of Ukraine increases annually by an average of 5–7 %, followed by the development of Diabetic Foot Syndrome, the pathogenesis of which is caused by massive microbial contamination. A comprehensive approach to the diagnosis and treatment of this pathology, incorporating both the microbiological aspect and the use of various classification scales, will facilitate the standardization of clinical assessment and simplify the selection of therapeutic strategies. Objective of the study: to determine the relationship between the severity of purulent-necrotic lesions in Diabetic Foot Syndrome in patients with Type 2 Diabetes Mellitus and the degree of microbial contamination according to the Wagner classification. The study included wound exudate obtained from 75 patients with Type 2 Diabetes Mellitus complicated by Diabetic Foot Syndrome. The severity of soft tissue destruction was assessed by stratifying patients using the Wagner classification. Microbiological analysis was performed at the Department of Microbiology, Virology, and Immunology of I. Horbachevsky Ternopil National Medical University. The study findings demonstrated that the peak incidence of Diabetic Foot Syndrome was observed in the 61–70 age group: 34.6 % among men and 13.3 % among women. Assessment of the degree of carbohydrate metabolism compensation revealed a predominance of the subcompensation stage (78.6 %). According to the Wagner classification, grade IV lesions were predominant (82.7 %), in which strains of *Klebsiella* spp. and *Pseudomonas aeruginosa* were identified. According to the Wagner classification, a high frequency (82.7 %) of grade IV lesions was established, with a predominance of deep purulent-necrotic lesions associated with the presence of antibiotic-resistant strains of *Klebsiella* spp. and *Pseudomonas aeruginosa*.

Keywords: Diabetes Mellitus; Diabetic Foot Syndrome; microorganisms; Wagner classification; microbiota.

Introduction

Diabetic Foot Syndrome (DFS) is a multifactorial complication of Type 2 Diabetes Mellitus (T2DM) that combines an infectious process, impaired perfusion, immune dysregulation, and progressive

tissue destruction, and requires radical approaches to the debridement of purulent-necrotic foci [1–3]. The development of this complication is closely associated with both microvascular and macrovascular complications, as well as microbial contamination.

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Microbiological analysis of wound exudate in patients with Diabetic Foot Syndrome allows for the identification of complex microbial associations, in which Gram-positive cocci have traditionally played a leading role. However, recently there has been a clear trend toward an increasing proportion of Gram-negative bacteria, particularly members of the family *Enterobacteriaceae*, in the structure of pathogens. Studies of the microbiome of poorly healing ulcers indicate the presence of specific microbial associations that suppress local immunity. As a rule, polymicrobial infections are more frequently observed in chronic cases that have previously been treated with antibiotics [4–6].

Particular concern is posed by staphylococci and representatives of the genus *Klebsiella*, which often act as dominant components of microbial communities. The prevalence of *Klebsiella pneumoniae* in diabetic foot infections is one of the significant challenges requiring the development of new therapeutic strategies. In addition to typical pathogens, rare microorganisms are increasingly being identified in the wounds of patients with Type 2 Diabetes Mellitus, such as *Raoultella ornithinolytica* and *Raoultella planticola*. The detection of such opportunistic pathogens indicates profound changes in the ecology of the wound process in the context of immunodeficiency states [7–9].

A detailed analysis of species composition is critically important for preventing the spread of the pathological process to deeper structures, including bone tissue.

In modern clinical practice, the Wagner classification is used to characterize the severity of ulcerative lesions and is the most widely applied system for assessing purulent-necrotic processes in the diabetic foot. This system enables diabetic ulcers to be classified into six levels based on wound depth. Level 0 indicates intact skin. Level 1 corresponds to a superficial ulcer. Level 2 denotes a deeper ulcer extending to tendons, bone, or joints. Level 3 represents a severe ulcer with an abscess or infected bone. Level 4 indicates the development of gangrene in the forefoot, while level 5 corresponds to gangrene involving the entire foot [6].

Prediction of the course of Diabetic Foot Syndrome and the development of individualized, comprehensive surgical treatment methods remain priority tasks, as a personalized approach can significantly reduce the number of major amputations. Assessment of the patient's condition using the Wagner classification allows for objective evaluation of lesion severity at the time of hospitalization. The combination of radical surgical debridement with pathogenetically justified correction of metabolic disorders is a key factor in improving the quality of life of such patients [10–12].

The aim of the study: to determine the relationship between the severity of purulent-necrotic lesions

in Diabetic Foot Syndrome in patients with Type 2 Diabetes Mellitus and the degree of microbial contamination according to the Wagner classification.

Materials and Methods

Wound contents from 75 patients aged 45–75 years with Type 2 Diabetes Mellitus complicated by Diabetic Foot Syndrome were examined. The patients were treated in the surgical department of the Ternopil Municipal Emergency Hospital (MNE) during the period from January 2025 to February 2026. Among the patients included in the study, the state of subcompensation of carbohydrate metabolism predominated (93.5 %), whereas signs of decompensation were observed in 8.5 % of individuals. The clinical presentation at the time of hospitalization was characterized by pronounced purulent-necrotic lesions of various localizations in the foot region.

The patient cohort was formed based on an analysis of clinical forms and the duration of the underlying disease. Exclusion criteria included: the presence of type 1 diabetes mellitus, concomitant somatic pathology in the stage of decompensation, as well as cases of Diabetic Foot Syndrome without disruption of skin integrity. All patients included in the study had a complicated course of Diabetic Foot Syndrome with manifestations of purulent-necrotic lesions (abscesses, phlegmon, purulent tenosynovitis and arthritis, gangrene), which required urgent surgical treatment.

The severity and depth of purulent-necrotic soft tissue destruction were assessed by stratifying patients according to the Wagner classification [12].

Biological material (wound exudate, purulent content) was collected under aseptic conditions in compliance with current regulatory protocols. The obtained samples, placed in sterile tubes, were transported within 2 hours to the microbiological laboratory of the Department of Microbiology, Virology, and Immunology of I. Horbachevsky Ternopil National Medical University. Primary inoculation of the material was performed on a broad range of differential diagnostic and selective media. Incubation was carried out at +37 °C for 24–48 hours.

Comprehensive identification of the isolated pathogens included the use of bacterioscopic and bacteriological methods.

All studies were conducted in accordance with fundamental bioethical standards and the requirements of the Declaration of Helsinki, as confirmed by the conclusion of the Bioethics Committee of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine (Protocol No. 77 dated April 18, 2024).

Results

The object of clinical and microbiological analysis was the wound content of 75 patients with Type 2 Diabetes Mellitus complicated by Diabetic Foot Syndrome. The age range of the examined cohort was 45–75 years.

The distribution of patients by sex and age characteristics demonstrated a predominance of males – 74.6 % (n=56) compared to females – 25.3 % (n=19). The mean age of patients was (64.3±4.7) years (Table 1).

A detailed analysis of the age structure revealed that the peak incidence occurred in the 61–70 age group. In this segment, the frequency of purulent-necrotic complications was the highest, accounting for 34.6 % among males and 13.3 % among females, which collectively defines this age category as the highest-risk group.

Comprehensive examination of patients was based on the use of clinical and instrumental methods, along with thorough analysis of complaints and medical history. The diagnostic program included verification of the type of diabetes mellitus and assessment of glycemic control (Table 2). Particular attention was paid to differentiation of the pathogenetic form of Diabetic Foot Syndrome, as well as detailed characterization of the localization, nature, and extent of the purulent-necrotic process.

According to the study results, the stage of subcompensation was identified in 61.3 % of male patients and in 17.3 % of female patients (Table 2). A

state of decompensation was observed in 21.3 % of all patients included in the study.

The severity and depth of purulent-necrotic tissue destruction in the foot were assessed in accordance with F. W. Wagner's classification criteria. According to the results of the analysis, grade I was diagnosed in only 2.7 % of cases (n=2), with the microbial flora comprising *S. aureus*, *R. planticola*, and *R. ornithinolytica*; Grade II was confirmed in 14.6 % of patients (n=11) with the presence of *E. faecalis* and *S. aureus*; Grade III was not observed in the study cohort (0 %); Grade IV was the most common and was recorded in 82.7 % of patients (n=62), where the greatest species diversity was observed: *S. aureus*, *S. haemolyticus*, *P. aeruginosa*, *C. amycolatum*, *S. agalactiae*, *P. fragi*, *P. taetrolens*, *E. faecalis*, *Rothia amara*, *K. pneumoniae*, *P. alimentarius* (Table 3, Fig.). The main types of surgical interventions included necrectomy (49 %), minor amputations (toe amputations and resections of metatarsophalangeal segments) – 25 %, as well as transmetatarsal amputations – 31 %. At the same time, in 64–75 % of cases, necrectomy was only the first stage of treatment, followed by the need for repeated surgical revisions or extension of the intervention volume, depending on the spread of the pathological process.

According to the results of the microbiological study, the leading role in the microbial profile of Diabetic Foot Syndrome belongs to Gram-positive microflora, particularly representatives of the genera

Table 1. Age distribution of patients with T2DM and DFU

Sex	Women		Men	
	n=19	%	n=56	%
Up to 50 years	0	0	5	6.6
51–60	7	9.3	20	26.6
61–70	10	13.3	26	34.6
Over 70 years	2	2.6	5	6.6

Table 2. Distribution of patients with T2DM complicated by DFU according to the grade of carbohydrate metabolism compensation

Sex	Grade of compensation					
	Compensation <10.0		Subcompensation <13.9		Decompensation >13.9	
	n=0	%	n=59	%	n=16	%
Women	0	0	13	17.3	6	8.0
Men	0	0	46	61.3	10	13.3

Table 3. Distribution of patients with DFU according to the depth of ulcer defect spread, according to the Meggitt – Wagner classification

Sex	Grade									
	I		II		III		IV		V	
	n=2	%	n=11	%	n=0	%	n=62	%	n=0	%
Women	1	2.7	4	5.3	0	0	11	14.7	0	0
Men	0	0	7	9.3	0	0	51	68.0	0	0

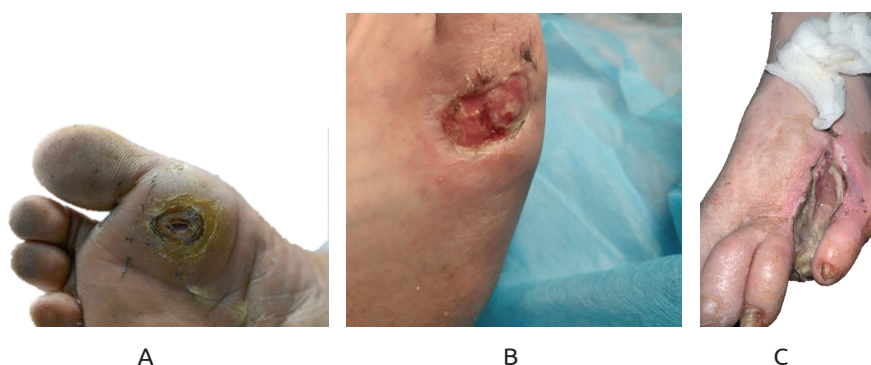


Fig. Grades of soft tissue involvement in patients with T2DM complicated by DFU according to the Wagner classification: A – Grade I, B – Grade II, C – Grade IV.

Staphylococcus spp. (31.0 %) and *Streptococcus spp.* (18.0 %).

A number of microorganisms, including *Micrococcus luteus*, *Streptococcus agalactiae*, *Acinetobacter lwoffii*, *Raoultella planticola*, and others, were identified with a frequency of less than 1.0 %.

Thus, the etiological structure of purulent-necrotic complications in Type 2 Diabetes Mellitus with Diabetic Foot Syndrome is predominantly formed by Gram-positive facultative anaerobic and aerobic cocci. At the same time, the leading role in the development of the pathological process belongs to *S. aureus*.

Transmetatarsal amputations were performed in cases of necrosis spreading to several rays of the foot or in total involvement of the forefoot. In this group of patients, polymicrobial associations predominated, involving *Klebsiella spp.* and *Pseudomonas aeruginosa*, which were characterized by a high level of antibiotic resistance. The presence of Gram-negative multidrug-resistant flora correlated with greater depth of tissue involvement, a more aggressive course of the infectious process, and the need for more extensive surgical intervention. Thus, a clear relationship is observed: Gram-negative multidrug-resistant microflora → more severe course → higher level of amputation.

Discussion

A characteristic feature of Type 2 Diabetes Mellitus is the tendency to develop various complications, among which a leading place is occupied by Diabetic Foot Syndrome, venous trophic ulcers of the lower extremities, as well as neoplastic and postoperative wounds. One of the determining factors that slows reparative processes and impairs physiological wound healing is bacterial infection. According to scientific data, the clinical manifestation of infection in the course of Diabetic Foot Syndrome is observed in approximately 30 % of patients [13, 14].

Given the complexity of the disease course, particular attention is paid to international classifications that allow standardization of the approach to assessing the severity of the patient's condition.

The Wagner scale is widely used to evaluate the severity of lesions and is based on the analysis of a range of local signs: hyperemia, edema, pain syndrome, wound size and depth, as well as the risk of amputation in severe cases.

At Grade 0 the skin of the foot remains intact, deformities, dryness, or calluses may be present, but without signs of ulceration, indicating an increased risk of further lesions; Grade 1 is characterized by the presence of a superficial ulcer limited to the epidermis and dermis; Grade 2 – the ulcerative process extends deeper and affects subcutaneous tissue and soft tissues, often accompanied by the development of infection; Grade 3 – a deep ulcer is observed, which may be associated with the formation of abscesses, osteomyelitis, or septic arthritis; Grade 4 is associated with the development of localized gangrene (dry or wet), involving one part of the foot, for example a toe, with necrosis of all tissue layers in this area; Grade 5 is characterized by the presence of extensive gangrene affecting a significant part or even the entire foot, often requiring radical surgical intervention, including amputation [15].

The intensification of tissue hypoxia and impairment of microcirculation, in combination with existing ischemia, are consequences of the superimposition of bacterial infection in the wound process.

The microbiota of Diabetic Foot Syndrome is a dynamic structure functioning within a polymicrobial matrix of purulent-necrotic lesions. Complex interspecies interactions of microorganisms in such an environment determine the pathogenesis of chronicity and significantly inhibit regenerative processes. According to the analysis of the literature, the most common isolates identified in diabetic ulcers include *Staphylococcus aureus*, *Streptococcus spp.*, *Klebsiella spp.*, *Corynebacterium spp.*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Enterococcus faecalis* [4, 5, 7].

The complex nature of the disease requires the use of modern and clinically validated classification systems, one of which is the PEDIS classification (Perfusion, Extent/size, Depth/tissue loss, Infection).

It encompasses not only the vascular component but also key parameters of the lesion, including the presence and nature of the infectious factor. In patients with Diabetes Mellitus, due to an impaired immune response, the infectious process develops rapidly, often with subtle clinical manifestations at early stages. All of the above significantly complicates timely diagnosis, allowing the infection to penetrate deep tissues, including muscles, fascia, and bone, causing osteomyelitis and leading to generalization of the process in the form of sepsis [16].

Conclusions

1. The results of the clinical and microbiological analysis confirm that Diabetic Foot Syndrome in Type 2 Diabetes Mellitus is not only an infectious but primarily a surgical problem requiring early and radical intervention. The high frequency of Grade IV according to the Wagner classification (82.7 %) indicates the

predominance of patients with deep purulent-necrotic lesions, gangrene, and probable involvement of bone structures, necessitating organ-preserving or amputation procedures.

2. The presence of polymicrobial microflora involving *Klebsiella* spp. and *Pseudomonas aeruginosa* has been established; these are characterized by a high level of antibiotic resistance and directly influence the severity of the infectious process.

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Conflict of interest

None.

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Мікробіологічна характеристика виразкових уражень при цукровому діабеті 2 типу з урахуванням класифікаційної моделі Wagner

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Анотація. Відповідно до моніторингових досліджень, щорічно відбувається збільшення числа хворих на цукровий діабет (ЦД) 2 типу серед населення України в середньому на 5–7 % із подальшим розвитком синдрому діабетичної стопи (СДС), патогенез якого зумовлений масивною мікробною контамінацією. Комплексний підхід до діагностики та лікування даної патології, який включатиме як мікробіологічний аспект, так і використання різноманітних класифікаційних шкал, сприятиме стандартизації клінічної оцінки та полегшуватиме вибір лікувальної тактики. Метою дослідження було встановити залежність ступеня тяжкості гнійно-некротичних уражень при СДС у хворих на ЦД 2 типу від мікробної контамінації відповідно до класифікації Wagner. У дослідженні використано рановий вміст, одержаний від 75 пацієнтів із ЦД 2 типу, ускладнений СДС. Оцінку тяжкості деструкції м'яких тканин проводили шляхом стратифікації хворих із використанням класифікації Wagner. Мікробіологічний аналіз здійснювали на базі кафедри мікробіології, вірусології та імунології Тернопільського національного медичного університету імені І. Я. Горбачевського МОЗ України. Результати дослідження показали, що пік СДС був у віковій групі 61–70 років: 34,6 % – серед чоловіків та 13,3 % – серед жінок. Оцінка ступеня компенсації вуглеводного обміну показала переважання стадії субкомпенсації (78,6 %). Згідно з класифікацією Wagner, домінуючим (82,7 %) виявився IV ступінь, при якому верифікувалися штами *Klebsiella* spp. та *P. aeruginosa*. Таким чином, за класифікацією Wagner встановлено високу (82,7 %) частоту IV ступеня та переважання глибоких гнійно-некротичних уражень з наявністю антибіотикорезистентних штамів *Klebsiella* spp. та *P. aeruginosa*.

Ключові слова: цукровий діабет; синдром діабетичної стопи; мікроорганізми; класифікація Wagner; мікрофлора.



