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Editors office address:
I. Horbachevsky Ternopil National Medical University
46001, 1 Maidan Voli, Ternopil, Ukraine
E-mail: info@ijmr.com.ua
www: https://ijmr.com.ua/

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Low cardiac output syndrome after cardiac surgery: A retrospective analysis

Ibrahim Bechri*
Doctor of Medicine, Assistant Professor
Hassan II University Hospital
30050, II Hassan Ave., Fes, Morocco
https://orcid.org/0000-0001-6245-8613

Ali Derkaoui
Doctor of Medicine, Professor
Hassan II University Hospital
30050, II Hassan Ave., Fes, Morocco
https://orcid.org/0000-0002-0549-6039

Abdelkarim Shimi
Doctor of Medicine, Professor
Hassan II University Hospital
30050, II Hassan Ave., Fes, Morocco
https://orcid.org/0009-0006-1040-4158

Mohammed Khatouf
Doctor of Medicine, Professor
Hassan II University Hospital
30050, II Hassan Ave., Fes, Morocco
https://orcid.org/0000-0003-4881-2123

Abstract. Low cardiac output syndrome is a prevalent complication observed after cardiac surgery, related to elevated rates of mortality and morbidity. The study aimed to pinpoint independent risk factors for low cardiac output through the analysis of post-cardiac surgery data. This is a single-centre, two-year retrospective study from January 2021 to December 2022, including all patients admitted to the A1 general intensive care unit for postoperative management of cardiac surgery. Variables from preoperative, intraoperative, and postoperative data were collected and evaluated with the statistical package for the social sciences, with a significance level set at $p < 0.05$. Overall, the median age was 44 years (22-80), with 60% being female. The prevalence of low cardiac output syndrome after cardiac surgery was 44% (n = 85). Significant risk factors for low cardiac output syndrome were identified: low preoperative left ventricular function (ejection fraction <40%), preoperative atrial fibrillation, impaired preoperative renal function, multiple valve replacement, prolonged extracorporeal circulation, and clamping time. Patients who experienced low cardiac output syndrome had longer hospital stays and a higher incidence of postoperative complications, including atrial fibrillation and kidney injury, as well as a higher mortality rate (7% versus 0%). Identification and treatment of low cardiac output syndrome can improve myocardial recovery and decrease mortality. A better understanding of its physiopathological mechanisms may help develop potential preventive strategies

Keywords: cardiopulmonary bypass; risk factors; inotrope; circulatory support; mortality rate

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*Corresponding author

Introduction

Low cardiac output syndrome (LCOS) is a significant complication observed in patients who have undergone cardiac surgery. Although definitions differ among studies, the most common include decreases in the cardiac index to < 2.2 L/min/m^2 requiring inotropic agents or mechanical circulatory support to keep the systolic pressure > 90 mmHg as well as the cardiac index > 2.2 L/min/m^2 [1].

J.L. Pérez Vela *et al.* [2] conducted a multicentre, prospective cohort analysis and found an incidence of 7.5% for LCOS after cardiac surgery. A.E. Duncan *et al.* [3] reported a higher incidence of 10% in a North American study involving 59,810 patients. LCOS was associated with significant morbidity and mortality, reaching up to 40%. Additionally, it required an extended intensive care unit (ICU) stay, increased resource utilization, and a heightened occurrence of respiratory, and neurological complications, and kidney injury, necessitating prolonged mechanical ventilation.

Several LCOS risk factors were identified in the literature. In a retrospective multicentre cohort study involving 781 patients, F. Biancari *et al.* [4] demonstrated that elderly age, diabetes, kidney injury, and malnutrition were clinically associated with a high LCOS risk. Q. Qing *et al.* [5] developed an individualised nomogram prediction model for LCOS after cardiac surgery. The results indicated that global longitudinal strain was a significant factor associated with LCOS after cardiac surgery.

Biologically, anaemia, elevated Brain Natriuretic Peptide (BNP) and pro-BNP were identified in cohort studies [6-8]. Surgically, the main factors identified were urgent surgery, longer Cardiopulmonary bypass (CPB) and cross-clamp times [9]. Research conducted in Lille also identified morning surgery as a risk factor for postoperative cardiac complications after aortic valve replacement, highlighting the circadian expression of specific genes. This result was not found in a recent cohort of 9700 patients with several types of surgery [10, 11]. The literature extensively describes the outcome of LCOS, indicating its association with heightened postoperative complications, prolonged stays in the ICU and on mechanical ventilation, and mortality rates up to 50-80% in the case of refractory LCOS [4]. However, the long-term outcome of LCOS is still poorly studied [12].

Several studies have been conducted to investigate LCOS after cardiac surgery. However patient outcomes and LCOS risk factors after cardiac surgery in Morocco remain unknown due to the limited access to cardiac surgery, the young age of patients, the high incidence of rheumatic heart disease and the poorly studied long-term LCOS outcomes. Recent advances illustrate the potential of expanding cardiac surgery with acceptable in-hospital mortality. The study aimed to identify independent risk factors influencing the outcome of LCOS after adult cardiac surgery by analysing preoperative, intraoperative, and postoperative data.