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Prospects for modern cardiac rehabilitation: synergy of perspectives among Healthcare professionals and specialists

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Abstract. In the context of a full-fledge war in Ukrainian, the local healthcare system is operating under significant strain, especially in the sphere of rehabilitation services. This situation creates a demand for new approaches to cardiac rehabilitation reflected in the new version of the Law of Ukraine "On Rehabilitation in the Healthcare" (2020). The modern concept of cardiac rehabilitation presumes the transition from short-term post-acute cardiovascular programs to a continuous model of lifelong cardiovascular health management. According to the World Heart Federation Roadmap recommendations (2026), key components of effective cardiac rehabilitation are considered to be a multidisciplinary approach, consisting of timely referral of patients, comprehensive clinical assessment, management of cardiovascular risk factors, psychosocial support, continuous monitoring of treatment outcomes, and implementation of modern healthcare models, including telerehabilitation and digital health techniques. The implementation of the above scenarios may improve access to rehabilitation services, increase patients' functional capabilities and life quality, and reduce the risk of recurrent cardiovascular events. The objective of the study was to analyze a dataset of contemporary approaches to cardiac rehabilitation and to assess the feasibility of their planting in the wartime Ukrainian healthcare system.

Keywords: cardiac rehabilitation; cardiovascular diseases; multidisciplinary approach; telerehabilitation; quality of life.

Introduction

The wartime Ukrainian healthcare system is struggling to deliver decent rehabilitation services to the population that does not take direct part in the hostilities and nevertheless featuring high trauma incidence. These circumstances can indirectly influence the prevalence of cardiovascular pathologies, and therefore the need for provision of appropriate rehabilitation care. According to the Law of Ukraine "On Rehabilitation in the Healthcare" (2020) [1], to achieve the optimal level of the physical component in sick individuals, a set of individualized measures for suitable social integration and everyday activities should be developed, including those related to interaction with the environment and personal independence. According to various sources, some 100–120 thousand people require direct cardiac rehabilitation in Ukraine. To cover largest possible number of such patients, it is necessary to widely implement modern methodological approaches to cardiac rehabilitation, as the one remains safe service featuring low risk of complications, offering such benefits as improved cardiovascular function, reduced hospitalization incidence, and better quality of life. One step in this direction is the implementation of the project "Rehabilitation in Ukraine" [2].

The aim of the study: to analyze modern literary sources on the aspects of implementing cardiac rehabilitation methods in modern conditions.

Materials and Methods

While searching the required materials for writing the article, we used PubMed, Google Scholar, Scopus, Web of Science databases, the electronic resources of the V. I. Vernadskyi National Library of Ukraine, the National Health Service (NSZU) website, and electronic archives

of domestic medical publications, and further processed the results using bibliosemantic and systematic analysis methods. We regarded sources published in the last 5 years our first choice.

Results

In the most common definition of recent decades, cardiac rehabilitation is considered a controlled list of interventions recommended for patients recovering from cardiovascular events. The interventions are emphasized to be aimed at reducing psychological and physiological stress, the risk of mortality, prevention of recurrent hospital admissions, and improvement of cardiovascular function for better quality of life. However, today, the modern paradigm of medicine is undergoing a fundamental transformation, shifting the focus from short-term treatment of acute conditions to long-term prevention and health maintenance, which requires a fresh glance at cardiac rehabilitation (CR) (Fig.1).

It is generally accepted that personalized cardiac rehabilitation programs are divided into 3 major segments: inpatient, outpatient, and long-term care. In the final phase, the emphasis is made on self-control, regular physical exercises, and continuous medical care for keeping the cardiovascular system safe [3]. The change of paradigm consists in certain modernization of approaches to planning, primarily in the third segment. In fact, part of the second segment and completely whole third one are considered an integral part of secondary prevention in management of almost all cardiovascular diseases, as they result from programs conceptually developed by multidisciplinary teams of specialists under the guidance of certified rehabilitation physicians (RP), thus presuming further management of risk

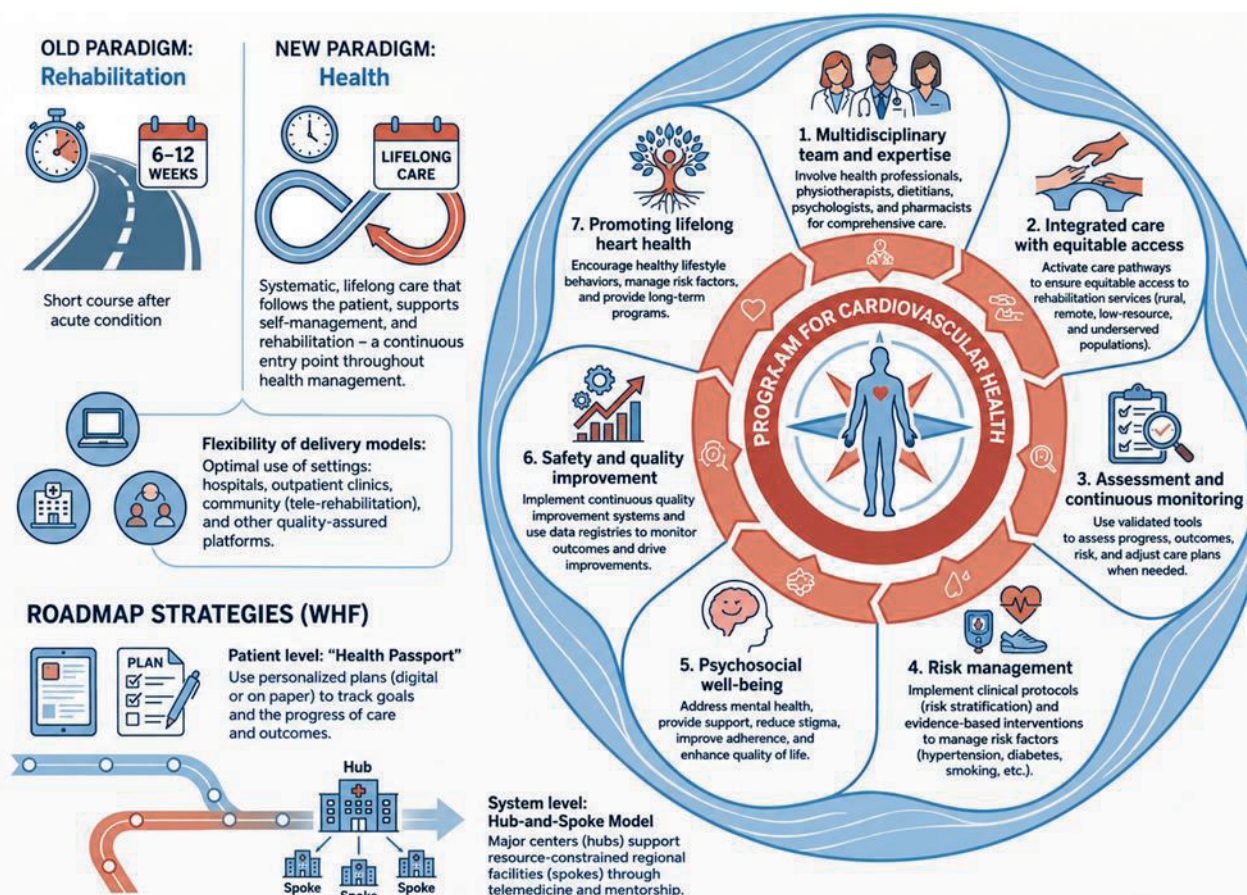


Fig. 1. Integrated model of a modern cardiac rehabilitation program: the transition from short-term prevention to systematic, lifelong patient management (Author's drawing courtesy of Notebook LM, Google AI Plus; developed by Google LLC (generated on July 28, 2026)).

factors, lifestyle changes, and long-term follow-up of serious cardiovascular events [4]. In practical terms, this makes kind of roadmap that describes the objective of cardiac rehabilitation efforts, which, in the opinion of the World Heart Federation (WHF), contribute to achieving the optimal level of sufferer's interaction with the environment, social integration, and independence of patients [5] (Fig. 2)

Discussions

So, the most important aspect of the future strategy is considered integrated CR model grounded on new organizational platform modernized in terms of changing social administration, personalized comprehension of the problems and aggregated recommendations by patients.

Beyond that, within the above CR model, one should pay attention to the fact that the recommendations emphasize the essential role of physical exercise:

- Exercise as "medicine": The exercise is considered a full-fledged therapeutic tool, comparable in efficacy to antihypertensive medicines [6, 7].
- Medicinal strategy combined with rehabilitation. Taking medicines for weight loss (GLP-1) must be accompanied by strength exercises to counter skeletal muscle loss [8, 9].

complicated by strength exercises to counter skeletal muscle loss [8, 9].

- General diabetes and metabolic control: Physical exercises increase muscle sensitivity to insulin, which works in synergy with antidiabetic medicines [1–12].
- Intensive lipid lowering to target figures in case of various pathologies: The standard is administration of multiple classes of medicines to achieve target LDL-C figures [13].
- Monitoring blood pressure and its changes during and post exercise [14].
- It should be borne in mind that physical exercise alone, even combined with a diet modification, will not be able to contribute to normalization of blood pressure and keeping the figures normal within 24-hour in case of high initial blood pressure readings [15, 16].
- Use of digital or hard "cardiovascular health passports" allowing patients to simultaneously track their medication schedule and physical activity for achieving goals [17].

In the future, it's quite possible to expect widespread implementation of the following new patient care techniques:

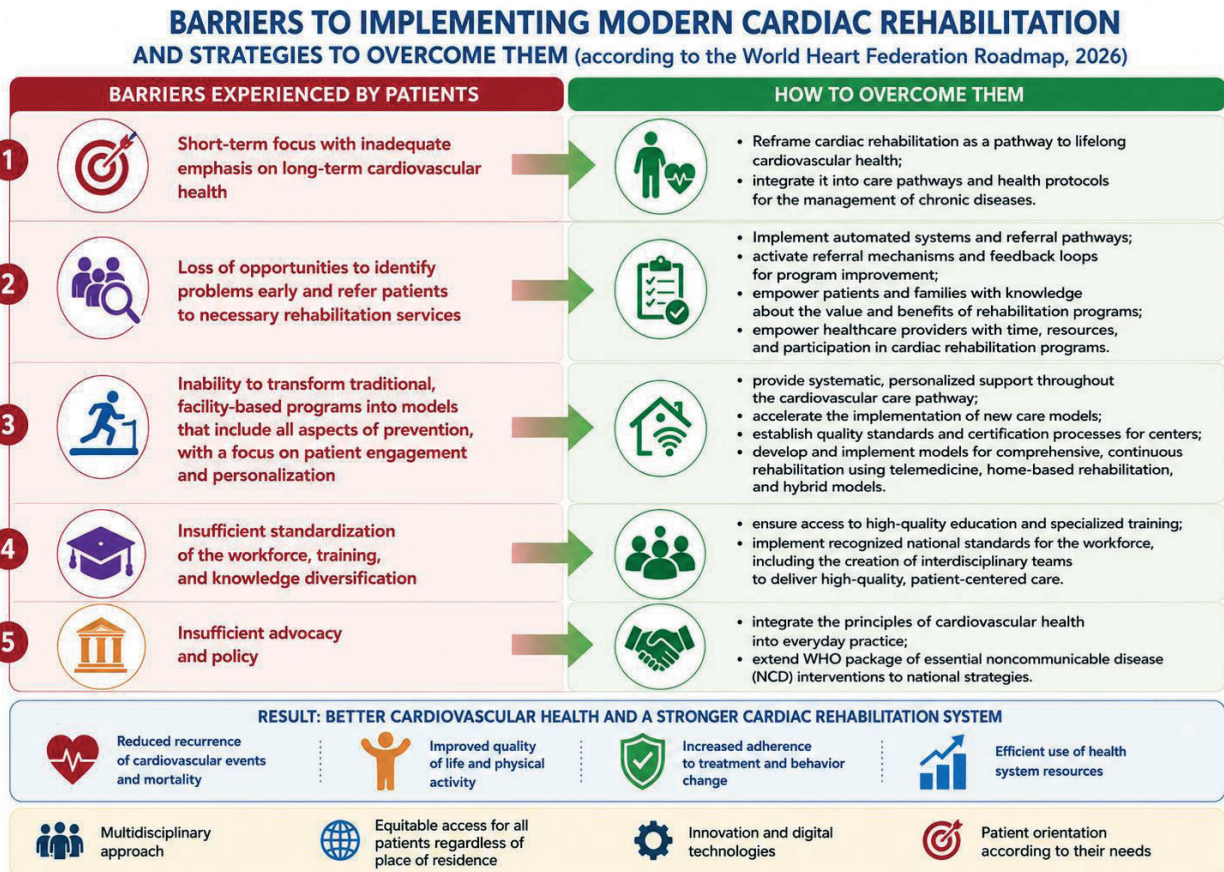


Fig. 2. Strategic solutions for overcoming five interconnected barriers that patients face when planning rehabilitation activities (Author's drawing courtesy of Chat GPT, Open AI (generated on July 31, 2026)).

• Hybrid models of rehabilitation programs: combining in-person visits with remote monitoring via wearables to allow maintaining exercise intensity and real-time monitoring of the patient's condition [18].

• Application of artificial intelligence (AI) for rehabilitation planning: it is considered a tool for personalizing training plans and predicting risks, although its widespread instrumentation still requires strict regulation [13].

New approaches will ensure the systemic CR nature: personalization, process improvement, patient-centeredness, changing terminology (parlance), and partnership [5]. All above measures will contribute to a paradigm shift from short-term programs to lifelong health management and ensuring cost-effective CR programs in general terms [22].

Conclusions

Modern cardiac rehabilitation is an integral part of

secondary prevention of cardiovascular diseases which should be considered a continuous, personalized process aimed at long-term reduction of cardiovascular risk, maintaining functional capacity of patients, and better life quality. The implementation of this concept in accordance with the recommendations of the World Heart Federation opens up new opportunities for better effectiveness of rehabilitation care with due account to current challenges to the Ukrainian healthcare system.

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Conflict of interest

The author declares no conflict of interest.

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Перспективи сучасних методів кардіореабілітації: синергія думок спеціалістів та фахівців у сфері охорони здоров'я

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Анотація. В умовах повномасштабної війни система охорони здоров'я України функціонує під значним навантаженням, особливо в наданні реабілітаційних послуг. Така ситуація підкреслює необхідність впровадження нових підходів до кардіологічної реабілітації, що передбачалось з прийняттям Закону України «Про реабілітацію у сфері охорони здоров'я» (2020 р.). Сучасна концепція кардіологічної реабілітації передбачає перехід від короткотривалих програм після гострих серцево-судинних подій до безперервної моделі довічного управління серцево-судинним здоров'ям. Відповідно до рекомендацій World Heart Federation Roadmap (2026) ключовими

компонентами ефективної кардіологічної реабілітації є мультидисциплінарний підхід, своєчасне направлення пацієнтів, комплексна клінічна оцінка, управління серцево-судинними факторами ризику, психосоціальна підтримка, безперервний моніторинг результатів лікування та впровадження сучасних моделей надання медичної допомоги, зокрема телереабілітації та цифрових технологій охорони здоров'я. Впровадження цих підходів може покращити доступ до реабілітаційних послуг, підвищити функціональні можливості та якість життя пацієнтів, а також знизити ризик рецидивів серцево-судинних подій. Метою було проаналізувати сучасні дані щодо оновлених підходів до кардіологічної реабілітації та оцінити доцільність їх впровадження в українській системі охорони здоров'я в умовах воєнного часу.

Ключові слова: кардіологічна реабілітація, серцево-судинні захворювання, мультидисциплінарний підхід, телереабілітація, якість життя.



Diagnostic significance of the HOMA-IR index in patients with obesity

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Abstract. Obesity is one of the leading medical and social problems of our time, accompanied by an increased risk of developing metabolic and cardiovascular diseases. One of the key pathophysiological mechanisms of metabolic disorders in obesity is insulin resistance, the timely detection of which is of great importance for early diagnosis and prevention of complications. The HOMA-IR index is an accessible calculated indicator that is widely used to assess tissue sensitivity to insulin. The aim of the study was to conduct a comparative analysis of the HOMA-IR index and carbohydrate metabolism indicators in patients with diabetes mellitus and in patients with diabetes mellitus combined with obesity, compared with practically healthy individuals. A statistically significant increase in the HOMA-IR index was established in patients with diabetes mellitus compared with practically healthy individuals, and the most pronounced changes were observed in patients with a combination of diabetes mellitus and obesity. A similar trend was established regarding carbohydrate metabolism indicators. Further study of HOMA-IR in patients with obesity and diabetes mellitus may contribute to improving the early diagnosis of insulin resistance, assessment of metabolic risk, and optimization of individualized preventive and therapeutic measures.

Keywords: obesity; insulin resistance; glucose; risk; insulin; metabolic disorders.

Introduction

Obesity is a chronic multifactorial disease characterized by excessive accumulation of adipose tissue in the body and accompanied by significant metabolic disturbances. In the modern world, the prevalence of obesity is steadily increasing, making it one of the leading public health problems. The importance of this pathology is determined not only by aesthetic aspects, but primarily by the high risk of developing severe complications such as type 2 diabetes mellitus,

atherosclerosis, ischemic heart disease, and arterial hypertension [1, 2].

A key pathophysiological mechanism that links obesity with the above conditions is insulin resistance-reduced sensitivity of peripheral tissues to insulin. This leads to compensatory hyperinsulinemia, which at early stages may maintain normal glycemia, but over time exhausts pancreatic β -cells and contributes to the development of disorders of carbohydrate metabolism [3].

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The HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index is one of the most widely used and informative methods for assessing insulin resistance in clinical practice and research studies. Insulin resistance is considered a key pathogenetic mechanism in the development of obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases. Under current conditions, with the increasing prevalence of obesity, the problem of early detection of metabolic disturbances has become especially relevant [4].

The HOMA-IR index is based on measuring fasting glucose and insulin levels and allows evaluating the degree of tissue sensitivity to insulin. Advantages of this method include simplicity of performance, availability, and high information value, which makes it convenient for screening studies and for assessing the risk of endocrine and metabolic disorders.

An increase in the HOMA-IR value indicates a decrease in insulin sensitivity of peripheral tissues and is associated with the progression of disturbances in carbohydrate and lipid metabolism. It has been established that insulin resistance is an important factor in the development of obesity complications, including arterial hypertension, atherosclerosis, and type 2 diabetes mellitus [5, 6].

Thus, determining the HOMA-IR index has important diagnostic and prognostic significance in patients with obesity, allowing timely detection of metabolic changes and implementation of prevention strategies for severe complications.

In clinical practice, early detection of insulin resistance is of crucial importance, as it enables timely initiation of preventive and therapeutic interventions. One of the most common indirect methods for evaluating it is the HOMA-IR index (Homeostasis Model Assessment of Insulin Resistance), which is based on measuring fasting glucose and insulin levels. The simplicity of calculation and sufficient informativeness have made this index widely used both in scientific studies and in routine clinical practice [7, 8].

HOMA-IR allows a quantitative assessment of the degree of insulin resistance and identification of patients with elevated metabolic risk even before the appearance of clinical manifestations of type 2 diabetes.

This is especially relevant for individuals with obesity, in whom significant disorders of insulin metabolism may already exist even when glucose levels remain relatively stable [9].

Therefore, studying the diagnostic value of the HOMA-IR index in patients with obesity is an important direction of modern endocrinology, contributing to early diagnosis of metabolic disorders, assessment of the risk of developing type 2 diabetes mellitus, and development of effective preventive strategies [10].

The aim of the study: to conduct a comparative analysis of the level of the HOMA-IR index and glucose in patients with obesity and without obesity.

Materials and Methods

Sixty patients who underwent outpatient treatment were examined. Specifically, 20 were practically healthy (control group), 20 were patients with diabetes mellitus (Group 1), and the remaining 20 were patients with diabetes mellitus in combination with obesity (Group 2). The mean age of patients was (50 ± 3) years.

The HOMA-IR index was calculated using the following formula:

$$\text{HOMA-IR} = (\text{fasting glucose, mmol/L} \times \text{fasting insulin, } \mu\text{IU/mL}) / 22.5.$$

The obtained index allows assessing the degree of insulin resistance. In most studies, values of HOMA-IR above 2.5–2.7 are considered evidence of decreased tissue sensitivity to insulin; however, reference ranges may differ depending on age, sex, and characteristics of the studied population.

The HOMA-IR method is an available, non-invasive, and informative way to detect metabolic disturbances at an early stage in patients with obesity.

Statistical processing of the obtained results was performed using methods of mathematical statistics with the STATISTICA 8.0 software package (StatSoft, USA).

The results are presented as the mean value and standard deviation. Differences were considered statistically significant at $p < 0.05$.

Results

When analyzing the obtained laboratory blood test results, significant differences in the indicators of different groups were revealed (Table).

Table. Indicators of the HOMA-IR index and glucose in the patients of the studied groups

Study Groups		
Control group (n=20)	Group 1 (n=20)	Group 2 (n=20)
HOMA-IR Index		
25,4±0,35	26,3±0,44*	40,1±0,46*#
Glucose mmol/L		
4,1±0,11	6,8±0,54*	7,5±0,25*#

Notes: 1. * – significance of differences compared to the control group ($p < 0.05$);

2. # – significance of differences compared to Group 1 ($p < 0.05$).

Comparative analysis of the HOMA-IR index showed a significant increase in the studied groups compared to the control group. In particular, in patients of Group 1, the HOMA-IR index was 3.5 % higher than in the control group (26.3 ± 0.44 vs. 25.4 ± 0.35 ; $p < 0.05$). In patients of Group 2, this indicator exceeded the control group values by 57.9 % (40.1 ± 0.46 vs. 25.4 ± 0.35 ; $p < 0.05$) and was 52.5 % higher compared to Group 1 ($p < 0.05$) (Fig. 1).

Analysis of blood glucose levels also confirmed significant metabolic disturbances in the patients of the studied groups. Thus, in Group 1, glucose levels were 65.9 % higher than in the control group (6.8 ± 0.54 mmol/L vs. 4.1 ± 0.11 mmol/L; $p < 0.05$). In patients of Group 2, glucose concentration exceeded the control group values by 82.9 % (7.5 ± 0.25 mmol/L vs. 4.1 ± 0.11

mmol/L; $p < 0.05$) and was 10.3 % higher than in Group 1 ($p < 0.05$) (Fig. 2).

The obtained results indicate a pronounced increase in insulin resistance and carbohydrate metabolism disorders in patients with obesity, especially in the presence of concomitant metabolic changes.

Discussion

Analysis of the relationship between HOMA-IR index and blood glucose levels revealed a pronounced positive correlation. As the HOMA-IR index increased, there was a proportional rise in glucose concentration, indicating a close association between the degree of insulin resistance and carbohydrate metabolism disorders.

The obtained data allow us to suggest that the intensification of insulin resistance is accompanied

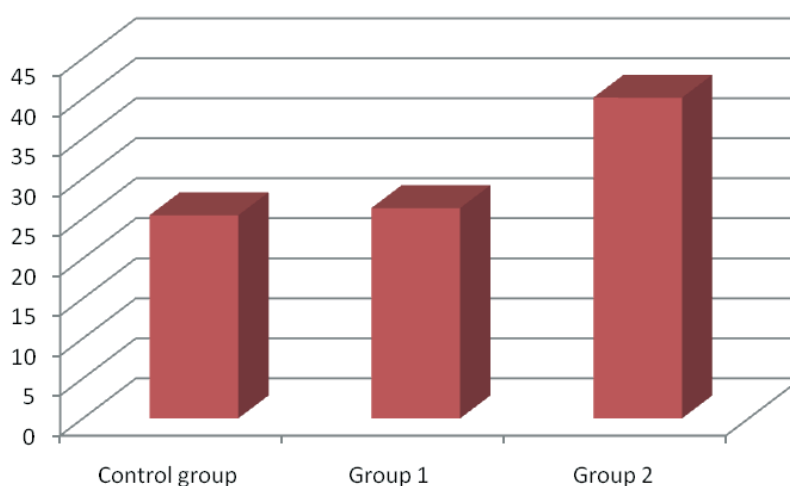


Fig. 1. Changes in the HOMA-IR index level in the blood of the studied groups.

Notes: 1. Significance of differences compared to the control group ($p < 0.05$);
2. Significance of differences compared to Group 1 ($p < 0.05$).

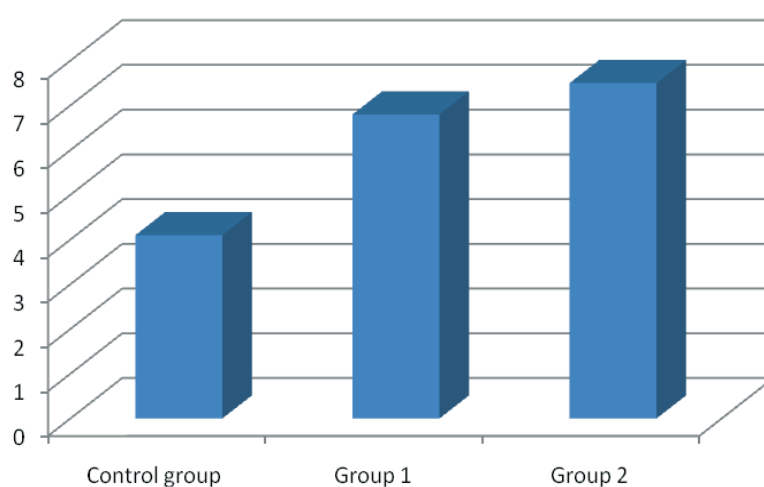


Fig. 2. Changes in blood glucose levels in the studied groups.

Notes: 1. Significance of differences compared to the control group ($p < 0.05$);
2. Significance of differences compared to Group 1 ($p < 0.05$).

by a progressive decrease in the efficiency of glucose utilization by tissues, clinically manifested as hyperglycemia. The strongest correlation was observed in patients of Group 2, which may indicate deeper metabolic disturbances in this cohort.

Thus, the HOMA-IR index can be considered not only as a separate diagnostic indicator of insulin resistance but also as a marker closely associated with glycemia levels, reflecting the overall degree of metabolic dysfunction in patients with obesity.

Conclusions

1. The results of the study indicate pronounced disturbances of carbohydrate metabolism and increased insulin resistance in patients with obesity. A significant increase in the HOMA-IR index and blood glucose levels was established in the studied groups compared to the control group. The most significant changes were observed in patients of patients with diabetes mellitus in combination with obesity, indicating progression of

metabolic disorders and reduced tissue sensitivity to insulin.

2. The increase in HOMA-IR values was accompanied by elevated blood glucose concentration, confirming a close relationship between insulin resistance and carbohydrate metabolism disorders. The data indicate high diagnostic informativeness of the HOMA-IR index in patients with obesity and the advisability of its use for early detection of metabolic changes and assessment of the risk of developing type 2 diabetes and other complications.

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Conflict of interest

The authors declare no conflict of interest.

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Діагностична значущість індексу НОМА-ІР у пацієнтів з ожирінням

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Анотація. Ожиріння є однією з провідних медико-соціальних проблем сучасності, що супроводжується підвищеним ризиком розвитку метаболічних та серцево-судинних захворювань. Одним із ключових патофізіологічних механізмів метаболічних порушень при ожирінні є інсулінорезистентність, своєчасне виявлення якої має важливе значення для ранньої діагностики та профілактики ускладнень. Індекс HOMA-IR є доступним розрахунковим показником, який широко використовується для оцінки чутливості тканин до інсуліну. Метою дослідження було провести порівняльний аналіз індексу HOMA-IR та показників вуглеводного обміну в пацієнтів із цукровим діабетом та у хворих на цукровий діабет, поєднаний з ожирінням, порівняно з практично здоровими особами. Встановлено статистично значуще підвищення індексу HOMA-IR у пацієнтів із цукровим діабетом, порівняно з практично здоровими особами, а найвираженіші зміни спостерігалися у хворих із поєднанням цукрового діабету та ожиріння. Аналогічна тенденція встановлена щодо показників вуглеводного обміну. Подальше вивчення HOMA-IR у пацієнтів з ожирінням та цукровим діабетом може сприяти вдосконаленню ранньої діагностики інсулінорезистентності, оцінці метаболічного ризику та оптимізації індивідуалізованих профілактичних і лікувальних заходів.

Ключові слова: ожиріння; інсулінорезистентність; глюкоза; ризик; інсулін; метаболічні порушення.



Modern Approaches to the Diagnosis, Prevention, and Management of Tuberculosis in People Living with Human Immunodeficiency Virus Infection

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Abstract. Tuberculosis and human immunodeficiency virus infection remain among the leading causes of infectious morbidity and mortality worldwide. The coexistence of these diseases is associated with a markedly increased risk of developing active tuberculosis, difficulties in timely diagnosis, the emergence of drug-resistant *Mycobacterium tuberculosis*, and considerable challenges in patient management, highlighting the need to improve current approaches to diagnosis, prevention, and treatment. Objective of the study: to summarize current scientific evidence regarding the epidemiology, pathogenesis, modern diagnostic methods, prevention, and treatment of tuberculosis in people living with human immunodeficiency virus infection. A comprehensive review of contemporary scientific publications and World Health Organization recommendations addressing the epidemiology, diagnosis, prevention, and management of tuberculosis in people living with human immunodeficiency virus infection was conducted. The analysis of current evidence demonstrated that human immunodeficiency virus infection substantially increases the risk of active tuberculosis through progressive impairment of cellular immune responses, whereas tuberculosis accelerates the progression of immunodeficiency. The highest diagnostic accuracy is achieved through the combined use of clinical screening, radiological examination, molecular diagnostic techniques, and bacteriological methods. Timely identification of latent tuberculosis infection and the initiation of preventive treatment after exclusion of active tuberculosis significantly reduce the incidence of active disease and tuberculosis-related mortality. Short-course rifamycin-containing preventive regimens have demonstrated high effectiveness and improved treatment adherence. Effective patient management requires an individualized therapeutic approach that considers clinically significant drug interactions between antituberculosis and antiretroviral medications. The synthesis of current evidence supports the implementation of comprehensive diagnostic algorithms, systematic screening for latent tuberculosis infection,

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timely preventive treatment, and individualized therapeutic strategies. These approaches may improve the quality of healthcare, optimize patient management, enhance treatment outcomes, and reduce mortality among people living with human immunodeficiency virus infection.

Keywords: tuberculosis; human immunodeficiency virus infection; tuberculosis/human immunodeficiency virus coinfection; latent tuberculosis infection; antiretroviral therapy; molecular diagnostics; drug resistance; tuberculosis preventive treatment.

Introduction

Early detection of tuberculosis (TB), followed by the timely initiation of effective treatment, remains a cornerstone of global efforts to control the disease. It is estimated that approximately 3 million cases of TB remain undiagnosed each year. Timely diagnosis and effective patient management can prevent the progression of severe disease, reduce mortality, and limit transmission of infection [1, 2].

Both naturally occurring (intrinsic) and acquired drug resistance in *Mycobacterium tuberculosis* (MTB) substantially limit the therapeutic options available for TB treatment. This underscores the need to develop and implement effective public health policies aimed at the rational use of new anti-TB drugs and the prevention of further emergence and spread of drug resistance [3].

Furthermore, tuberculosis and human immunodeficiency virus (HIV) infection mutually accelerate disease progression, with each condition exacerbating the adverse effects of the other. Thus, TB/HIV coinfection is characterized by an unfavorable bidirectional interaction. People living with HIV have an approximately 22-fold higher risk of developing active TB than individuals with intact immune function [1].

Analysis of contemporary challenges in TB control is essential for achieving the objectives of the global End TB Strategy. Such an analysis may provide new opportunities to strengthen global TB control and identify a comprehensive set of measures required to accelerate progress toward TB elimination. This review examines the major challenges in the current era of TB control, including drug resistance, TB/HIV coinfection, diagnostic limitations, and treatment-related challenges [1, 3].

The aim of the study: to summarize current scientific evidence regarding the epidemiology, pathogenesis, modern diagnostic methods, prevention, and treatment of tuberculosis in people living with human immunodeficiency virus infection.

Materials and Methods

A comprehensive review of contemporary scientific publications and World Health Organization recommendations addressing the epidemiology, diagnosis, prevention, and management of tuberculosis in people living with human immunodeficiency virus infection was conducted.

Results

Tuberculosis (TB) and human immunodeficiency virus (HIV) infection remain among the most serious global public health threats. Although HIV-related mortality has declined substantially in recent years, progress in reducing TB-related mortality remains insufficient. In 2014, TB ranked alongside HIV as one of the leading causes of death from infectious diseases worldwide [1, 2].

During the 1990 s, the HIV epidemic became one of the major drivers of the resurgence of TB, and TB continues to disproportionately affect people living with HIV (PLHIV). TB remains a leading cause of death among PLHIV. HIV infection substantially increases the risk of progression from latent tuberculosis infection (LTBI) to active TB disease. According to WHO estimates, PLHIV have a markedly higher risk of developing active TB than people without HIV infection [1, 4].

Thus, HIV infection and TB demonstrate a pronounced lethal synergy: HIV-associated immunosuppression substantially increases susceptibility to TB, while TB, in turn, may accelerate HIV disease progression, thereby contributing to increased morbidity and mortality among affected individuals [1, 4].

Among HIV-negative individuals with LTBI, the lifetime risk of developing active TB is generally estimated at approximately 5–10%. In contrast, the risk among PLHIV is substantially higher, reflecting the impaired immune control of *Mycobacterium tuberculosis* infection.

Importantly, the increased risk of TB develops soon after HIV acquisition, even when CD4⁺ T-cell counts remain relatively preserved. Some of the most compelling evidence for the early increase in TB risk following HIV infection comes from studies of South African gold miners who worked and lived in conditions of close communal contact, experienced substantial exposure to *Mycobacterium tuberculosis*, and were under regular medical surveillance that included repeated HIV testing [5].

In one such study, the incidence of TB doubled during the first year after HIV seroconversion compared with HIV-negative individuals. Although an increased risk of TB was observed even among individuals with recently acquired HIV infection and relatively preserved immune function, the risk increased further with longer duration of HIV infection [5].

Timely diagnosis of TB among PLHIV remains challenging because of the high prevalence of smear-negative disease and extrapulmonary TB. Clinical screening alone has limited sensitivity in this population and may fail to identify a substantial proportion of laboratory-confirmed TB cases, particularly among pregnant women living with HIV. Important opportunities for improving early diagnosis are associated with the use of highly sensitive molecular diagnostic methods and lateral flow assays, which may provide improved diagnostic performance in people living with HIV [6–8].

Treatment of TB in people living with HIV (PLHIV) is also challenging because of multiple drug–drug interactions between anti-TB drugs and antiretroviral therapy (ART), as well as overlapping drug toxicities. Nevertheless, findings from a large international cohort study involving children demonstrated that initiation of ART within the first eight weeks after starting anti-TB treatment was associated with more favourable clinical outcomes [9].

TB prevention in PLHIV is likewise associated with several challenges. Although isoniazid preventive therapy has demonstrated substantial efficacy, concerns have been raised that its widespread use could contribute to the emergence and transmission of *Mycobacterium tuberculosis* strains resistant to isoniazid. However, available evidence indicates that, in settings with a controlled or declining TB epidemic, the benefits of preventive treatment in PLHIV in terms of reducing TB incidence and mortality outweigh the potential risk of selection for drug resistance [10–13].

PLHIV should be systematically assessed for TB disease and, where indicated, for TB infection. The timing and approach to testing for TB infection should be determined according to the epidemiological and clinical context, national policies, and individual risk factors. In individuals with a negative test for TB infection who remain at substantial risk of exposure to *Mycobacterium tuberculosis*, including healthcare workers and persons with ongoing close contact with individuals with TB, repeat testing may be considered according to the level and persistence of individual risk [14, 15].

When a test for TB infection is positive, the priority is to exclude active TB disease before initiating TB preventive treatment (TPT). This assessment should include clinical evaluation and, where indicated, chest radiography and microbiological testing using rapid molecular or other appropriate diagnostic methods.

Both the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) can be used to detect TB infection. WHO recommendations recognize both approaches, with the choice depending on availability, laboratory capacity, cost, programmatic considerations and the epidemiological context. WHO's updated

diagnostic guidance also includes newer TB infection testing technologies based on *M. tuberculosis*-specific antigens [14, 15].

In PLHIV, a TST induration of ≥ 5 mm, assessed 48–72 hours after administration of tuberculin, is generally considered positive in clinical guidelines. Important limitations of TST include the requirement for a second visit to assess the result, reduced specificity in BCG-vaccinated populations, and reduced sensitivity in individuals with advanced immunosuppression [14].