Materials and Methods

This is a single-centre two-year retrospective study from January 2021 to December 2022, including 190 patients admitted to the A1 intensive care unit for postoperative management of cardiac surgery. Criteria for inclusion encompassed adult individuals subjected to cardiac surgery with CPB, regardless of the specific surgical procedure. Exclusion criteria included pregnant females, children, and individuals lacking complete data, such as echocardiographic measurements or perioperative hemodynamic information. Additionally, those undergoing surgical interventions for penetrating cardiac injury or pericardial effusion were excluded from the study.

LCOS was defined following the most common definition from previous reports: decrease in the cardiac index to < 2.2 L/min/m^2 requiring inotropic agents or mechanical circulatory support to maintain the systolic pressure > 90 mmHg and the cardiac index > 2.2 L/min/m^2 [1]. Vasoconstricting medication to improve peripheral vascular resistance was not considered an LCOS. All pre- and in-hospital patient records were reviewed, and data were collected using standardised forms. Baseline variables were divided into three groups pre-operative factors, intra-operative factors, and post-operative factors:

- Preoperative variables: gender (male and female), age, comorbidities, heart rate (sinus or atrial fibrillation), preoperative echocardiographic parameters; preoperative ejection fraction (> 40% or ≤ 40%), left ventricular diameter diastolic (LVDD), left ventricular diameter systolic (LVDS).
- Intraoperative variables: type of intervention (isolated or multiple valve replacement, coronary artery bypass graft (CABG), cardiopulmonary bypass (CPB) and cross-clamp times.
- Postoperative variables: inotropic use, EF at 0 h, 4 h and 24 h, complications (acute pulmonary oedema, kidney injury, neurological, respiratory, infectious complications), duration of mechanical ventilation, length of stay in the intensive care unit, and mortality rate.

Statistical Package for the Social Sciences (SPSS), and Statistics software at the Laboratory of Epidemiology and Public Health of Fez, Morocco were used to analyse the data. Descriptive statistics were employed to calculate frequencies, with mean and standard deviation utilised for continuous variables. Univariate proportions were assessed using the chi-squared test, and statistical significance was determined at p-values < 0.05. Predictive factors of mortality were studied with a logistic regression model with multivariate analysis to compare patients who developed with those who did not. The study adhered to the ethical norms of the Declaration of Helsinki [13] and was approved by the Hassan II University Hospital's ethics committee (No. 18/2023). Informed consent was deemed unnecessary given the retrospective nature of the study. The study did not use information that could be employed for the identification of individuals who participated in the research.

Results and Discussion

In general, 85 of 190 patients (44%) had LCOS, confirmed by a low cardiac index of less than 2,2 L/min/m^2. Patient characteristics were divided into 3 groups: preoperative, intraoperative, and postoperative.

Preoperative data analysis in cardiac surgery

This study observed a higher proportion of women compared to men, resulting in a gender ratio of 1.7. The median age recorded was 44 years (22-80).

Comorbidities: the main comorbidities were atrial fibrillation (N: 83, 44%), smoking (N: 29, 16.3%) and hypertension (N: 26, 13%) (Table 1).

Table 1. Patient comorbidities

Variables	Frequency (%)
Cardiac history	
Hypertension	26 (13%)
Atrial fibrillation	83 (44%)
Endocarditis	9 (4.7%)
History of cardiac surgery	8 (5%)
Diabetes	12 (6.3%)
Kidney failure	8 (5%)
Smoking	29 (16.3%)

Source: compiled by the authors

Preoperative echocardiographic parameters: 145 patients had preserved ejection fraction, while 17 patients had preoperative low ejection fraction, 17 patients (8.9%) had a left ventricular dilatation, the median of the right ventricular end-diastolic area was 48 mm ± 7 and the median of pulmonary artery systolic pressure was 33 mmHg (Table 2).

Table 2. Preoperative echocardiographic parameters

Parameters	Frequency (%)
Left ventricular ejection fraction	
> 60%	145 (76%)
40 % a 60%	37 (19.4%)
< 40%	7 (3.6%)
LEVDD >56 mm	17 (8.9%)
Right ventricular end-diastolic area (mm)	48 ± 7
Pulmonary artery systolic pressure (mmHg)	33

Notes: LEVDD – left ventricular end-diastolic diameter
Source: compiled by the authors

No significant difference in gender was observed, patients with LCOS were not older. Atrial fibrillation was statistically different between the two groups. Patients with low ejection fraction (EF< 40%) were at greatest risk (7 patients in the group with LCOS in comparison with none in the group without LCOS, $p < 0.01$). Other clinical and echocardiographic parameters, such as diabetes, history of cardiac surgery, New York Heart Association (NYHA) status [14], left ventricular end-diastolic diameter, and pulmonary artery systolic pressure, exhibited no significant differences between the LCOS and Non-LCOS patient groups (all $p > 0.05$) (Table 3).