IGRAs generally have higher specificity than TST because they use antigens specific to the *M. tuberculosis* complex that are absent from BCG vaccine strains and most non-tuberculous mycobacteria. This reduces the likelihood of false-positive results associated with prior BCG vaccination. However, IGRA performance may also be affected by immunosuppression, and indeterminate results may occur more frequently in individuals with advanced HIV-associated immunodeficiency.

Current recommendations do not establish a universal preference for either TST or IGRA in PLHIV. The choice should be guided by the clinical and epidemiological context, test availability, laboratory capacity and programmatic resources. When serial testing is performed, variability in IGRA results and the potential booster phenomenon associated with repeated TST should be taken into account.

Although discordance between TST and IGRA results is relatively common, a positive result with either test is associated with an increased risk of subsequent TB disease. Nevertheless, neither test has sufficient predictive accuracy to determine at the individual level which person with TB infection will subsequently develop active disease.

Current WHO recommendations emphasize that the decision to provide TPT to PLHIV should not be based exclusively on the result of a TST or IGRA. After active TB disease has been excluded, TPT may be offered to PLHIV according to epidemiological risk, national policy and the individual's clinical circumstances. In high TB-burden settings, TPT may be provided to PLHIV regardless of the result of TB infection testing, provided that active TB has been excluded. In lower-incidence settings, TST or IGRA may be used as part of the assessment for eligibility for preventive treatment. WHO currently recommends several short-course preventive regimens, including 3HP, 1HP and 3HR, with the choice depending on drug availability, potential drug–drug interactions and individual clinical circumstances [10–13].

Adding chest radiography to symptom-based screening can increase the detection of TB disease, but its specificity may be limited and its implementation can increase the cost and logistical complexity of screening programmes. Moreover, chest radiography may fail to identify a proportion of subclinical or

atypical TB cases, particularly among PLHIV with advanced immunosuppression. A normal chest radiograph therefore does not exclude TB in PLHIV, especially in individuals with a low CD4⁺ T-cell count or extrapulmonary disease. In such cases, laboratory-based diagnostic methods, particularly rapid molecular testing and culture, are essential [14, 15].

Historically, sputum smear microscopy for acid-fast bacilli (AFB) was one of the most widely used methods for laboratory confirmation of pulmonary TB. Its advantages include technical simplicity, relatively low cost, rapid availability of results and high specificity in many clinical settings. However, its sensitivity is limited because a relatively high bacillary burden is required for reliable microscopic detection, making the method particularly insensitive in paucibacillary disease [14, 15].

In PLHIV, the sensitivity of sputum smear microscopy is substantially lower than in people without HIV because smear-negative disease is more common and the bacillary burden in clinical specimens is often lower. Consequently, smear microscopy alone is insufficient for the initial diagnosis of TB in PLHIV when WHO-recommended rapid diagnostic tests (WRDs) are available. Current WHO guidance prioritizes rapid molecular testing over smear microscopy as the initial diagnostic approach.

WHO-recommended rapid diagnostic tests (WRDs) are now prioritized for the initial diagnosis of TB. These include rapid molecular tests capable of detecting *M. tuberculosis* and, depending on the test, resistance to rifampicin. Xpert MTB/RIF Ultra is one of the widely used molecular assays in this category and provides improved analytical sensitivity compared with earlier Xpert MTB/RIF technology, which is particularly relevant in paucibacillary disease, including TB in PLHIV, smear-negative TB and paediatric TB [14–16].

The 2025 WHO diagnostic framework further consolidates Xpert MTB/RIF Ultra and Truenat MTB Plus with appropriate rifampicin-resistance testing within the low-complexity automated nucleic acid amplification test (LC-aNAAT) class. The updated guidance also emphasizes the use of concurrent testing of respiratory and non-respiratory specimens in PLHIV in appropriate clinical circumstances, thereby increasing the likelihood of detecting TB when disease is extrapulmonary, disseminated or paucibacillary [14–16].

Culture of *M. tuberculosis* using liquid or solid media remains an important reference method for microbiological confirmation and phenotypic drug susceptibility testing (DST). Culture generally provides higher analytical sensitivity than smear microscopy and allows isolates to undergo further phenotypic susceptibility testing. However, the relatively long turnaround time limits its role as the sole initial

diagnostic method, and it is therefore increasingly complemented by rapid molecular diagnostics.

Although sputum-processing procedures such as concentration, centrifugation and fluorescence microscopy can improve the yield of smear microscopy, their diagnostic performance remains inferior to that of rapid molecular tests. Accordingly, smear microscopy is now primarily considered an adjunctive or alternative diagnostic method in settings where rapid molecular testing is unavailable or inaccessible.

According to current WHO recommendations, PLHIV should undergo systematic screening for TB disease at appropriate intervals and whenever clinically indicated. After TB disease has been excluded, PLHIV at increased risk of progression from TB infection to disease should be considered for TPT as part of a comprehensive TB prevention strategy [10,11,13].

Results from randomized clinical trials and systematic reviews have demonstrated that TPT reduces the risk of developing active TB among PLHIV and can contribute to reductions in mortality, particularly when combined with effective ART [10–12].

In contrast to earlier strategies in which six months of isoniazid monotherapy (6H) was widely used, current WHO recommendations favour shorter preventive regimens when they are appropriate and available. These include 3HP (isoniazid plus rifapentine administered once weekly for three months), 1HP (daily isoniazid plus rifapentine for one month), and 3HR (daily isoniazid plus rifampicin for three months). Longer isoniazid-containing regimens, such as 6H or 9H, remain options when rifamycin-based regimens cannot be used because of drug–drug interactions, contraindications or lack of availability.

TPT should only be initiated after active TB disease has been appropriately excluded. Depending on the clinical context, this may require symptom-based screening, chest radiography and rapid molecular testing of appropriate clinical specimens. Reliance on symptom assessment alone may be insufficient in individuals with advanced immunosuppression or atypical and extrapulmonary disease [14, 15].

Concerns that TPT could promote the emergence of isoniazid resistance have not been consistently supported by available evidence. When active TB is appropriately excluded before treatment, TPT has not been associated with a clinically significant increase in the risk of developing drug-resistant TB. Ensuring adequate diagnostic assessment before initiation of preventive treatment remains essential.

The effectiveness of TB prevention is further enhanced by timely initiation of ART, which substantially reduces the risk of TB among PLHIV. TPT and ART should therefore be regarded as complementary components of comprehensive TB prevention and HIV care.

Overall, contemporary TB diagnostic strategies in PLHIV rely on the integrated use of systematic clinical screening, chest radiography when indicated, WHO-recommended rapid molecular diagnostics, culture-based testing and drug susceptibility testing. This multimodal approach is particularly important for detecting paucibacillary, subclinical, disseminated and extrapulmonary TB in individuals with advanced HIV-associated immunosuppression [14–16].

The development and implementation of accessible, rapid and highly sensitive molecular diagnostic technologies remain key components of the WHO End TB Strategy, particularly for improving early TB detection among PLHIV. Timely diagnosis is especially important in this population because TB frequently presents with atypical clinical and radiological features, a low bacillary burden, extrapulmonary involvement and subclinical disease.

According to current WHO recommendations, WRDs should be used as initial diagnostic tests in individuals with suspected TB, including PLHIV. Xpert MTB/RIF Ultra and Truenat-based technologies are among the established rapid molecular platforms, while the updated WHO diagnostic framework also recognizes new diagnostic classes that may expand access to rapid testing. The use of these technologies facilitates the simultaneous detection of *M. tuberculosis* and, where applicable, molecular markers of rifampicin resistance, thereby shortening the time to diagnosis and initiation of appropriate treatment [14–16].

For more comprehensive assessment of drug resistance, molecular tests and line probe assays (LPAs) can provide rapid information on resistance-associated genetic mutations. First-line LPAs can detect mutations associated with resistance to rifampicin and isoniazid, whereas second-line LPAs can be used for detection of resistance to selected fluoroquinolones and second-line injectable agents. Their use should be integrated into diagnostic algorithms according to WHO recommendations and local laboratory capacity [14, 15].

Targeted next-generation sequencing (NGS) represents an increasingly important approach to rapid detection of drug resistance. These technologies can identify resistance-associated mutations across multiple anti-TB drugs and may provide more comprehensive information than individual targeted molecular assays. WHO has incorporated targeted NGS into its diagnostic framework as an approach for detecting resistance to a range of anti-TB drugs. Whole-genome sequencing (WGS) also has an important role in molecular epidemiology, surveillance and investigation of transmission patterns and may assist, in selected settings, in distinguishing relapse from reinfection. However, its routine clinical implementation remains dependent on laboratory infrastructure, sequencing capacity and bioinformatic expertise [14, 17, 18].

An important area of ongoing development is the use of biomarker-based diagnostic approaches. Urine lipoarabinomannan (LAM) testing has particular clinical relevance for PLHIV with advanced immunosuppression or severe illness. WHO recommends lateral flow LAM (LF-LAM) testing as an adjunct to the diagnosis of active TB in specific groups of PLHIV, including hospitalized patients with signs and symptoms suggestive of TB and individuals with advanced HIV disease or severe illness, according to the applicable clinical criteria [8, 19, 20]. The use of urine as a diagnostic specimen is particularly valuable in patients who are unable to produce an adequate sputum sample and may facilitate earlier diagnosis in severely ill patients.

Research is also ongoing into transcriptomic biomarkers, protein signatures and metabolomic profiles for the early detection of active TB and prediction of progression from TB infection to disease. Although these approaches are promising, most remain under clinical validation and are not yet recommended for widespread routine use [21].

Despite substantial advances in TB diagnostic technologies, their widespread implementation remains constrained by the cost of equipment, the need for appropriate laboratory infrastructure and trained personnel, and reliable supply chains for consumables. Ensuring equitable access to rapid and accurate diagnostic technologies therefore remains a major priority of global TB control programmes, particularly in countries with a high burden of TB and HIV-associated TB.

Thus, contemporary laboratory diagnosis of TB in PLHIV is based on the preferential use of rapid molecular diagnostics, complemented by culture-based testing, drug susceptibility testing, targeted sequencing technologies and selected biomarker-based approaches. The integrated use of these diagnostic modalities can facilitate earlier detection of TB, more rapid identification of drug resistance and timely initiation of effective treatment, thereby contributing to reduced morbidity and mortality among people with TB/HIV coinfection [14–21].

Discussion

An analysis of recommendations from international professional organizations indicates that the diagnostic strategy for TB in people living with HIV has changed substantially over recent years. Whereas sputum smear microscopy was historically the principal laboratory method for confirming TB, current practice prioritizes rapid molecular diagnostic technologies, which enable earlier detection of *M. tuberculosis* and, in appropriate assays, simultaneous identification of drug-resistance markers. The 2025 WHO diagnostic framework further expands this approach by consolidating recommendations for TB infection, TB disease and

drug-resistance testing and by introducing new diagnostic technology classes and updated testing algorithms [14–19].

At the same time, implementation of modern diagnostic technologies remains constrained by their cost, laboratory infrastructure requirements, availability of trained personnel and unequal access across health systems, particularly in high-burden settings. Consequently, alongside the introduction of innovative diagnostic methods, systematic clinical screening, appropriate TB preventive treatment and timely initiation of ART remain essential components of comprehensive TB/HIV care. Together, these measures can improve early case detection, reduce progression to active TB and contribute to lower morbidity and mortality among PLHIV.

Conclusions

1. Human immunodeficiency virus (HIV) infection substantially increases the risk of developing active tuberculosis (TB), complicates its diagnosis, and is associated with poorer clinical outcomes.

2. WHO-recommended rapid molecular diagnostic tests should be prioritized for the early detection of TB, as they provide high diagnostic sensitivity and, depending on the assay, enable simultaneous detection of molecular markers of drug resistance.

3. The integrated use of systematic clinical screening, rapid molecular diagnostics, culture-based methods, drug susceptibility testing, and emerging molecular technologies facilitates timely diagnosis and supports the selection of appropriate treatment strategies.

4. TB preventive treatment following appropriate exclusion of active TB disease, together with timely initiation of antiretroviral therapy (ART), remains a key component of TB prevention among people living with HIV (PLHIV).

5. Further expansion of equitable access to modern diagnostic technologies, particularly rapid molecular and drug-resistance testing, represents a major priority for improving TB control and reducing morbidity and mortality among people with TB/HIV coinfection.

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Conflict of interest

The authors declare no conflict of interest.

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Сучасні підходи до діагностики, профілактики та лікування туберкульозу в осіб, які живуть з вірусом імунодефіциту людини

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Анотація. Туберкульоз та інфекція, спричинена вірусом імунодефіциту людини (ВІЛ), залишаються одними з провідних причин інфекційної захворюваності та смертності у світі. Поєднання цих хвороб асоціюється зі значним підвищенням ризику розвитку активного туберкульозу, труднощами у своєчасній діагностиці, виникненням лікарсько-стійких форм *Mycobacterium tuberculosis* та значними труднощами у веденні пацієнтів, що зумовлює необхідність удосконалення сучасних підходів до діагностики, профілактики та лікування. Метою дослідження було узагальнити сучасні наукові дані щодо епідеміології, патогенезу, сучасних методів діагностики, профілактики та лікування туберкульозу в осіб, які живуть з ВІЛ-інфекцією. Проведено комплексний огляд сучасних наукових публікацій, рекомендацій Всесвітньої організації охорони здоров'я, настанов міжнародних професійних товариств та національних клінічних рекомендацій, присвячених питанням діагностики, профілактики та

лікування туберкульозу в осіб, які живуть з ВІЛ-інфекцією. Аналіз сучасних даних продемонстрував, що інфекція, спричинена вірусом імунодефіциту людини, суттєво підвищує ризик розвитку активного туберкульозу внаслідок прогресуючого порушення клітинної імунної відповіді, тоді як туберкульоз пришвидшує прогресування імунодефіциту. Найвища діагностична точність досягається завдяки комплексному застосуванню клінічного скринінгу, променевих методів дослідження, молекулярно-генетичних та бактеріологічних методів діагностики. Своєчасне виявлення латентної туберкульозної інфекції та призначення профілактичного лікування після виключення активного туберкульозу суттєво знижують частоту розвитку активного захворювання та смертність, пов'язану з туберкульозом. Короткострокові схеми профілактичного лікування, що містять рифаміцини, продемонстрували високу ефективність та сприяють кращій прихильності до лікування. Ефективне ведення пацієнтів потребує індивідуалізованого терапевтичного підходу з урахуванням клінічно значущих лікарських взаємодій між протитуберкульозними та антиретровірусними препаратами. Узагальнення сучасних наукових даних підтверджує доцільність впровадження комплексних діагностичних алгоритмів, систематичного скринінгу на латентну туберкульозну інфекцію, своєчасного призначення профілактичного лікування та застосування індивідуалізованих терапевтичних стратегій. Реалізація цих підходів може сприяти підвищенню якості медичної допомоги, оптимізації ведення пацієнтів, покращенню результатів лікування та зниженню смертності серед людей, які живуть з ВІЛ-інфекцією.

Ключові слова: туберкульоз; інфекція, спричинена вірусом імунодефіциту людини; коінфекція туберкульоз / ВІЛ; латентна туберкульозна інфекція; антиретровірусна терапія; молекулярна діагностика; лікарська стійкість; профілактичне лікування туберкульозу.



Exposure settings, tick removal practices, and underdiagnosis risks of Lyme Borreliosis in student of I. Horbachevsky Ternopil National Medical University: a cross-sectional study

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Abstract. This article presents a comprehensive analysis of epidemiological survey results from 275 higher education students, aimed at studying the frequency of *Ixodidae* tick attacks, exposure settings, level of awareness regarding vector-borne disease transmission risks, and tick removal practices. Despite the predominantly urban sample (69,8 % of respondents residing in urban areas), a high intensity of contact with ticks was established: 54,9 % of all respondents reported exposure to these arthropods, and 46,6 % reported direct tick attachment. An investigation into attack locations revealed that peak tick activity occurs in forest and meadow biocoenoses. However, 3,6 and 1,8 % of respondents reported attacks in parks and gardens, respectively, indicating the potential for arthropod exposure within residential areas. The highest number of tick attacks occurred in the Ternopil region (16,4 % of all respondents), likely related to their place of residence, while 15,3 % could not recall the exact territory. The highest number of attacks was recorded in June and July (14,9 and 12,0 % of all respondents, respectively), whereas in May and August, these rates were 8,7 and 5,1 %. The majority of surveyed students discovered ticks by chance or during self-examination following exposure to high-risk areas. This highlights the crucial role of self-inspection, which enabled most individuals to detect ticks within the first 24 hours of attachment. An analysis of the behaviors of 128 respondents who reported tick attachment revealed that only 28,1 % sought professional medical care. In 53,1 % of cases, ticks were removed by non-medical third parties, while 18,8 % removed them independently, significantly increasing the risk of trauma and infection. Although laboratory-confirmed Lyme borreliosis was documented in only 4 cases, the presence of pathognomonic erythema migrans in 35,2 % of victims, against a background of low diagnostic testing rates (only 21,8 %), suggests substantial

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underdiagnosis of tick-borne diseases. These findings underscore the urgent need to intensify health education efforts among youth, implement effective personal prophylaxis strategies, and improve health literacy regarding post-tick-bite action algorithms.

Keywords: *Ixodidae* ticks; tick bites; vector-borne diseases; Lyme Borreliosis; erythema migrans; epidemiological survey; health literacy; student; Ternopil region.

Introduction

The problem of the spread of *Ixodidae* ticks in western Ukraine remains highly relevant due to extensive forest cover, high-humidity climatic conditions, and the socio-economic situation of a country at war. Abandoned agricultural lands overgrown with shrubs have become ideal breeding grounds for rodents, which serve as hosts for ticks [1]. Migration processes in Ukraine during the full-scale invasion have altered the country's demographic structure. Internally displaced persons, who previously resided in the urbanized regions of southern and eastern Ukraine, now live in different climatic conditions, where warm winters allow ticks to remain active even in December or February. Cold regions and highlands are becoming habitable for ticks during earlier winter periods. This explains the upward movement of ticks into mountainous areas, as well as their colonization of urban landscapes. Tick populations adapt well to urban environments, meaning human-vector contact occurs not only in forests but also during routine city walks [2]. Urban parks, public gardens, and suburban dacha plots have become ideal biotopes for ticks, while high population density increases the frequency of contact between the host and the blood-sucking parasite. This, in turn, facilitates the spread of tick-borne diseases transmitted by the *Ixodidae* family, including tick-borne encephalitis, Lyme borreliosis, and so-called "co-infections" involving simultaneous infection with *Borrelia*, *Anaplasma*, and *Babesia* [3]. The extraordinary plasticity of the *Ixodidae* family makes them exceptionally successful from an epidemiological standpoint, necessitating the continuous updating of data on their distribution to inform the public and improve tick control methods.

Large regional universities accumulate youth from many villages, towns, and regions, which allows for the representation of various territories through the method of so-called active citizen participation, or "citizen science" [4]. Young people lead an active lifestyle and frequently visit natural tick biotopes, such as parks, public gardens, meadows, and forests, not only in their places of residence but also around their places of study; therefore, they have a high probability of coming into contact with blood-sucking parasites.

The aim of the study: to assess the prevalence of *Ixodidae* tick bites, exposure settings, and the level of awareness regarding vector-borne disease risks and removal practices among students at I. Horbachevsky

Ternopil National Medical University (TNMU), through a cross-sectional survey.

Materials and Methods

To achieve this goal, an online survey consisting of 30 questions was created using the Google Forms service. Convenience sampling strategy was applied; the link to the online form was distributed via corporate email to first- to third-year students from TNMU. Students on these courses, aged between 17 and 21, took part in an anonymous the survey, following the analysis of the responses, only the fully completed questionnaires were selected, numbering 275. Incomplete responses were excluded from the sample.

Results

The first section of the questionnaire included questions about the student's course of study, gender and place of residence. The vast majority of our respondents, accounting for 69,9 % (192 out of 275), were urban residents, 19,6 % (54 out of 275) permanently resided in rural areas, and only 10,5 % (29 out of 275) of the students lived in urban-type settlements. More than half (62,5 % – 172 out of 275) of the higher education students, denied visiting locations with a high probability of encountering *Ixodidae* ticks, such as forests, forest-park zones, public gardens, and meadows. Frequently, 23,7 % (65 out of 275) of individuals visited areas with an increased risk of tick contact, while 13,8 % (38 out of 275) of the students did so quite rarely. However, 46,5 % (128 out of 275) reported being bitten by ticks, with the majority of them consisting of individuals who had been bitten twice 16,7 % (46 out of 275), or more within a single spring-summer season (8,4 % 23 out of 275). Nevertheless, the number of respondents who detected a tick on their clothing or body was slightly higher 54,9 % (151 out of 275), which underscores the importance of self-examination after spending time in high-risk areas. Nearly a third of the respondents, totaling 38,9 % (107 out of 275), detected a tick on themselves after being in a forest, 3,6 % (10 out of 275) in a park zone, 2,9 % (8 out of 275) in a meadow, and 1,8 % (5 out of 275) of the students in a garden, while 7,6 % (21 out of 275) of the respondents could not associate the tick attack with staying in any of the aforementioned locations.

When asked about the locality where the attachment of the parasite occurred 16,4 % (45 out of 275) respondents reported tick bite in Ternopil Region (Fig.1).

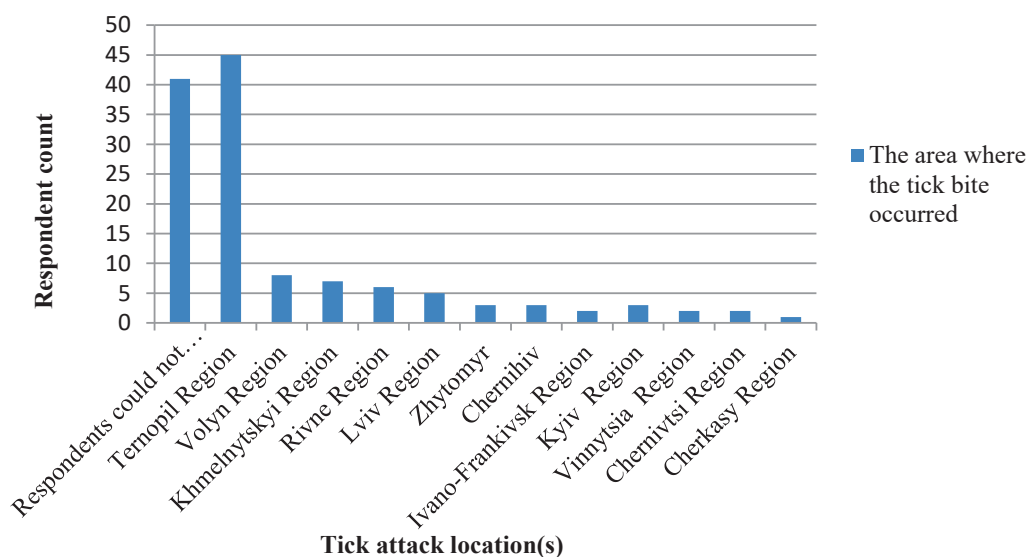


Fig. 1. Area(s) with reported tick attacks / bites.

Meanwhile, 15,3 % (42 out of 275) of the respondents reported attacks by the arthropod parasite in their places of permanent residence. Most frequently, bites were reported by residents of Volyn Region (8 individuals), Khmelnytskyi Region (7), Rivne Region (6), and Lviv Region (5). These results are evidently related to the geography of applicants entering TNMU and are consistent with the data from [5, 6]. However, many (14,9 % – 41 out of 275) respondents could not recall the locality of the parasite attack.

When asked about the specific location of the tick bite, respondents primarily referred to the area around Ternopil. Specifically, 12 % of the students (33 out of 275) reported being bitten on the outskirts of Ternopil, in a meadow, or in a forest, while 4,4 % (12

out of 275) experienced a tick bite during a walk in green areas, such as urban parks or public gardens. Residents of other regions were unable to specify the precise location, likely because the bites had occurred in the distant past.

Considering that the activity of *Ixodidae* ticks depends on the interaction of key climatic factors and has a seasonal nature [7], it was expedient to analyze the responses of the students regarding the time of year when they detected a tick bite.

The respondents answers indicate that the highest number of tick attacks occurred in June and July, accounting for 14,9 % (41 out of 275) and 12 % (33 out of 275) of the respondents, respectively, while attacks in April and May were reported by 1,9 % (5 out of 275)

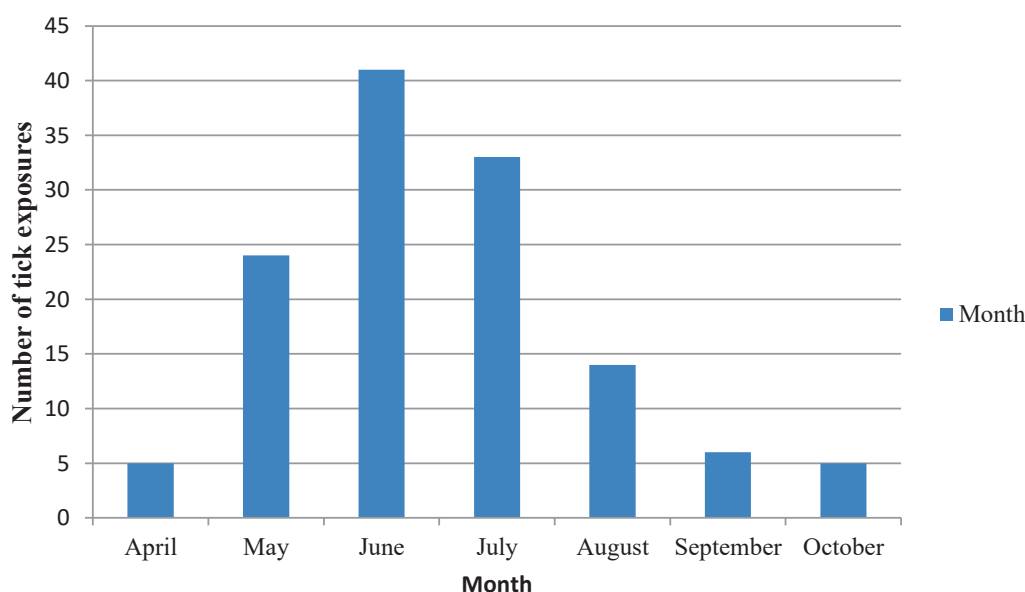


Fig. 2. The month in which the tick bite occurred.

and 8,7 % (24 out of 275) of those surveyed, respectively (Fig. 2). Tick attachment in August was reported by 5,1 % (14 out of 275) of the higher education students, whereas in September and October, it was noted by only 2 % (6 out of 275) and 1,8 % (5 out of 275) of the respondents, respectively. Recent studies demonstrate a similar trend toward a summer peak in ixodid tick activity across European countries, and these data may be linked to the activity patterns of different tick developmental stages [8, 9].

Many warm-blooded vertebrates, ranging from mice and rats to ungulates, can serve as hosts for various developmental stages of *Ixodidae* ticks. Among domestic animals, cats and dogs are of significant epidemiological importance, as they primarily inhabit or visit the same locations as humans. Indeed, 25 higher education students, representing 9 % of all respondents, indicated that the tick bite was associated with walking domestic pets (dogs, cats). Furthermore, 121 respondents (44 % of all surveyed) reported detecting a tick on a dog, 73 individuals (26,5 % of those surveyed) on a cat, and only 7 individuals (2,5 %) detected a tick on domestic ungulates.

As mentioned above, the proportion of students who found ticks on their clothing or body was quite high 54,9 % (151/275). The vast majority of the that respondents, accounting for 51,6 % (78/151) detected a tick on their clothing or body by chance; 44,4 % (67/151) of the higher education students noticed the parasite during self-examination after staying in a green area, and only 4 % (6/151) of the respondents found the parasite when they felt pain at the site of tick attachment.

Furthermore, an analysis of the questionnaires revealed that 46,5 % of respondents (128/275) had been bitten by ticks. Among those who experienced tick attachment, three-quarters (75,0 % – 96/128) detected the tick within 24 hours (Table 1). Additionally, 14,8 % (19/128) did so the following day, while only 3,9 % (5/128) found it after several days. Finally, 6,3 % (8/128) of respondents could not recall when the tick was removed.

More than half of the bitten respondents 53,1 % (68/128) had the tick removed with the help of non-medical third parties; 18,8 % (24/128) extracted the ectoparasite independently, and 28,1 % (36/128) sought assistance from healthcare professionals.

These facts are quite alarming, since incorrect removal of the ectoparasite may cause its contents to enter the wound, or part of it may remain in the skin. This increases the risk of contracting tick-borne infections, including Lyme disease, and can also lead to potential wound suppuration and prolonged healing. The use of dangerous "folk methods," such as applying oil, alcohol, creams, or cauterization, can stimulate the secretion of a larger volume of saliva containing potential infectious pathogens into the wound.

Overall, 45 out of 128 students (35,2 % of those who reported tick attachment) noted the appearance of erythema. Among these respondents, 35,6 % (16/45) reported erythema at the bite site, 8,9 % (4/45) observed it in areas distant from the bite site, and 55,6 % (25/45) could not recall its exact localization. Regarding the onset of erythema, 31 of these respondents (68,9 %) did not remember when it appeared. Meanwhile, 8 individuals (17,8 %) noted its onset within 24 hours, 1 student reported redness within 24–48 hours after tick detection, 3 respondents stated that erythema appeared after 3 days, and 1 respondent each detected erythema 7 and 14 days post bite, respectively.

Laboratory testing for *Borrelia* was conducted by only 28/128 respondents, representing 21,8 % of the students who reported tick attachment. Among them, 85,7 % respondents (24/28) tested negative, while only 14,3 % (4/28) received a positive result. Rather than indicating low infection rates, this suggests an insufficient level of screening, which in turn increases the risks of untimely diagnosed cases, potentially significantly complicating treatment and contributing to the development of complications [10].

Discussion

The higher education students indicated the emergence of unusual symptoms after detecting a tick on themselves. In particular, 2 individuals each noted the development of fever and headache. A decrease in concentration during classes was reported by 1 individual. Enlargement of lymph nodes near the bite site or itching at the bite site was noted by 1 individual each. One student reported facial nerve palsy, and 2 students noted the development of joint inflammation. Evidently, the appearance of symptoms prompted 46 individuals representing 35,9 % of the 128 students who reported tick attachment, to

Table 1. Distribution of respondents by tick bite status and detection timing

Time to tick detection following attachment	Respondent count	Method of tick removing	Respondent count
24 hours	96	with assistance from others	68
48 hours	19	independently	24
more than 48 hours	5	with medical assistance	36
could not recall	8		
	Total 128		Total 128

consult a physician, of whom 15 students received treatment. Following the tick bite, 22 individuals were under dispensarization (follow-up monitoring) by a dermatologist, 10 individuals by a cardiologist, and 3 individuals by a neurologist. Diagnoses that could be associated with a tick bite were established in 7 respondents. Treatment for chronic tick-borne diseases was received by 15 individuals, accounting for 11,7 % of the students who reported tick attachment.

There is a high probability that the friends and relatives of individuals who have suffered a tick bite may also be at risk. This is explained by the fact that they often share the same environmental conditions, visiting the same natural areas (forests, parks, suburban dacha plots), and engaging in shared recreational activities or outdoor pursuits. Ticks are not transmitted directly from person to person; however, their prevalence in a particular locality poses an equal threat to everyone present in that environment. Therefore, if a bite is detected in one individual, it is expedient to consider their close social circle as also belonging to a high-risk group. Indeed, according to our survey results, 127 higher education students, representing 46,2% of the surveyed respondents, answered affirmatively regarding tick attacks on their relatives or acquaintances. Moreover, 72 individuals noted that their close ones had been bitten twice, 4 individuals developed complications following a bite, and 2 individuals were diagnosed with borreliosis.

Conclusions

1. A high prevalence rate of tick bites was established among student youth (46,5 % of all respondents), with 9 % of respondents linking them to walking pets. Tick attacks occurred most frequently in natural biotopes. Respondents listed natural biotopes – forests and meadows at 38,9 and 2,9 %, respectively – as the most common locations where tick attacks took place; tick attacks in parks and gardens were reported by 3,6 and 1,8 %, respectively, although 7,6 % of students could not specify the exact location of the tick attack.

2. Ticks attached most frequently in 16,4 % of respondents while they were in the Ternopil region

and neighboring regions; however, 15,3 % of higher education students could not recall the territory where the attack occurred.

3. The highest number of tick contacts occurred in June – July, reported by 14,9 and 12 % of respondents, respectively. Significantly fewer attacks took place in May, August, and September – October, reported by 8,7, 5,1, and 2 % of respondents, respectively. These results may be related to the activity of different life cycle stages of ticks in the corresponding months.

4. More than half of those surveyed (54,9 %, 151/275) discovered a tick on their clothing or body by chance. The vast majority of these respondents indicate finding the tick by chance or after performing a self-examination, which highlights its importance following exposure to high-risk areas.

5. Among the respondents who reported a tick bite (46,5 %, 128/275), three-fourths (75 individuals) discovered the tick within 24 hours of attachment. However, more than half of these respondents (53,1 %, 68/128) had the tick removed by non-medical third parties, or removed it themselves (18,8 %, 24/128), which could have increased the risk of injury and infection due to unprofessional actions. A low level of seeking professional medical care was recorded at 28,1 % of those surveyed (36/128).

6. Despite the low percentage of laboratory-confirmed cases of Lyme borreliosis (4 individuals), the presence of erythema migrans in 35,2 % (45/128) of respondents who reported a tick bite, against the backdrop of a low testing rate (21,8 %, 28/128), suggests potential underdiagnosis of the disease. The risk of infection extends to the students immediate circle due to shared exposure in endemic areas.

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Умови інфікування, способи видалення кліщів та діагностика хвороби Лайма серед студентів Тернопільського національного медичного університету імені І. Я. Горбачевського: перехресне дослідження

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Анотація. У статті представлено комплексний аналіз результатів епідеміологічного опитування 275 студентів із Тернопільського національного медичного університету імені І. Я. Горбачевського, спрямованого на вивчення частоти нападів іксодових кліщів, умов контакту з ними, рівня обізнаності щодо ризиків передачі трансмісивних захворювань та практики видалення кліщів. Попри те, що більшість опитаних (69,8 %) проживали в міській місцевості, було встановлено високу інтенсивність контактів із кліщами: 54,9 % респондентів повідомили про

контакт із цими членистоногими, а 46,6 % – про випадки їх безпосереднього присмоктування. Аналіз місць нападу показав, що пік активності кліщів припадає на лісові біоценози. Водночас 3,6 і 1,8 % респондентів зазнали нападу кліщів у парках і садах відповідно, що вказує на ймовірність контакту з ними у межах населених пунктів. Найбільшу кількість випадків нападу кліщів зафіксовано в Тернопільській області (16,4 % серед усіх опитаних), що, ймовірно, пов'язано з місцем їхнього проживання, тоді як 15,3 % не змогли точно вказати територію, де стався напад кліща. Найвищі показники нападів припали на червень і липень (14,9 та 12,0 % відповідно), тоді як у травні та серпні вони становили 8,7 і 5,1 % відповідно. Більшість опитаних здобувачів виявляли кліщів випадково або під час самоогляду після перебування в зонах підвищеного ризику. Це підкреслює важливість самоогляду, завдяки якому більшість осіб змогли виявити кліщів протягом першої доби після присмоктування. Аналіз дій 128 респондентів, у яких було зафіксовано присмоктування кліща, показав, що лише 28,1 % звернулися за професійною медичною допомогою. В 53,1 % випадків кліщів видаляли сторонні особи без медичної освіти, а у 18,8 % – їх самостійно, що значно підвищувало ризик травмування та інфікування. Хоча лабораторно підтверджений Лайм-бореліоз було задокументовано лише у 4 випадках, наявність патогномонічної мігруючої еритеми у 35,2 % постраждалих на тлі низького рівня діагностичного тестування (лише 21,8 %) свідчить про значну недодіагностику захворювання. Отримані результати підкреслюють нагальну потребу в посиленні санітарно-просвітницької роботи серед молоді, впровадженні ефективних стратегій індивідуальної профілактики та підвищенні рівня обізнаності щодо алгоритмів дій після укусу кліща.