Table 3. Preoperative data of patients with LCOS

		Groupe with LCOS N =	Groupe without LCOS N =	p
Female / male		**65/40**	**49/36**	**0.5**
Age (yr.)		**47 ± 12**	**42 ± 11**	**0.113**
		History		
Cardiac history	Hypertension	20	6	> 0.05
	Atrial fibrillation	20	63	**0.01**
	Endocarditis	3	4	> 0.05
Cardiac surgery		2	6	> 0.05
Diabetes		10	2	0.26
Chronic renal failure		2	6	0.22
Smoking		12	17	> 0.05
NYHA III et IV		20	31	0.22
EF < 40%		7	0	**<0.01**

Continued Table 3

	Groupe with LCOS N =	Groupe without LCOS N =	p
LVEDD > 56 mm	8	17	>0.05
PAPS > 35 mmHg	47	70	>0.05

Notes: PASP – pulmonary artery systolic pressure; LVEDD – left ventricular end-diastolic diameter
Source: compiled by the authors

Intraoperative data collection and analysis in cardiac surgery

Types of cardiac surgery and inotropic agents: the most common surgery was valve replacement, mainly isolated valve replacement (42%), 20% of patients underwent multiple valve replacement and 18% coronary Artery Bypass Graft. Dobutamine was the main agent used (89%) in patients with LCOS, the *Median* of *time* receiving inotropes was 31 hours (Table 4), 100% of patients with LCOS used at least one inotrope (+/– one vasopressor), The use of multiple inotropes (or vasopressors) was higher in LCOS group.

Table 4. Inotropes used for LCOS

	N (%)
Number of used inotropes (all patients):	
0	105 (56%)
1	68 (35%)
≥ 2	17 (7.3%)
The main drug used:	
Dobutamine	75 (92%)
Milrinone	10 (11%)
Adrenaline	9 (10.5%)
Dose of dobutamine (µg · kg-1.min-1)	
Minimal-initial	8.2 +- 2.3
Maximal	14.0 +- 3.4
Median duration of treatment (hours):	31 [8 - 54]

Source: compiled by the authors

Cardiopulmonary bypass and cross-clamp times: the median duration of cardiopulmonary bypass was 80 minutes (± 35), and the median duration of aortic cross-clamping was 55 minutes (+/– 30). When studying the patient characteristics during surgery, patients who underwent multiple valve surgery replacement had more risk of developing LCOS. A significant correlation was observed between prolonged cardiopulmonary bypass (CPB) (> 1 h 30 hour, p = 0.05) and/or aortic clamping time (> 1 hour, p = 0.02) and the occurrence of a low output cardiac surgery (Table 5).

Table 5. Intraoperative data of patients with LCOS

	Groupe with LCOS N=	Groupe without LCOS N=	P
Surgical procedures			
Isolated valve	36	44	> 0.05
Multiple valves	7	31	< **10^{-3}**
Coronary artery bypass graft	32	2	> 0.05
Urgent timing	9	14	> 0.05
Duration			
Cardiopulmonary bypass (> 1 h 30)	38	54	**0.05**
Crosscalmp time (> 1 h)	35	50	**0.02**

Notes: CABG – coronary artery bypass graft
Source: compiled by the authors

Postoperative data assessment in cardiac surgery

Patients with LOSC had higher postoperative complication rates, including postoperative atrial fibrillation (AF) (18 vs 12), the average time to onset was 1.4 days from the surgery, Amiodarone was the only antiarrhythmic used, atrial fibrillation (AF) duration was 24.0 hours; 60% of cases resolved within 36 hours. LCOS group also had a higher incidence of kidney injury (6 vs 0), longer post-operative

ICU stay (4.5 vs 2 days), and increased mortality rate (7% vs 0 deaths). Among the 190 patients studied, all who expired had LCOS (Table 6).

Post-operative left ventricular systolic function (EF≤ 40%) at three times 0 h, 4 h and 24 h after surgery were higher in patients with LCOS P<0.05 (Table 7).

Table 6. Postoperative data of patients with LCOS

	Groupe with LCOS	Groupe without LCOS
Postoperative troponin levels (ng/mL)	3.9	2.7
Postoperative atrial fibrillation (N)	18	12
Postoperative kidney injury (N)	6	0
ICU stay (days)	4.5	2
Mortality rate (%)	7	0

Source: compiled by the authors

Table 7. Dynamic of ejection fraction

Parameters		Groupe with LCOS N =	Groupe without LOSC N =	p
Preoperative low FE (≤ 40%)		7	0	**< 0.01**
EF: 0 h	> 40%	35	100	**< 0.01**
	≤ 40%	50	5	
EF: 4 h	> 40%	30	100	**< 0.01**
	≤ 40%	55	5	
EF: 24 h	> 40%	30	102	**< 0.01**
	≤ 40%	55	3	

Source: compiled by the authors

Predictors of LCOS after cardiac surgery

The outcome of patients with LCOS was assessed. In univariate analysis, statistically significant differences ($p < 0.05$) were observed between the groups "with LCOS" and "without LCOS". The preoperative risk factors ncluded atrial fibrillation and low preoperative ejection fraction. Intraoperative risk factors comprised longer cardiopulmonary bypass and cross-clamp times, as well as multiple valve surgery. The patients' risk factors for LCOS are detailed in Table 8.

Table 8. Risk factors for LCOS

Risk factor	Groupe with LCOS n = 85	Groupe without LOSC n = 105	p
Atrial fibrillation	30	63	**$\leq 10^{-3}$**
EF < 40%	7	0	**≤0.01**
CBP time (>1 h 30)	38	54	**0.05**
Cross clamp time (>1 h)	35	50	**0.02**
	Surgery:		
Isolated valve	36	44	
Multiple valves	7	31	**$\leq 10^{-3}$**
CABG	32	2	

Notes: CABG – coronary artery bypass graft; CPB – cardiopulmonary bypass
Source: compiled by the authors

The analysis of 190 patients revealed a notable incidence of LCOS in this study, especially in those with pre-existing ventricular dysfunction and those who underwent high-risk procedures, such as multiple valve replacement and had prolonged CPB and cross-clamp time. Compared to the group without LCOS, patients with LCOS, stay longer in hospital, develop more complications, and have poor outcomes.