Ключові слова: іксодові кліщі; укуси кліщів; трансмісивні хвороби; хвороба Лайма (бореліоз); мігруюча еритема; епідеміологічне дослідження; рівень обізнаності; здобувачі; Тернопільська область.



Functional Food-Derived Peptides as Multitarget Antidiabetic Agents: *in Silico* and Biochemical Aspects

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Abstract. This article summarizes current data on the application of *in silico* approaches, particularly molecular docking, for the screening of dietary bioactive peptides of animal origin with potential hypoglycemic properties, and evaluates the prospects of their utilization in the development of functional anti-diabetic products. It was found that dietary animal-derived bioactive peptides represent promising antidiabetic agents owing to their multitarget mechanisms of action (inhibition of key enzymes of carbohydrate metabolism, including dipeptidyl peptidase-4 (DPP-4) and α -glucosidases; regulation of insulin-related signaling pathways, enhancing of peripheral tissue sensitivity to insulin, reducing postprandial hyperglycemia, and exhibition of antioxidant and anti-inflammatory activities). Camel, bovine, and caprine milk remain the most extensively studied sources of dietary peptides with confirmed inhibitory activity against DPP-4 and α -glucosidase, while the half-maximal inhibitory concentration (IC_{50}) value serves as a universal criterion for comparing peptide inhibitory potency, thereby ensuring a standardized approach to their evaluation. At the same time, the efficiency of peptide formation and their biological properties largely depend on the type of protein substrate, its amino acid composition, and the method of enzymatic hydrolysis or fermentation.

Keywords: type 2 diabetes mellitus; nutraceuticals; dietary proteins; bioactive peptides; enzymatic hydrolysis; molecular docking; molecular targets; functional foods.

Introduction

Type 2 diabetes mellitus (T2DM) remains one of the most pressing biomedical challenges of modern society due to its rapidly increasing prevalence, high risk of complications, and substantial socio-economic burden. In 2024, the global number of adults aged 20–79 years living with diabetes reached 589 million, and projections indicate that this figure will rise to 853 million by

2050. Notably, T2DM accounts for approximately 96 % of all registered cases [1, 2]. T2DM is characterized by a complex multifactorial pathogenesis, the principal components of which include impaired insulin production and insulin resistance (IR) in peripheral tissues. These processes are mediated through mechanisms such as α -cell dedifferentiation, mitochondrial dysfunction, chronic low-grade inflammation, and

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oxidative stress. Dysfunction of pancreatic β -cells leads to a reduction in insulin secretion, resulting in the inability to maintain physiological glucose levels. At the same time, IR stimulates hepatic glucose production and reduces glucose utilization in muscle, liver, and adipose tissue, thereby establishing a “vicious cycle” between insulin secretion and its action, which ultimately culminates in hyperglycemia [3, 4]. Despite advances in modern pharmacotherapy, a substantial proportion of patients with T2DM fail to achieve or maintain recommended glycemic targets (e.g., HbA1c < 7.0 %). Such suboptimal glycemic control is a major driver of severe microvascular and macrovascular complications – including nephropathy, retinopathy, cardiovascular disease, and increased mortality. This, in turn, imposes a considerable economic burden on healthcare systems and significantly diminishes patients' quality of life [5]. Therefore, the search for novel, safe, and effective agents to support glycemic homeostasis remains highly relevant. In this context, the investigation of bioactive peptides formed during enzymatic hydrolysis, fermentation, or digestion of animal-derived dietary proteins acquires particular importance, as these compounds may serve as potential antidiabetic agents [6–12]. There is evidence that these peptides are capable of modulating multiple aspects of T2DM pathogenesis, particularly by inhibiting the activity of key enzymes such as α -amylase, α -glucosidase, and dipeptidylpeptidase-4 (DPP-4), interacting with the glucagon-like peptide-1 receptor (GLP-1R), and influencing insulin signalling pathways. These properties render them promising candidates for incorporation into functional foods and nutraceutical formulations [13–14]. It should be noted that DPP-4 is most frequently identified as a molecular target in antidiabetic research. This enzyme serves as a key regulator of insulin-stimulating hormones – namely, glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Inhibition of DPP-4 enhances the activity of endogenous GLP-1 and GIP, which ultimately improves β -cell function and reduces blood glucose levels, glucagon secretion, and hepatic glucose production [15]. On the other hand, the experimental identification of bioactive amino acid sequences is a labor-intensive process due to the extraordinarily large number of potential peptides. Consequently, *in silico* approaches, particularly molecular docking, are increasingly employed as they enable rapid preliminary screening of peptides, prediction of their interactions with molecular targets, assessment of binding energy and affinity, identification of key amino acid residues within protein active sites, and rational selection of the most promising candidate compounds for subsequent *in vitro* and *in vivo* investigations [13, 16].

The aim of the study: to summarize current evidence on the application of *in silico* approaches,

particularly molecular docking, for the screening of dietary bioactive peptides of animal origin with potential hypoglycaemic properties, and to evaluate the prospects of their utilization in the development of functional anti-diabetic products.

Materials and Methods

For the preparation of this narrative review, a comprehensive search, analysis, and synthesis of scientific publications was conducted, focusing on bioactive peptides of animal origin with antidiabetic properties, their mechanisms of action, sources of origin, and modern *in silico* approaches for the identification and evaluation of their biological activity and safety. The literature search was performed in major international scientometric databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The analysis primarily included original research articles and review papers published between 2021 and 2026, as well as selected earlier studies of fundamental importance for elucidating the mechanisms underlying the antidiabetic activity of bioactive peptides. During the literature search, the following keywords were employed: bioactive peptides, antidiabetic peptides, food-derived peptides, nutraceuticals, DPP-4 inhibitory peptides, α -glucosidase, α -amylase, molecular docking, molecular dynamics, virtual screening and *in silico*. For the processing of literature sources, bibliosemantic, comparative, and analytical methods were applied, along with content analysis, systematization, and synthesis of scientific data. No statistical data analysis was performed within the scope of this study, as the work is of a review nature.

Results

Modern data indicate that promising peptide inhibitors of key targets in T2DM can be derived from a wide range of dietary proteins. Among the earliest and most extensively investigated are milk-derived peptides, with camel milk attracting particular interest. Its proteins serve as a source of bioactive peptides capable of modulating crucial pathways in the pathogenesis of T2DM, including carbohydrate-metabolizing enzymes, insulin signalling pathways, and mechanisms of IR. In the study conducted by S. S. Sakr and H. Barakat, it was established that fermented camel milk, enriched with probiotic cultures and Ajwa date pulp, exhibits pronounced antidiabetic activity through the inhibition of α -amylase and α -glucosidase [6]. The highest activity was demonstrated by the sample FCM15D+L, for which the half-maximal inhibitory concentration (IC_{50}) value was 111.43 μ g/mL for α -amylase and 77.21 μ g/mL for α -glucosidase.

P. Mudgil and co-authors also demonstrated a significant antidiabetic potential of camel milk-derived peptides [17]. Following probiotic fermentation,

pronounced inhibition of pancreatic α -amylase was observed, with fermented camel milk exhibiting the lowest IC_{50} value 2.39 μ g/mL among all types of milk investigated. Molecular docking revealed that the peptides MMPY, IMEQQTETEQQDK, DQHQAAMKPWTQPK, and RELEELNVPGE possess high affinity for the active site of α -amylase, interacting with key amino acid residues Trp58, Tyr62, Asp197, Glu233, and Asp300. These findings highlight their potential as natural inhibitors of carbohydrate-digesting enzymes.

In addition to their effects on carbohydrate-metabolizing enzymes, camel milk-derived peptides may also modulate insulin signalling pathways. I. K. Mohamed and co-authors investigated peptides obtained after simulated gastrointestinal digestion of camel milk, employing a combination of liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), virtual screening, and molecular docking [9]. Out of the 232 identified peptides, four were selected as the most promising: TYYPPQ, FEPVP, TVWPE, and ELTVGAGP. The peptide TYYPPQ demonstrated the highest biological activity. In a model of insulin-resistant HepG2 cells, it promoted the restoration of insulin receptor expression and partial reactivation of the AKT signalling pathway, whose key proteins include phosphatidylinositol-3-kinase (PI3K) and AKT (protein kinase B). Molecular docking revealed that TYYPPQ interacts with critical amino acid residues of the kinase domain of the insulin receptor, notably Glu1047 and Asp1150. It was established that this peptide primarily exerts an allosteric activation mechanism, stabilizing the receptor's active conformation.

Cow's milk is among the most extensively studied sources of bioactive peptides with potential antidiabetic activity. Particular interest is directed toward peptides capable of inhibiting DPP-4, as well as compounds exhibiting dual inhibitory activity against both DPP-4 and angiotensin-converting enzyme (ACE). Such activity may provide a simultaneous impact on glycemic control and cardiometabolic status. A particularly promising source of antidiabetic peptides is cow's milk lactoferrin. In the study conducted by C. Elisha and co-authors, *in silico* hydrolysis with pepsin-trypsin yielded 129 peptides, a substantial proportion of which demonstrated potential DPP-4 and ACE inhibitory activity [18]. Further analysis revealed that 43% of the peptides possessed potential DPP-4 inhibitory activity, while 28% exhibited potential ACE inhibition. According to molecular docking results, among the DPP-4 inhibitors, the most promising was the peptide WQWR, with a binding energy of -9.3 kcal/mol, whereas among the ACE inhibitors, the peptide EPYF demonstrated the best performance, with a binding energy of -10.1 kcal/mol. Subsequent *in vitro* analysis confirmed the high biological activity

of the hydrolysates: the IC_{50} value for ACE inhibition was (0.48 ± 0.01) mg/mL, while for DPP-4 inhibition it was (0.93 ± 0.02) mg/mL. LC-MS/MS analysis further verified the presence of the key peptides EPYF and WQWR within the hydrolysate composition.

In the study by A. Iwaniak and co-authors, cow's milk protein preparations were analyzed as a source of bioactive peptides using a combined *in silico* and *in vitro* approach [7]. Based on the BIOPEP-UWM database, the formation of 59 bioactive peptides was predicted following enzymatic hydrolysis of milk proteins, with short di- and tripeptides predominating. The most numerous group consisted of DPP-4 inhibitory peptides. After simulated gastrointestinal digestion, all tested samples exhibited pronounced DPP-4 inhibitory activity. The best result was obtained for the MBP D sample, with an IC_{50} value of 0.0067 mg/mL. Moreover, 23-27 DPP-4 inhibitory peptides were identified in the hydrolysates, depending on the type of milk protein preparation. Importantly, all samples also demonstrated antioxidant activity, which represents an additional advantage given the role of oxidative stress in the pathogenesis of IR and T2DM.

Goat's milk is likewise considered a promising source of bioactive peptides with antidiabetic properties, owing to the high biological value of its proteins, good digestibility, and the ability to generate short functionally active peptide fragments during enzymatic hydrolysis. In the study by M. Liu and co-authors, the search for DPP-4 inhibitory peptides from goat milk proteins was conducted using an integrated approach that combined *in silico* hydrolysis, virtual screening, molecular docking, molecular dynamics simulation, and *in vitro* experimental validation [19]. After computational hydrolysis of the 11 major goat milk proteins, 319 peptides with lengths ranging from 3 to 15 amino acid residues were obtained. Through multilevel screening, three peptides were identified as the most promising: MMSF, MPFPK, and GPFPII. Subsequent analysis using high-performance liquid chromatography (HPLC) confirmed their presence in the goat milk hydrolysate. *In vitro* studies demonstrated that all three peptides exhibit DPP-4 inhibitory activity, with the highest activity observed for MPFPK ($IC_{50} = 0.32$ mM). The IC_{50} value for MMSF was 0.69 mM, and for GPFPII it was 2.83 mM. Molecular docking revealed that all three peptides interact with key amino acid residues of the DPP-4 active site, including His740, Tyr631, Tyr547, Ser630, Glu205, and Glu206. The most stable complex was formed by MPFPK, which established five hydrogen bonds with residues E205, E206, R125, T662, and Y631. Additionally, the absence of significant cytotoxicity in the Caco-2 cell model indicates the potential safety of these peptides as nutraceutical components.

In the study by Y. Wu and co-authors, employing peptidomics, *in silico* screening, and experimental

validation, two novel DPP-4 inhibitors were identified from the goat milk protein hydrolysate: the tetrapeptide LLLP and the tripeptide YPF [15]. From the 698 identified peptides, a multistep selection process led to the synthesis of 12 candidates for experimental validation, among which LLLP and YPF exhibited the highest DPP-IV inhibitory activity. In a cell-free system, the IC_{50} values were (213.99 ± 0.64) mM for LLLP and (368.54 ± 12.97) mM for YPF. In the Caco-2 cell model, these peptides demonstrated even greater efficacy, with IC_{50} values of (154.96 ± 8.41) mM and (159.46 ± 17.40) mM, respectively, indicating their ability to retain biological activity under cellular conditions. Furthermore, both peptides exhibited no cytotoxicity within the concentration range of 0.025–1 mg/mL, underscoring their potential safety as nutraceutical components. Molecular docking analysis demonstrated that their inhibitory activity is associated with the formation of multiple non-covalent interactions with key amino acid residues of the DPP-4 active site, including Arg358, Phe357, Glu205, Tyr547, Tyr662, and Tyr666, thereby ensuring stable ligand–enzyme binding. The obtained results indicate that LLLP and YPF represent promising food-derived peptides for the development of functional foods and nutraceuticals with potential antidiabetic effects.

P. Mudgil and co-authors conducted a comprehensive study of peptides obtained through probiotic fermentation of cow, goat, camel, and sheep milk [8]. It was established that fermentation significantly enhances the degree of proteolysis and promotes the generation of low-molecular-weight bioactive peptides with pronounced antidiabetic properties. Comparative analysis revealed that different types of milk vary in their ability to produce peptides with DPP-4 inhibitory activity. The highest level of proteolysis was observed in fermented goat milk, indicating its strong capacity to generate functionally active peptides. At the same time, camel milk exhibited the most pronounced antidiabetic activity, as evidenced by its inhibitory effects on both DPP-4 and α -amylase. Among the probiotic strains of lactic acid bacteria, the most effective was identified as *Pediococcus pentosaceus* PP-957, which facilitated the formation of peptides with the highest DPP-4 inhibitory activity. Following fermentation, the IC_{50} values were markedly reduced compared to non-fermented samples: for cow's milk to 0.17 mg/mL, for camel milk to 0.12 mg/mL, and for goat milk to 0.25 mg/mL. Molecular docking confirmed that the generated peptides interact with key amino acid residues of the active sites of target enzymes, forming stable ligand–enzyme complexes. These findings indicate that different types of milk can serve as effective sources of nutraceutical peptides with multitarget antidiabetic activity.

Fish and meat protein hydrolysates are also regarded as promising sources of peptide-based

nutraceuticals with antidiabetic potential. Fish protein hydrolysates contain a substantial number of short peptides with potential antidiabetic activity. Specifically, in Baltic herring hydrolysates, more than 2000 peptides were identified, among which over 950 candidates with predicted DPP-4 inhibitory activity were selected following *in silico* analysis [20]. Subsequent experimental validation confirmed the biological activity of individual peptides, while the application of hydrolysates in a diet-induced obesity model was associated with improved glucose tolerance, reduced insulin resistance, suppression of DPP-4 activity, increased levels of GLP-1, and decreased production of pro-inflammatory cytokines. These findings suggest that fish-derived peptides may exert an antidiabetic effect through simultaneous modulation of carbohydrate metabolism and chronic low-grade inflammation. The study of sturgeon skeletal muscle proteins further confirmed the potential of fish-derived raw materials [21]. The identified peptides VT-9 and LE-9 exhibited competitive inhibition of α -glucosidase, and molecular docking results demonstrated their stable interaction with the catalytic site of the enzyme. Beyond their enzyme-inhibitory activity, these peptides enhanced glucose uptake in HepG2 cells, stimulated glycogen synthesis, and reduced oxidative stress, indicating a multifaceted impact on the cellular mechanisms of impaired carbohydrate metabolism.

Similar trends are also observed for meat-derived raw materials. Specifically, a number of potentially hypoglycemic peptides were identified from porcine collagen, among which the most promising was the tetrapeptide NWYR. It exhibited strong α -glucosidase inhibitory activity, surpassing that of acarbose, as well as high affinity for DPP-4, according to molecular docking results. Furthermore, the application of network pharmacology methods revealed interactions of NWYR with several molecular targets of T2DM, including DPP-4, ACE, matrix metalloproteinases 2 and 9, and coagulation factor II (F2, prothrombin), thereby indicating the multitarget nature of its biological activity [11].

In recent years, edible insects have been considered a promising alternative protein source for obtaining bioactive peptides with antidiabetic properties. Particular interest has been directed toward peptides derived from the larvae of the yellow mealworm (*Tenebrio molitor*), which are capable of simultaneously targeting several key enzymes associated with T2DM, including α -glucosidase, α -amylase, and DPP-4. Y. Zhu and co-authors employed a comprehensive approach that integrated proteomic analysis, enzyme assays, a cellular model of insulin resistance, and molecular docking to identify antidiabetic peptides from *Tenebrio molitor* [22]. Six bioactive peptides (DYGPPFK, WSPDPK, GMDFQPR, FNPFDLTK, SLFLPK,

and DPFDALPK) were identified, all of which exhibited α -glucosidase inhibitory activity. The lowest IC_{50} values were demonstrated by DPFDALPK (5.58 mg/mL) and DYGPFFK (5.76 mg/mL). Meanwhile, the peptide GMDFQPR showed the highest DPP-IV inhibitory activity ($IC_{50}=0.64$ mg/mL), highlighting its potential to prolong incretin hormone action and improve glycemic regulation. Particular emphasis was placed on molecular docking, which revealed strong affinity of the peptides for the active sites of α -glucosidase and DPP-4. The formation of stable hydrogen and hydrophobic interactions with key amino acid residues of the enzymes explains their pronounced antidiabetic activity and confirms the promise of these peptides as multitarget nutraceuticals.

F. M. de Matos and R. J. S. de Castro investigated hydrolysates of *Tenebrio molitor* flour and protein concentrate obtained using the proteases Flavourzyme, Alcalase, and Neutrase [12]. Enzymatic hydrolysis markedly enhanced the ability of the hydrolysates to inhibit α -amylase and α -glucosidase, and in the fraction with a molecular weight below 3 kDa, 38 peptides were identified. The most promising was the peptide LPAIL, for which computational analysis predicted a high probability (66.25 %) of DPP-4 inhibitory activity. The researchers attributed this effect to the presence of proline, isoleucine, and leucine residues in its structure, amino acids frequently found in known DPP-4 inhibitors. These findings confirm the effectiveness of *in silico* approaches for the primary screening of bioactive peptides and highlight the potential of *Tenebrio molitor* proteins as a source of functional ingredients with antidiabetic properties.

Discussion

Modern strategies for the discovery of bioactive peptides increasingly rely on the integration of traditional peptide generation techniques with advanced bioinformatic approaches. As emphasized by M. Hajfathalian and colleagues, the most promising direction involves the combination of enzymatic and virtual protein hydrolysis, bioinformatic analysis, molecular docking, and subsequent experimental validation [23]. Molecular docking is one of the most widely used *in silico* methods for predicting the interactions of bioactive peptides with target enzymes, such as DPP-4, α -glucosidase, α -amylase, and GLP-1R. This approach enables the modelling of the spatial orientation of a peptide within the active site of a protein, the evaluation of intermolecular interactions, and the prediction of ligand-receptor affinity. The principal evaluation criterion is the binding energy (docking score), usually expressed in kcal/mol, where more negative values correspond to higher predicted stability of the peptide-enzyme complex. At the same time, binding energy alone

is not a sufficient evaluation criterion; therefore, docking results are analyzed comprehensively, taking into account the localization of the peptide within the active site, its interactions with catalytic amino acid residues, as well as the formation of hydrogen bonds, hydrophobic contacts, electrostatic interactions, and π -interactions. To confirm the stability of the complex, docking is increasingly combined with molecular dynamics simulations, which involve the analysis of root mean square deviation (RMSD), root mean square fluctuation (RMSF), and the radius of gyration (Rg). RMSD characterizes the overall structural stability of the complex throughout the simulation; small RMSD fluctuations indicate stable peptide-enzyme binding. RMSF reflects the mobility of individual amino acid residues within the protein, thereby allowing the identification of regions undergoing the greatest conformational changes upon ligand binding. Rg is employed to assess the compactness of the protein's spatial structure; its stability during the simulation indicates preservation of the structural integrity of the complex. A comprehensive analysis of binding energy together with RMSD, RMSF, and Rg values provides a more objective evaluation of the potential efficacy of antidiabetic peptides and enhances the reliability of *in silico* screening results [15, 24].

One of the key experimental indicators of the efficacy of antidiabetic peptides is IC_{50} , which reflects the peptide concentration required to inhibit 50% of the activity of a target enzyme, such as DPP-4, α -glucosidase, or α -amylase. Owing to its universality and quantitative nature, IC_{50} is widely employed as a standardized criterion for comparing the inhibitory potency of different bioactive peptides, regardless of their origin or amino acid sequence. Determination of IC_{50} is based on the analysis of the dose-dependent response of an enzyme to the action of an inhibitor. Depending on the study design and the method of expressing concentration, results may be reported in various units, most commonly nM, μ M, mM, μ g/mL, or mg/mL. The use of uniform measurement units or their conversion is an essential prerequisite for the correct comparison of the inhibitory activity of different peptides. Lower IC_{50} values indicate higher inhibitory potency; therefore, this parameter is widely employed to compare the efficacy of peptides of diverse origins and to facilitate the primary selection of promising candidates. At the same time, cross-study comparisons require caution due to differences in experimental conditions, enzyme sources, substrates, and measurement units. Once determined, IC_{50} is often utilized to guide the choice of concentrations in cell-based assays and to support the interpretation of results obtained from molecular docking and molecular dynamics simulations [25, 26].

The comparative analysis highlights that different animal milks yield bioactive peptides with distinct anti-

diabetic mechanisms. S. S. Sakr and H. Barakat showed that fermented camel milk enriched with probiotics and Ajwa date pulp strongly inhibits α -amylase and α -glucosidase, reducing postprandial hyperglycemia [6]. P. Mudgil et al. confirmed its lowest IC₅₀ values for α -amylase inhibition [17], while I. K. Mohamed et al. demonstrated that peptides such as TYYPPQ restore insulin receptor expression and partially reactivate the PI3K/AKT pathway [9]. C. Elisha et al. identified lactoferrin-derived peptides with dual DPP-4 and ACE inhibitory activity, suggesting benefits for both glycemic control and cardiometabolic regulation [18]. A. Iwaniak et al. further showed that bovine milk hydrolysates generate numerous short peptides with strong DPP-4 inhibition and antioxidant properties, addressing insulin resistance and oxidative stress [7]. M. Liu et al. reported peptides with significant DPP-4 inhibitory activity and no cytotoxicity [15], while Y. Wu et al. discovered novel inhibitors that retained activity under cellular conditions, reinforcing goat milk's safety and efficacy as a nutraceutical source [19]. P. Mudgil et al. demonstrated that probiotic fermentation enhances proteolysis and peptide generation, markedly reducing IC₅₀ values [17]. Camel milk showed the strongest multitarget activity, while goat milk exhibited the highest proteolysis capacity. Thus camel milk emerges as the most potent multitarget source, cow milk contributes dual enzyme inhibition with antioxidant support, and goat milk provides safe and effective DPP-4 inhibitors. Fermentation consistently amplifies bioactivity, positioning probiotic-fermented milk products as promising functional foods for T2DM management. Sturgeon and porcine sources further confirm the potential of animal-derived peptides, with VT-9 and LE-9 from sturgeon improving glucose uptake and reducing oxidative stress, while the porcine collagen peptide NWYR demonstrated potent, multitarget activity against α -glucosidase, DPP-4, ACE, and other T2DM-related enzymes, surpassing acarbose in inhibitory strength [11, 21]. Edible insects, particularly *Tenebrio molitor*, have emerged as a promising source of antidiabetic peptides, with several sequences showing strong inhibitory activity against α -glucosidase, α -amylase, and DPP-4, alongside molecular docking evidence of stable enzyme binding. In addition, results reported by Y. Zhu

et al., and de Matos F.M. and de Castro R.J.S., confirm the multitarget nutraceutical potential of insect-derived proteins for T2DM management [12, 22]. Thus, the findings of narrative review indicate that bioactive peptides derived from animal dietary proteins exhibit promising antidiabetic potential. Regardless of their source – whether milk from various livestock species, fish, meat, or edible insects – bioactive peptides are characterized by multitarget mechanisms of action, including inhibition of key carbohydrate-metabolizing enzymes such as DPP-4 and α -glucosidase, regulation of insulin-related signalling pathways, enhancement of peripheral tissue insulin sensitivity, reduction of postprandial hyperglycemia, as well as antioxidant and anti-inflammatory activities. Camel, bovine, and caprine milk remain the most extensively studied sources of peptides with confirmed inhibitory activity against DPP-4 and α -glucosidase, while the IC₅₀ value serves as a universal criterion for comparing peptide inhibitory potency, thereby ensuring a standardized approach to their evaluation. At the same time, the efficiency of peptide formation and their biological properties largely depend on the type of protein substrate, its amino acid composition, and the method of enzymatic hydrolysis or fermentation.

Conclusions

Animal-derived bioactive dietary peptides represent promising antidiabetic agents owing to their multitarget mechanisms of action. Among the most extensively investigated sources are different animals milk proteins, with the IC₅₀ value providing a standardized measure of their efficacy. Future research should focus on the integration of modern *in silico*, *in vitro*, and *in vivo* approaches to optimize peptide selection and facilitate the development of novel nutraceuticals for the prevention and treatment of T2DM.

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Conflict of interest

The authors declare no conflict of interest.

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Функціональні харчові пептиди як мультитаргетні антидіабетичні агенти: *in silico* та біохімічні аспекти

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Анотація. У статті узагальнено сучасні дані щодо застосування підходів *in silico*, насамперед молекулярного докінгу, для скринінгу харчових біоактивних пептидів тваринного походження із потенційними цукрознижувальними властивостями та оцінено перспективи їх використання у створенні функціональних продуктів антидіабетичного спрямування. Встановлено, що такі пептиди є перспективними антидіабетичними агентами завдяки мультитаргетним механізмам дії: інгібування ключових ферментів вуглеводного метаболізму (зокрема DPP-4 та α -глюкозидази), регуляція інсулінозалежних сигнальних шляхів, підвищення чутливості периферичних тканин до інсуліну, зниження постпрандіальної гіперглікемії та володіння антиоксидантною й протизапальною активністю. Найкраще дослідженими джерелами харчових пептидів залишаються верблюже, коров'яче та козяче молоко, для яких підтверджено інгібіторну активність проти DPP-4 та α -глюкозидази. При цьому значення напівмаксимальної інгібувальної концентрації (IC_{50}) є універсальним критерієм для порівняння інгібіторної потужності пептидів, забезпечуючи стандартизований підхід до їх оцінювання. Водночас ефективність утворення та біологічні властивості пептидів значною мірою залежать від виду білкової сировини, її амінокислотного складу, способу ферментативного гідролізу або ферментації.

Ключові слова: цукровий діабет 2 типу; нутрицевтики; харчові білки; біоактивні пептиди; ферментативний гідроліз; молекулярний докінг; молекулярні мішені; функціональні харчові продукти.



Subjective and objective assessment of cognitive function in patients with bronchial asthma, arterial hypertension, and their comorbidity

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Abstract. Bronchial asthma and arterial hypertension are common chronic conditions that have both been associated with impaired cognitive function. The coexistence of these conditions may be associated with greater impairment of memory and attention, highlighting the need to assess both subjective cognitive complaints and objective cognitive performance in this patient population. The aim of this study was to analyze the characteristics of subjective and objective assessment of cognitive function in patients with asthma, arterial hypertension, and their comorbidity. The study included 82 patients stratified into three groups: Group I comprised patients with bronchial asthma ($n=25$), Group II comprised patients with arterial hypertension ($n=20$), and Group III comprised patients with coexisting bronchial asthma and arterial hypertension ($n=37$). The control group (CG) included 21 apparently healthy individuals. Subjective assessment was based on the analysis of cognitive complaints, whereas objective assessment was performed using the Montreal Cognitive Assessment and Schulte tables. Statistical analyses were performed using Statistica 10.0 software, with the Mann – Whitney U test, Pearson's chi-square test, and Spearman's rank correlation coefficient applied as appropriate. Cognitive complaints were most frequently reported by patients with coexisting bronchial asthma and arterial hypertension (59.5 %). This group also had the lowest median Montreal Cognitive Assessment score, 22.00 [20.00; 24.00], and the longest median Schulte table completion time, 54.00 s [47.00; 59.00]. Schulte table completion time was significantly longer among patients reporting cognitive complaints in the asthma group and in patients with coexisting asthma and arterial hypertension, whereas no statistically significant difference was observed in group II. Spearman correlation analysis revealed weak to moderate correlations between the number of cognitive complaints and objective measures of cognitive performance. The number of complaints correlated negatively with the MoCA score and positively with Schulte table completion time. Cognitive complaints were associated with poorer performance on objective cognitive tests; however, weak and moderate correlations suggest that the number of subjective complaints does not always reflect the severity of cognitive impairment. These findings underscore the importance of cognitive assessment in patients with coexisting bronchial asthma and arterial hypertension, based not only on subjective complaints but also on standardized cognitive test results.

Keywords: bronchial asthma; arterial hypertension; cognitive function; complaints; Montreal Cognitive Assessment; Schulte tables.

Introduction

Bronchial asthma (BA) is a common chronic noncommunicable disease with substantial clinical and public health significance. A systematic analysis of the Global Burden

of Disease Study 2021 estimated that approximately 260 million people worldwide had asthma [1].

Arterial hypertension (AH) is a common and clinically relevant comorbidity in patients with asthma. According

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to the BADA study (Blood Pressure Levels, Clinical Features and Markers of Subclinical Cardiovascular Damage of Asthma Patients), the prevalence of hypertension among adults with asthma was 45 % and increased to 75 % when cases identified by 24-h ambulatory blood pressure monitoring were included [2]. According to a review by Cazzola *et al.* [3], coexisting asthma and cardiovascular comorbidities, including hypertension, may complicate disease management and reflect shared pathobiological mechanisms, including chronic systemic inflammation, oxidative stress, and endothelial dysfunction. Visca *et al.* found that neutrophilic airway inflammation may contribute to the association between asthma and hypertension, as a neutrophil percentage of ≥ 61 % in induced sputum was an independent predictor of hypertensive status in patients with asthma [4].

In a systematic review and meta-analysis, Bushi *et al.* reported a pooled prevalence of cognitive impairment of 16.3 % among patients with asthma; this condition was also associated with an increased risk of cognitive decline and dementia [5]. Proposed mechanisms underlying this association include chronic systemic inflammation and hypoxic episodes [6]. Wei *et al.* highlighted the role of hypertension as a major modifiable risk factor for cognitive decline, with its adverse cognitive effects linked to cerebral small vessel disease, neurovascular dysfunction, impaired cerebral perfusion, and white matter lesions [7]. Existing studies on the coexistence of asthma and hypertension have focused primarily on clinical characteristics and the bidirectional clinical burden of these conditions [8], whereas evidence regarding cognitive status in this patient population remains limited.

Complaints involving memory, attention, and other cognitive functions are an important component of the initial cognitive assessment, as they may reflect subjective cognitive decline [9] and may also be associated with objective evidence of cognitive impairment [10]. In their meta-analysis, Van Patten *et al.* reported an inconsistent relationship between subjective and objective cognitive functioning, with effect sizes often ranging from null to weak across different clinical conditions [11]. Therefore, studies of cognitive changes should include subjective cognitive complaints and standardized objective cognitive test results [12]. Early identification of cognitive impairment in patients with chronic diseases is clinically important, as it may affect treatment adherence and patients' ability to self-manage their disease [13]. Therefore, assessing both subjective cognitive complaints and objective cognitive test performance in patients with asthma, hypertension and coexisting bronchial asthma and arterial hypertension may be clinically useful for optimizing patient management. The aim of this study was to evaluate subjective cognitive complaints

and objective cognitive performance in patients with asthma, hypertension and their coexistence.

Materials and Methods

The study included 82 patients stratified into three groups: Group I comprised patients with bronchial asthma ($n=25$), Group II comprised patients with arterial hypertension ($n=20$), and Group III comprised patients with coexisting bronchial asthma and arterial hypertension ($n=37$). The control group (CG) comprised 21 apparently healthy individuals aged 45–70 years who had no history or clinical evidence of asthma, hypertension, or any of the other conditions listed in the exclusion criteria.

Patients aged 45–70 years with moderate persistent asthma, stage II, grade 2 hypertension, or both were eligible for inclusion. Patients with asthma were required to have had no exacerbations during the 4 weeks before enrollment, whereas patients with hypertension were required to have had no hypertensive crisis during the same period.

Arterial hypertension was diagnosed in accordance with the Unified Clinical Protocol for Primary and Specialized Medical Care "Hypertensive Disease (Arterial Hypertension)", approved by Order of the Ministry of Health of Ukraine No. 1581 dated September 12, 2024. Asthma was diagnosed in accordance with the Unified Clinical Protocol for Primary and Secondary (Specialized) Medical Care "Bronchial Asthma", approved by Order of the Ministry of Health of Ukraine No. 868 dated October 8, 2013, and the 2026 Global Initiative for Asthma (GINA) recommendations.

Exclusion criteria included secondary hypertension; other chronic respiratory diseases; obstructive sleep apnea; a history of stroke or myocardial infarction; angina pectoris; severe cardiovascular, neurological, renal, or hepatic disease; diabetes mellitus; dementia; diagnosed anxiety, depressive, or other psychiatric disorders; severe visual or hearing impairment; alcohol or drug dependence; the use of medications with marked sedative effects that could influence cognitive test performance.

At enrollment, patients with asthma were receiving maintenance therapy with a fixed-dose combination of an inhaled corticosteroid and a long-acting β_2 -agonist, as recommended by GINA. Patients with hypertension were receiving free- or fixed-dose combinations of antihypertensive agents in accordance with the current national clinical protocol.

The study was approved by the Bioethics Committee of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine (Protocol No. 85 dated April 1, 2026). All participants provided written informed consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Subjective cognitive complaints were assessed using a structured interview. All participants were asked the same nine questions about common difficulties with memory, attention, executive functioning, language, and processing speed. Participants who answered “yes” to at least one question were classified as having subjective cognitive complaints. The frequency of each complaint and the total number reported by each participant were also analyzed.

Objective cognitive performance was evaluated using the Montreal Cognitive Assessment (MoCA), with scores ranging from 0 to 30; a score below 26 was considered indicative of cognitive impairment. Sustained attention was assessed using the Schulte Table test, in which participants were instructed to identify the numbers from 1 to 25 in ascending order as quickly as possible; completion time was recorded, with longer times indicating poorer performance.

Statistical analyses were performed using Statistica version 10.0. Quantitative variables with non-normal distributions are presented as the median and first and third quartiles (Me [Q1; Q3]), and categorical variables as n (%). The Kruskal – Wallis test was used to compare quantitative variables across the four groups, followed by pairwise comparisons using the Mann – Whitney U test. Categorical variables were compared using Pearson's χ^2 test. The Bonferroni correction was applied to multiple pairwise between-group comparisons. Associations were assessed using Spearman's rank correlation coefficient (r_s).

Results

The clinical and demographic characteristics of the study groups are summarized in Table 1. No statistically

significant between-group differences were found in age ($p=0.968$), sex ($p=0.433$), place of residence ($p=0.914$), educational level ($p=0.429$), employment status ($p=0.600$), or smoking status ($p=0.760$). The duration of asthma did not differ significantly between patients with asthma alone and those with coexisting asthma and hypertension ($p=0.83$). Similarly, the duration of hypertension did not differ significantly between patients with hypertension alone and those with coexisting asthma and hypertension ($p=0.215$).