LCOS is a frequent and serious complication in patients who have undergone cardiac surgery. Definitions differ among studies, as, based on hemodynamic parameters or the use of inotropes or circulatory assistance, the most common includes decreases in the cardiac index to < 2.2 L/min/m^2 requiring inotropes or mechanical circulatory support to keep the systolic pressure > 90 mmHg as well as the cardiac index > compiled by the authors 2.2 L/min/m^2. [1, 2, 15]. The LCOS incidence after cardiac surgery in this study was 44%, which is higher than incidences reported in several studies varying from 13 to 30% [16, 17].

This study identified factors contributing to the LCOS risk, which include atrial fibrillation, low preoperative ejection fraction, prolonged CBP and cross-clamp times and multiple valve replacement, consistent with other

studies [16-18]. Compared to the group without LCOS, the incidence of complications, ICU stay, and mortality rates are higher. J. Wang *et al.* [18], in an observational study of 212 patients, demonstrated the following pre-operative parameters with low cardiac output: atrial fibrillation, kidney failure, hyponatremia, high central venous pressure and low ejection fraction. N.T. Luan [17] identified the following independent risk factors in a descriptive study on 60 patients undergoing valve replacement surgery: pre-operative low EF, prolonged time to extracorporeal and clamp aorta.

The most common parameters used in clinical practice for assessment of Left ventricular ejection fraction (LVEF) are visually estimated (eyeballing) ejection fraction or manually traced biplane Simpson's rule. A low LVEF is a significant predictor of LCOS after cardiac surgery. K.B. Rana *et al.* [19] found in their prospective study of 200 patients undergoing CABG a relation between pre-operative left ventricular dysfunction and LCOS after surgery, which was significantly different in patients with pre-operative ejection fraction < 40%, compared to ejection fraction ≥ 40%. P. Amabili *et al.* [20] used the systolic global longitudinal strain to evaluate left ventricular function and determine that GLS was a significant risk factor for LCOS after cardiac surgery, while analysis of myocardial strain appears to improve the prediction of LCOS. In this study, pre-operative low EF frequency was 8.2% in LCOS patients, while no patient had pre-operative low EF in the group without LCOS.

Several studies showed the relationship between pre-operative right ventricular dysfunction and postoperative LCOS. P.C. Ting *et al.* [21] recognised the right ventricular global longitudinal strain (RVGLS) as a factor independently associated with a heightened need for postoperative vasoactive inotropic support. E.L. Posada-Martinez *et al.* [6] also conducted a prospective observational study involving 75 patients with severe aortic stenosis and preserved ejection fraction (EF) to examine the correlation between right ventricular free wall longitudinal strain (RVFWSL) and LCOS, they identified a RVFWSL < 17.3% as a predictor of LCOS. Consistent with prior research, this study established a reduced left ventricular ejection fraction as a notable predictor of LCOS.

L. Hong *et al.* [22] developed machine learning (ML) techniques to predict LCOS in patients after cardiac surgery using ML approaches, predictive parameters included LVEF, lactate level, LVEDD, mean artery blood pressure, age, and blood loss during surgery were used to validate the predictive algorithms. Regarding age, it was not identified as a factor, which contrasts with other studies. L. Zhao *et al.* [23], in a retrospective study involving 117 patients aged over 60 years, demonstrated that age over 70 years is an independent factor for the development of LCOS. Most patients in this study are young with rheumatic valve disease and they have several risk factors for developing postoperative LCOS, compared to most elderly patients who had undergone coronary bypass surgery with few risk factors of LCOS.

Atrial fibrillation has been recognised as an independent risk factor for postoperative LCOS. However, the surgical correction of valvulopathy along with atrial fibrillation enhances the long-term prognosis for these patients. Additionally, preoperative ejection fraction was related to a significantly increased postoperative LCOS risk [2, 3]. Surgeon experience with ageing has also been reported as a factor in decreasing LCOS and improving outcomes in cardiac surgery [24]. In Morocco, the number of cardiac surgeons is extremely limited, this factor cannot be studied. CBP time was identified as an independent predictor of LCOS which is consistent with several other studies [2, 16]. Protocols aiming to optimise CPB time could improve postoperative cardiac function.

Regarding the surgical procedure, A.E. Duncan *et al.* [3] identified the combined procedure (valve + bypass) as a surgical risk factor, while isolated valve surgery (aortic valve) was a protective factor. Multiple valve surgery was identified as a surgical risk factor in this study. Patients who developed LCOS are more likely to suffer postoperative complications, require longer intensive care unit stays, with increased risk of postoperative kidney injury, several studies have confirmed the association between low postoperative cardiac output and a high incidence of postoperative complications. LCOS is a factor for higher in-hospital mortality, varying from 12% to 33%, increasing to 40-80% in refractory LCOS requiring hemodynamic support [2, 4]. Among the 85 patients with LCOS, six (7%) died perioperatively.

In this study conducted in a Moroccan centre, the main differences found in patients with LCOS compared to literature were the high incidence of LCOS, the age was not identified as a factor, which contrasts with other studies, the other risk factors and the outcome of patients with LCOS were similar to most series, which can be explained by the young age of patients, the high incidence of rheumatic heart disease most often with pre-existing ventricular dysfunction.

Conclusions

This study evaluated the clinical parameters of patients who developed LCOS after cardiac surgery by analysing preoperative, intraoperative, and postoperative data to determine independent risk factors of LCOS after adult cardiac surgery, and how they influenced the outcome of patients after cardiac surgery. The results showed LCOS is a severe complication after cardiac surgery, 44% in this study. Preoperatively low preoperative ejection fraction (EF < 40%), and atrial fibrillation were associated with LCOS, other characteristics in particular gender and age were similar in both groups. During surgery, patients who underwent multiple valve replacement had more risk of developing LCOS, and a significant correlation was observed between prolonged cardiopulmonary bypass and/or aortic clamping time and the occurrence of a low-output cardiac surgery. LCOS profoundly impacts patient outcomes with increased morbidity and mortality, patients with LOSC had higher rates of

postoperative complications including postoperative atrial fibrillation, higher incidence of kidney injury, longer postoperative ICU stay and increased mortality rate. Among the 190 patients studied, all who had expired had low cardiac output syndrome.

LCOS after cardiac surgery is a multifactorial complication resulting in cardiac dysfunction, determine LCOS risk factors may help identify possible preventive strategies, like to preserve kidney function, safe myocardial protection and optimising pre-existing ventricular dysfunction that could improve LCOS after cardiac surgery in high-risk patients. Subsequent investigations should delve deeper into the underlying pathophysiological mechanisms of LCOS in order. The ultimate goal is to leverage this knowledge to improve outcomes and care strategies for patients afflicted with LCOS.

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Conflict of Interest

The authors declare no conflict of interest.

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Синдром низького серцевого викиду після операції на серці: ретроспективний аналіз

Ібрахім Бехрі
Доктор медицини, асистент
Університетська лікарня Хасана II
30050, просп. Гасана, II, м. Фес, Марокко
https://orcid.org/0000-0001-6245-8613

Алі Деркауі
Доктор медицини, професор
Університетська лікарня Хасана II
30050, просп. Гасана, II, м. Фес, Марокко
https://orcid.org/0000-0002-0549-6039

Абделькарім Шімі
Доктор медицини, професор
Університетська лікарня Хасана II
30050, просп. Гасана, II, м. Фес, Марокко
https://orcid.org/0009-0006-1040-4158

Мохамед Хатуф
Доктор медицини, професор
Університетська лікарня Хасана II
30050, просп. Гасана, II, м. Фес, Марокко
https://orcid.org/0000-0003-4881-2123

Анотація. Синдром низького серцевого викиду є поширеним ускладненням, що спостерігається після кардіохірургічного втручання, і пов'язаний із підвищеними показниками смертності та захворюваності. Метою даного дослідження було визначити незалежні фактори ризику низького серцевого викиду шляхом аналізу даних після кардіохірургічних втручань. Дане одноцентрове дворічне ретроспективне дослідження проходило з січня 2021 року по грудень 2022 року та включало всіх пацієнтів, які були госпіталізовані до відділення загальної інтенсивної терапії А1 для післяопераційного лікування кардіохірургії. Змінні були зібрані з передопераційних, інтраопераційних та післяопераційних даних і оцінені з використанням статистичного пакету для соціальних наук, з рівнем значущості, встановленим на рівні $p < 0,05$. Загалом медіана віку становила 44 роки (22-80), 60 % – жінки, поширеність синдрому низького серцевого викиду після кардіохірургічного втручання – 44 % ($n = 85$). Виявлено значущі фактори ризику синдрому низького серцевого викиду: низька передопераційна функція лівого шлуночка (викид фракції <40 %), передопераційна фібриляція передсердь, порушення передопераційної функції нирок, множинна заміна клапана, подовження екстракорпорального кровообігу та час затискання. Пацієнти, у яких спостерігався синдром низького серцевого викиду триваліше перебували в лікарні та мали підвищену частоту післяопераційних ускладнень, включаючи фібриляцію передсердь та пошкодження нирок, а також вищий рівень смертності (7 % проти з 0 %). Діагностика та лікування синдрому низького серцевого викиду може поліпшити відновлення міокарда та зменшити смертність; краще розуміння його фізіопатологічних механізмів може допомогти розробити потенційну профілактичну стратегію

Ключові слова: серцево-легеневе шунтування; фактори ризику; інотроп; підтримка кровообігу; смертність

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Comparative analysis of the glomerular filtration rate effect on the course of COVID-19 in patients with coronary heart disease with and without concomitant coronavirus disease

Serhii Mostovyi*
PhD in Medical Sciences, Doctoral Student
Bogomolets National Medical University
01601, 13 Tarasa Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-8783-3819