The analysis then focused on subjective cognitive complaints. Participants were classified as having such complaints if they reported at least one difficulty involving memory, attention, executive functioning, or language. The prevalence of subjective cognitive complaints differed significantly across the study groups ($\chi^2=11.95$, $p=0.008$). The highest prevalence was observed in Group III, where 59.5% of patients with coexisting asthma and hypertension reported at least one complaint of memory impairment, difficulty concentrating, or language problems (Table 2). Pairwise comparisons showed that the prevalence was significantly higher in this group than in the CG ($p=0.00084$). Group I also had a higher prevalence of cognitive complaints than the control group ($p=0.015$); however, this difference did not meet the Bonferroni-adjusted significance threshold ($p<0.0083$). No other pairwise between-group differences were statistically significant.

The profile of the most frequent cognitive complaints was further analyzed in the overall sample. Complaints were categorized according to the main cognitive domains: memory, attention, executive function, language, and processing speed (Table 3).

Table 1. Clinical and demographic characteristics of the study groups

Characteristic	Group I, n=25	Group II, n=20	Group III, n=37	CG, n=21
Age, years	55 [48,00; 60,00]	53,5 [51,00; 60,50]	52 [48,50; 59,50]	55 [51,50; 61,50]
Sex				
Male	12 (48,0 %)	14 (70,0 %)	23 (62,2 %)	11 (52,4 %)
Female	13 (52,0 %)	6 (30,0 %)	14 (37,8 %)	10 (47,6 %)
Place of residence				
Urban	16 (64,0 %)	13 (65 %)	23 (62,2 %)	15 (71,5 %)
Rural	9 (36,0 %)	7 (35 %)	14 (37,8 %)	6 (28,5 %)
Educational level				
Higher education	14 (56,0 %)	7 (35,0 %)	15 (37,0 %)	11 (52,3 %)
Secondary vocational education	11 (44,0 %)	13 (65 %)	22 (63 %)	10 (47,3 %)
Employment status				
Employed	15 (60 %)	13 (65 %)	22 (59,5 %)	16 (76,2 %)
Not employed	10 (40 %)	7 (35 %)	15 (40,5 %)	5 (23,8 %)
Duration of asthma, years	20,00 [12,00; 29,00]	–	17,5 [10,00; 30,50]	–
Duration of hypertension, years	–	8,50 [7,00; 10,50]	7,00 [3,50; 11,00]	–
Smoking status				
Never smoker	19 (76 %)	11 (55 %)	25 (67,6 %)	13 (62,0 %)
Former smoker	5 (20 %)	6 (30 %)	10 (27 %)	6 (28,5 %)
Current smoker	1 (4 %)	3 (15 %)	2 (5,4 %)	2 (9,5 %)

Table 2. Prevalence of cognitive complaints among patients with BA alone, AH alone, and both conditions

Group	Complaints present		Complaints absent	
	n	%	n	%
Group I, n=25	12	48,0	13	52,0
Group II, n=20	7	35,0	13	65,0
Group III, n=37	22	59,5*	15	40,5
CG, n=21	3	14,3	18	85,7

Note: * Statistically significant compared with the control group after Bonferroni correction ($p < 0.0083$).

Table 3. Distribution of cognitive complaints among patients with BA alone, AH alone, and both conditions, n (%)

Cognitive domain	Complaints	Group I, n=25		Group II, n=20		Group III, n=37		CG, n=21	
		n	%	n	%	n	%	n	%
Memory	«trouble remembering new information»	7	28,8	4	20,0	15	40,5	1	4,8
	«forgetting where I put things»	5	20,0	2	10,0	13	35,1	1	4,8
	«feeling that my memory had become worse»	7	28,0	4	20,0	16	43,2	–	–
Attention	«trouble concentrating»	4	16,0	6	30,0	16	43,2	1	4,8
	«losing my train of thought during conversation»	3	12,0	3	15,0	8	21,6	–	–
Executive function	«forgetting to complete planned tasks»	4	16,0	2	10,0	7	18,9	1	4,8
	«making mistakes when doing tasks»	3	12,0	2	10,0	8	21,6	–	–
Language	«trouble finding the right word»	8	32,0	4	20,0	14	37,8	1	4,8
Processing speed	«feeling mentally foggy»	4	16,0	3	15,0	10	27,0	2	9,5

In Group I, language- and memory-related complaints were the most common: trouble finding words was reported by 32.0 % of participants, while trouble remembering new information and feeling that memory had become worse were each reported by 28.0 %. In Group II, trouble concentrating was reported by 30.0 % of patients, and memory- and language-related complaints were also frequently noted. In the group with coexisting asthma and arterial hypertension, the most common complaints were feeling that memory had become worse and trouble concentrating, each reported by 43.2 % of participants, followed by trouble remembering new information (40.5 %) and trouble finding words (37.8 %). Overall, these findings suggest that patients with coexisting asthma and arterial hypertension present with a broader spectrum of subjective cognitive complaints.

Objective cognitive functioning in the study groups was assessed using the MoCA and Schulte table tests (Table 4).

Cognitive performance differed significantly across the groups in terms of both MoCA scores ($p < 0.001$) and Schulte Table completion time ($p < 0.001$).

The lowest cognitive performance on both tests was observed in patients with combined asthma and arterial hypertension. Group III showed significantly poorer results than Groups I and II and the control group. The median MoCA score in Group III was 22.00 [20.00; 24.00], which was 12.0 % lower than in Group I, 10.2 % lower than in Group II, and 20.0% lower than in the control group (Fig. 1). The median Schulte table completion time in Group III was 54.00 [47.00; 59.00] s, exceeding the values observed in Group I by 9.00 s (20.0 %), in Group II by 10.50 s (24.1 %), and in the control group by 20.00 s (58.8 %) (Fig. 2).

Moreover, participants in Groups I and II had significantly lower MoCA scores than the control group, whereas no significant difference was observed between Groups I and II. The time required to complete the Schulte tables was also significantly longer in both groups than in the control group.

Table 4. Cognitive performance assessed using the MoCA and Schulte table test in the study groups, median [Q1; Q3]

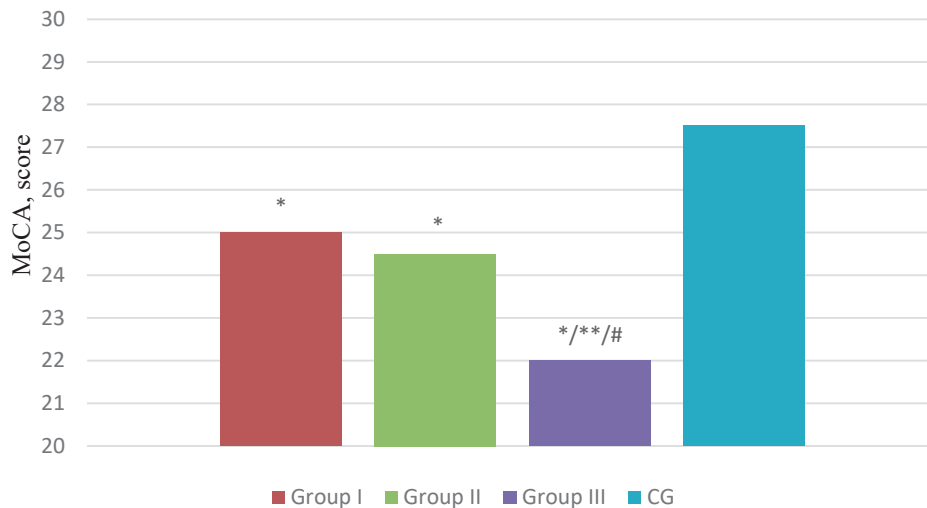
Parameter	Group I, n=25	Group II, n=20	Group III, n=37	CG, n=21
MoCA, score	25,00 [23,00; 26,00]*	24,50 [22,50; 26,00]*	22,00 [20,00; 24,00]*/**/#	27,50 [25,75; 28,00]
Schulte table completion time, s	45,0 [39,00; 49,00]*	43,50 [40,00; 51,00]*	54,0 [47,00; 59,00]*/**/#	34,00 [30,50; 39,00]

Notes: The Bonferroni-adjusted significance threshold for pairwise Group comparisons was $p < 0.0083$.

1. * Statistically significant compared with the control Group;

2. ** Statistically significant compared with Group I;

3. # Statistically significant compared with Group II.

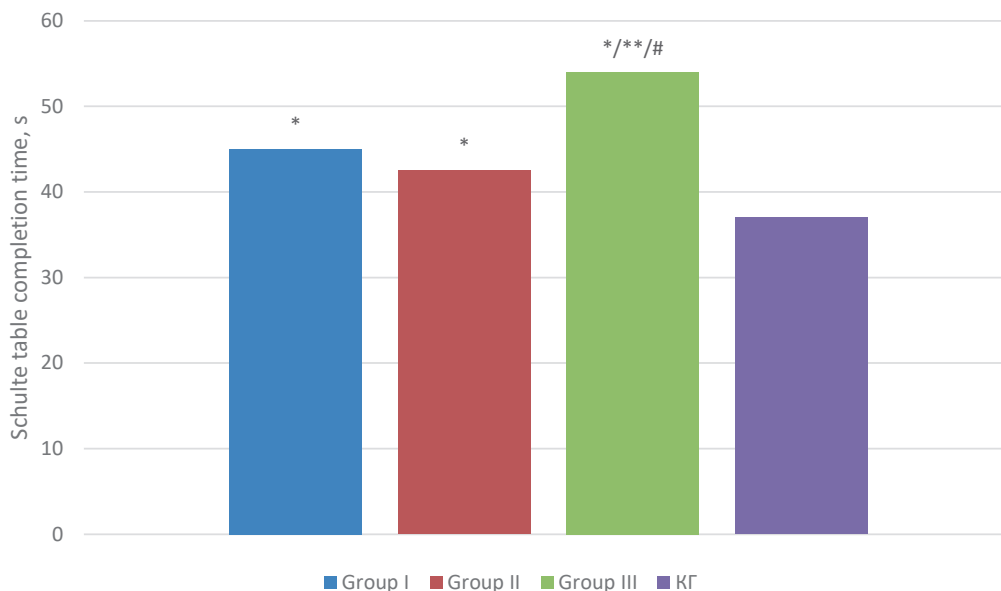
**Fig. 1.** MoCA scores in patients with BA alone, AH alone, and both conditions.

Notes: The Bonferroni-adjusted significance threshold for pairwise group comparisons was $p < 0.0083$.

1. * Statistically significant compared with the control group;

2. ** Statistically significant compared with Group I;

3. # Statistically significant compared with Group II.

**Fig. 2.** Schulte table completion time in patients with BA alone, AH alone, and both conditions/

Notes: The Bonferroni-adjusted significance threshold for pairwise Group comparisons was $p < 0.0083$.

* Statistically significant compared with the control Group;

** Statistically significant compared with Group I;

Statistically significant compared with Group II.

In addition, participants in Groups I and II had significantly lower MoCA scores than those in the CG, whereas no significant between-group difference was observed between Groups I and II. Schulte table completion time was significantly longer in Groups I and II than in the CG.

To assess the association between subjective cognitive complaints and objective measures of cognitive performance, MoCA scores and Schulte table completion time were compared between participants with and without complaints within each study group (Table 4).

Across all clinical groups, patients reporting cognitive complaints had significantly lower MoCA scores than those without complaints. Schulte table completion time was significantly longer among patients with complaints in Groups I and III, whereas no statistically significant difference was found for this parameter in Group II.

To evaluate the relationship between subjective cognitive complaints and objective cognitive performance, correlation analysis was performed between the number of different cognitive complaints, MoCA score, and Schulte table completion time (Table 5).

In Groups I and II, the number of cognitive complaints showed moderate negative correlations with MoCA scores. In patients with coexisting asthma and hypertension, this correlation was also statistically significant, although weak ($r_s = -0.376$; $p < 0.05$). This finding may suggest a weaker relationship between subjective cognitive complaints and objective cognitive

test performance in patients with comorbid asthma and hypertension.

Moderate positive correlations were observed between the number of complaints and Schulte table completion time in Groups I and III, whereas no statistically significant association was found in Group II.

Discussion

One of the key findings of this study was that patients with coexisting asthma and hypertension had the highest prevalence of cognitive complaints and the poorest performance on objective cognitive tests. These findings are consistent with those of Hu et al. [14], who reported an association between asthma and poorer attention and processing speed, and Muela et al. [15], who found lower MoCA scores in patients with hypertension than in individuals without hypertension.

Across all clinical groups, patients who reported cognitive complaints had significantly lower MoCA scores than those who did not. This result is consistent with Vintimilla et al. [16], who found that subjective cognitive difficulties in patients with hypertension were associated with poorer performance on objective cognitive tests. The presence of cognitive complaints should therefore be considered during clinical assessment and may indicate the need for further evaluation using standardized cognitive tests.

The findings indicate that the associations between the number of cognitive complaints and objective cognitive measures were predominantly weak to moderate, with no strong correlations identified.

Table 4. MoCA scores and Schulte table completion time according to the presence of cognitive complaints in the study groups

Group	Cognitive complaints	MoCA, score median [Q1;Q3]	p	Schulte table completion time, s median [Q1;Q3]	p
Group I, n=25	Present, n=12	22,50 [21,50; 25,00]	0,027*	48,50 [44,00; 54,00]	0,016*
	Absent, n=13	26,00 [24,00; 26,00]		41,00 [38,00; 45,00]	
Group II, n=20	Present, n=7	24,00 [22,00; 24,00]	0,032*	46,00 [42,00; 58,00]	0,152
	Absent, n=13	25,00 [24,00; 26,00]		42,00 [33,00; 50,00]	
Group III, n=37	Present, n=22	21,00 [20,00; 22,00]	0,017*	57,50 [52,00; 64,00]	0,005*
	Absent, n=15	23,00 [21,00; 24,00]		49,00 [43,00; 55,00]	
CG, n=21	Present, n=3	25,00 [25,00; 28,00]	0,058	36,00 [32,00; 40,00]	0,075
	Absent, n=18	27,00 [26,00; 28,00]		32,00 [29,50; 36,00]	

Notes: * $p < 0.05$ for the comparison between participants with and without complaints; comparisons were performed using the Mann – Whitney U test.

Table 5. Associations between the number of cognitive complaints and objective measures of cognitive performance in the study groups

Group	Number of complaints and MoCA score, r_s	Number of complaints and Schulte table completion time, r_s
Group I, n=25	-0,460*	0,521*
Group II, n=20	-0,517*	0,341
Group III, n= 37	-0,376*	0,454*
CG, n=21	-0,160	-0,078

Notes: r_s , Spearman's rank correlation coefficient; * $p < 0.05$ indicates a statistically significant correlation.

This suggests that, in patients with bronchial asthma, arterial hypertension, and both conditions, the number of cognitive complaints does not always reflect the severity of objectively confirmed cognitive impairment. Therefore, cognitive complaints in these patients, regardless of their number, should be interpreted in conjunction with standardized cognitive test results.

Conclusions

Coexisting asthma and hypertension were associated with more frequent cognitive complaints, significantly lower MoCA scores, and longer Schulte table completion times than asthma or hypertension alone. Complaints related to memory, attention, and thinking were associated with poorer performance on objective cognitive tests. Weak to moderate correlations between the number of complaints and objective

cognitive measures suggest that subjective perception of cognitive impairment does not always correspond to the severity of objectively confirmed cognitive changes. These findings highlight the importance of cognitive assessment in patients with asthma, hypertension and both conditions, based not only on subjective complaints but also on standardized cognitive test results.

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Conflict of interest

None.

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Анотація. Бронхіальна астма та артеріальна гіпертензія є поширеними хронічними захворюваннями, які часто асоціюються з порушенням когнітивних функцій. Їх поєднаний перебіг може мати потенційно більш негативний вплив на пам'ять та увагу, що зумовлює необхідність оцінки як суб'єктивних скарг, так і об'єктивних когнітивних показників у таких хворих. Метою дослідження було проаналізувати особливості суб'єктивної та об'єктивної оцінки когнітивних функцій у пацієнтів з астмою, артеріальною гіпертензією та їх поєднанням. У дослідження включено 82 особи, яких поділили на три групи: I група – пацієнти з бронхіальною астмою (n=25), II – з артеріальною гіпертензією (n=20), III – з поєднаним перебігом бронхіальної астми та артеріальної гіпертензії (n=37). До контрольної групи (КГ) було включено 21 практично здорову особу. Суб'єктивну оцінку здійснювали шляхом аналізу когнітивних скарг, об'єктивну – за допомогою тесту Montreal Cognitive Assessment (MoCA) та таблиць Шульте. Найвищу частоту когнітивних скарг виявлено у хворих із поєднаним перебігом астми та артеріальної гіпертензії – 59,5 %. У цій групі також встановлено найнижчі показники MoCA – 22,00 [20,00; 24,00] бала та найбільший час виконання таблиць Шульте – 54,00 [47,00; 59,00] с. У пацієнтів зі скаргами в усіх клінічних групах спостерігали достовірно нижчі значення MoCA порівняно з особами без скарг. Час виконання таблиць Шульте був значущо більшим в осіб зі скаргами в I та III групах, тоді як у II статистично достовірної різниці не встановлено. У контрольній групі статистично значущих відмінностей за показником MoCA та часом виконання таблиць Шульте, залежно від наявності скарг, не виявлено. У клінічних групах аналіз показав слабкий та помірний кореляційний зв'язок між кількістю скарг і результатами об'єктивного тестування когнітивних функцій: із показником MoCA – зворотний, тоді як із часом виконання таблиць Шульте – прямий. Поєднаний перебіг бронхіальної астми і артеріальної гіпертензії асоціювався з більшою частотою когнітивних скарг, достовірно нижчими показниками MoCA та тривалішим часом виконання таблиць Шульте порівняно з ізольованим перебігом цих захворювань. Наявність скарг асоціювалася з гіршими результатами об'єктивного когнітивного тестування, однак слабка та помірна сила цих кореляційних зв'язків свідчить, що кількість суб'єктивних скарг не завжди відображає ступінь когнітивного зниження. Отримані дані підкреслюють важливість оцінки когнітивного стану хворих на астму, артеріальну гіпертензію, а також їх поєднання, яка має ґрунтуватися не лише на аналізі суб'єктивних скарг, а й на результатах стандартизованих тестів.

Ключові слова: бронхіальна астма; артеріальна гіпертензія; когнітивні функції; скарги; Монреальська шкала оцінки когнітивних функцій; таблиці Шульте.

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