Abstract. The research relevance is determined by the COVID-19 pandemic, which has led to serious medical consequences, including high levels of infectiousness, development of diseases accompanied by complications of kidney and cardiovascular system function, and increased mortality. Therefore, the research aims to study and compare the impact of glomerular filtration rate on the course of COVID-19 in patients with and without coronary heart disease. A retrospective analysis of 410 patients with coronavirus was conducted, who were divided into 2 groups: those with chronic coronary heart disease and those without this disease. During the hospital period (14.7 ± 5.3 days), the composite endpoint of all-cause and cardiovascular deaths in combination with major adverse cardiovascular events was assessed. The thresholds for glomerular filtration rate associated with an increase in the incidence of the composite endpoint were determined: for patients with COVID-19, less than 35 mL/min×1.73 m^2 ($p < 0.01$); for patients with coronary heart disease and COVID-19, less than 60 mL/min×1.73 m^2 ($p<0.01$). Independent predictors of decreased renal filtration capacity in patients in group 1 were: age over 65 years, type 2 diabetes mellitus, high cholesterol, D-dimer, C-reactive protein, and ferritin. Patients in group 2 were adversely affected by type 2 diabetes mellitus, arterial hypertension, and high levels of D-dimer and C-reactive protein ($p < 0.05$). The difference was explained by the influence of the applied therapy on the anticoagulant and renin-angiotensin systems. This study will allow to stratify patients with coronavirus in terms of renal impairment and risk factors, as well as to identify effective strategies for their management depending on the glomerular filtration rate

Keywords: arterial hypertension; risk factors; comorbidity; mortality

Introduction

The COVID-19 pandemic made a significant impact on Ukraine, given its influence on the healthcare system and public health. The increase in the number of cases has led to an excessive burden on the healthcare system, including a shortage of beds, intensive care, medical equipment, and staff [1]. As reported by I. Seriakova *et al.* [2], the pandemic has also led to the postponement or cancellation of necessary medical procedures and surgical interventions, which has led to an increase in cardiovascular and renal pathologies. The increased mortality rate among patients with pre-existing cardiovascular and renal diseases indicates a serious impact of the pandemic on these body systems. In addition, A. Shishkin *et al.* [3] found that the pandemic has increased the risk of severe COVID-19 complications for the target group of patients with cardiovascular and renal diseases, such as pneumonia and thrombosis, and is accompanied by increased levels of stress and psychological problems, which can affect the general condition of these systems. Thus, research and monitoring are critical to understanding and mitigating the negative impact of the COVID-19 pandemic on the cardiovascular and renal health of the Ukrainian population.

As of 22 July 2023, about 5.5 million people were infected in Ukraine, of whom 112.5 thousand died, which

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*Corresponding author

accounts for a 2% fatality rate [4]. D. Chumachenko & T. Chumachenko [5] point out that due to Russia's full-scale armed invasion of Ukraine, the epidemiological situation with coronavirus infection has only worsened – the destruction of infrastructure and human resources has made it difficult to diagnose, identify cases, impossible to hospitalise, and lack of funds for adequate treatment and prevention. Therefore, even though the incidence of COVID-19 is on a downward trend and has lost its status as a global emergency, Ukraine still faces risks associated with this infection in both the short and long term.

The consequences of COVID-19 are pathophysiologically associated with the development of a cytokine storm, which causes endothelial dysfunction and endotheliitis, which in turn leads to the development of microvascular thrombi, ischaemia, and multiple organ failure, which determines the multisystemic nature of the lesion [6]. Several studies confirm the fact that patients with cardiovascular disease and COVID-19 are prone to severe disease and have a higher risk of death [7-9]. Similar mechanisms are responsible for direct and indirect renal dysfunction, characterised by a decrease in renal filtration capacity and organic damage [10]. V.P. Chavda *et al.* [11] point out that COVID-19 in combination with other therapeutic diseases (obesity, type 2 diabetes mellitus, coronary heart disease, renal failure, fatty liver, etc.) is more prone to severe course of all associated diseases, so comorbidity is an important predictor of complications. Considering the relationship between coronary heart disease (CHD) and chronic kidney disease (CKD), the conference Kidney Disease: Improving Global Outcomes (KDIGO) conference in 2020, presents data showing that the progression of cardiovascular damage increases with the progression of renal dysfunction, despite the correction of traditional cardiovascular risk factors [12].

Thus, it is important to study the relationship between cardiovascular risks, renal damage and coronavirus infection. The research aims to study and compare the effect of glomerular filtration rate on the course and development of COVID-19 complications in patients with CHD and COVID-19 without CHD.

Materials and Methods

The study retrospectively analysed data from 410 patients with coronavirus disease, treated at Kyiv City Clinical Hospital No. 18 and the private medical centre Medbud from 2 March 2020 to 31 December 2022. The diagnosis of COVID-19 was confirmed by detecting the ribonucleic acid (RNA) of the SARS-CoV-2 pathogen in samples from the upper respiratory tract using polymerase chain reaction (PCR). Multidetector computed tomography (MDCT) was used to assess the presence and extent of COVID-19-related lung damage. Verification of the diagnosis of CHD was performed according to current guidelines [13]. COVID-19 and its complications were treated following the guidelines of the Ministry of Health of Ukraine dated 2 April 2020, No. 762 [14]. All patients were informed about their participation in the study and signed an informed consent to the processing of personal data.

Exclusion criteria for the study include the following conditions: acute coronary syndrome, previously documented acute cerebrovascular accident, type 1 diabetes mellitus, severe and/or decompensated major comorbidities (including malignancies), history of heart valve replacement, vaccination against COVID-19, and lack of informed consent.

Among the 210 patients with COVID-19 without CHD (group 1), there were 85 women (40%) with a mean age of 52 ± 21.6 years and 125 men (59%) with a mean age of 49 ± 21 years. There were 200 patients with CHD in combination with COVID-19 (group 2), including 124 men (62%) with a mean age of 62.4 ± 12.6 years and 76 women (38%) with a mean age of 62.2 ± 9.5 years. The control group consisted of 35 healthy volunteers, and 90 patients with coronary heart disease without COVID-19 who matched the study sample in terms of age distribution and gender ratio were examined as a comparison.

The standard examination of all patients included general clinical examination of blood and urine, biochemical blood tests (lipid spectrum, blood glucose, creatinine), cardiac ultrasound, and electrocardiography. The glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (1) using an online calculator:

$$GFR = 141 \times \min\left(\frac{\text{Scr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{\text{Scr}}{\kappa}, 1\right)^{-1.209} \times \\ \times 0.993^{Age} \times 1.018^{[\text{if female}]} \times 1.159^{[\text{if black}]}, \quad (1)$$

where Scr – serum creatinine (mg/dl), κ – 0.7 for women and 0.9 for men, α – -0.329 for women and -0.411 for men, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

The development of cardiovascular events was assessed during the hospital period, which averaged 14.7 ± 5.3 days. The date of hospitalisation was considered the start of observation. The composite endpoint (CEP) was all-cause death (including cardiovascular) and major adverse cardiovascular events (non-fatal myocardial infarction (MI), acute cerebrovascular accident, pulmonary embolism, and acute left ventricular failure > Killip class I).

Statistical processing was performed using Statistica v.7.0 and SPSS Statistics v.27.0. Continuous variables are expressed as mean (M) and standard deviation (σ), and their differences were assessed using analysis of variance or unpaired t-test. Pearson's $\chi 2$ test was used for categorical variables. The Cox model was used to estimate the odds ratio (OR) and confidence interval (CI) within the framework of multivariate regression analysis. The log-rank test and the Kaplan-Meier method were used to analyse the significance of differences in survival. The difference in the values at $p < 0.05$ was considered statistically significant.

All procedures performed in studies involving human subjects complied with the ethical standards of the institutional and national research committee, as well as the Declaration of Helsinki [15]. The study was approved by the National Ethics Committee of the Bogomolets National Medical University.

Results

The clinical and anamnestic characteristics of the study patients in group 1 (200 patients with CHD+COVID-19) and group 2 (210 patients with COVID-19) are shown in Table 1. The majority of patients were male (60.7%) and over 60 years of age, and since the subjects were selected from the usual contingent treated during the COVID-19 pandemic, this preliminarily indicates a greater vulnerability of men in the older age group. A retrospective analysis of the medical records revealed that more than half of the patients had hypertension (64%) and chronic heart failure in 42% of cases, with most of them having preserved ejection fraction. CKD was observed in 11.2% of patients, with only one-third (31.0%) of patients having normal GFR and 42.2% with slightly reduced GFR. Given the fact that the study was based on a retrospective analysis, the stage of CKD was determined solely by GFR, and the level of albuminuria could not be considered. The body mass index revealed that obesity was present in almost half of the cases (42.0%) and dyslipidaemia in 24%, although there were 48.8% of patients with CHD in the study cohort, which may indicate the effectiveness of the therapeutic intervention.

Table 1. Clinical and anamnestic characteristics of patients with COVID-19

Indicators	Indicator value
Age, years (M±SD)	61.2 ± 10.7
Men, n (%)	249 (60.7%)
Women, n (%)	161 (39.3%)
Body mass index, kg/m^2	25.9 ± 7.3
Smokers, n (%)	86 (21%)
Arterial hypertension, n (%)	262 (64%)
Type 2 diabetes, n (%)	114 (28%)
History of myocardial infarction, n (%)	64 (15.6%)
History of left ventricular anterior wall myocardial infarction, n (%)	45 (11%)
Coronary arteriography, n (%)	190 (46%)
Glucose, mmoL/L	5.8 ± 2.3
Dyslipidaemia, n (%)	98 (24%)
Creatinine μmoL/L	112.7 ± 9.5
GFR ≥ 90 mL/min×1.73 m^2, n (%)	127 (31%)
GFR = 60-90 mL/min×1.73 m^2, n (%)	173 (42%)
GFR = 30-60 mL/min×1.73 m^2, n (%)	89 (21.7%)
GFR < 30 mL/min×1.73 m^2, n (%)	21 (5.3%)
Chronic heart failure, n (%)	172 (42%)
Release fraction, %.	43.5 ± 12.7
Duration of CHD, years (M ± SD)	7.5 ± 3.9
Angina pectoris class II-IV, n (%)	69 (17%)
Low molecular weight heparins (enoxaparin)	265 (64.6%)
Treatment before hospitalisation with a diagnosis of COVID-19:	
Acetylsalicylic acid	114 (27.8%)
Clopidogrel	86 (35.2%)
Angiotensin-converting enzyme inhibitors	112 (27.3%)
Beta-blockers	103 (42.2%)
Diuretics	62 (15%)
Calcium channel blockers	37 (9%)
Angiotensin-II receptor blockers	88 (21.5%)
Nitrates	74 (18%)
Statins	170 (41.4%)

Notes: M – mean value of the parameter; SD – standard deviation of the mean
Source: compiled by the author

Considering medications, it is worth noting that antithrombotic therapy with enoxiparin was performed in 98.7% of patients, and 92.3% required antibiotic therapy (ceftriaxone, levofloxacin mofloxacin) for the prevention and treatment of bacterial complications, and 66.5% of patients were prescribed glucocorticosteroids (dexamethasone, hydrocortisone, methylprednisolone), considering the pathogenetic features of the infectious process. Patients were prescribed antiviral drugs and an interleukin-6 inhibitor in circumstances related to their coronavirus infection. In cases where patients were infected with COVID-19, antiviral drugs such as remdesivir and favipiravir were prescribed in 29% of cases. In addition, an interleukin-6 inhibitor such as tocilizumab was used in 18% of patients to modulate the immune response and treat the inflammation that occurs with coronavirus. These measures were aimed at improving the clinical condition and treatment outcomes of these patients, especially in the context of the pandemic.

All patients with chronic coronary syndrome were taking antiplatelet, antianginal and statin therapy (acetylsalicylic acid, clopidogrel, nitrates and statins). It should be noted that the incidence of bleeding has not been studied. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-II receptor blockers (ARBs) and β-blockers (BABs) were prescribed in 80.2% of patients, respectively, to correct chronic heart failure and hypertension. It is important to note that by the time of hospitalisation and treatment adjustment, less than half of the patients were taking the medications prescribed for their chronic comorbidities, and none of the patients with diagnosed type 2 diabetes (28%) were on glucose-lowering therapy.

A preliminary assessment of the possible association between the occurrence of the critical endpoint and the value of GFR is shown in Figure 1. In patients of both groups, the frequency of adverse outcomes of COVID-19 had an inverse correlation with the kidney function indicator. However, it was found that in patients with COVID-19 with a GFR of less than 60 mL/min×1.73 m^2, the incidence of CEP was significantly higher than in patients with CHD+COVID-19. Thus, among patients in group 2 with a GFR of 45-59 mL/min×1.73 m^2, CEP occurred in 15.1% versus 10.2% in patients in group 2, in patients with a GFR of 31-44 mL/min×1.73 m^2 – in 17.2 and 14.6%, and patients with a GFR ≤ 30 mL/min×1.73 m^2 – in 27.5 and 21.6%, respectively ($p < 0.05$). This difference in favour of CHD seemed unclear, as a history of cardiovascular disease would increase the percentage of patients with the primary endpoint. When re-analysing (30 days later) the clinical and anamnestic characteristics of patients, it was suggested that ACEIs and ARBs had a positive effect on renal function and cardiovascular risk reduction.

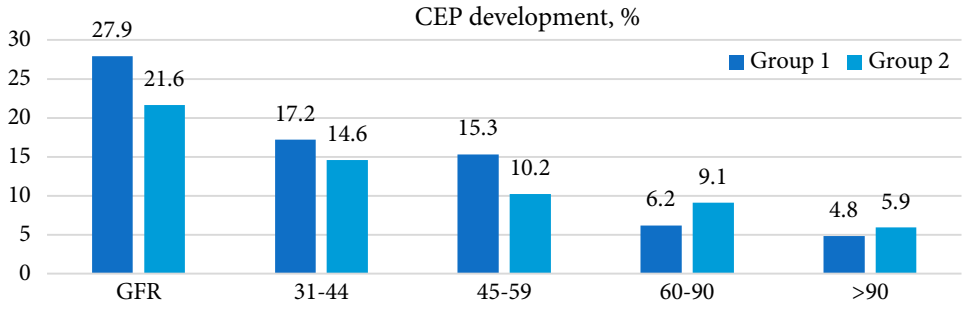

Figure 1. Incidence of the composite endpoint depending on GFR in patients in groups 1 (COVID-19) and 2 (CHD+COVID-19)

Source: compiled by the author

In order to determine the probability of developing the combined endpoint in patients with COVID-19 and CHD+COVID-19, depending on the value of GFR, cut-off values were sought separately for each group. After calculating the odds ratio for the onset of CEP at stepwise values of GFR, the following thresholds were established that were associated with an unfavourable course of COVID-19:

- For group 1, this value was GFR ≤ 35 mL/min×1.73 m^2 (OR 3.7; 95% CI 1.8-7.6, $p < 0.01$);
- For group 2 – ≤60 mL/min×1.73 m^2 (OR 4.1; 95% CI 2.1-9.8, $p < 0.01$).

When constructing Kaplan-Meier curves in patients with COVID-19 19 without CHD with a GFR ≤ 34 mL/min×1.73 m^2 compared with patients with a GFR > 34 mL/min×1.73 m^2, a significantly lower survival rate with the development of a combined cardiovascular endpoint throughout the hospital period was found ($p = 0.042$), as shown in Figure 2(a). At the same time, a significantly higher proportion of patients with CHD+COVID-19 with the development of a combined cardiovascular event according to the logarithmic criterion was detected in patients with a GFR ≤ 52 mL/min×1.73 m^2 compared with those with a GFR > 52 mL/min×1.73 m^2 ($p = 0.04$) (Fig. 2(b)). Multivariate regression analysis revealed independent decrease predictors of GFR ≤ 34 mL/min×1.73 m^2 in group 1 and ≤52 mL/min×1.73 m^2 in group 2. These data can be interpreted in such a way that chronic renal hypoperfusion occurs in concomitant chronic coronary syndrome, and, accordingly, in concomitant infectious disease, compensatory mechanisms fail at a higher level than without concomitant cardiovascular disease, and a decision on renal replacement therapy should be made as soon as possible in such patients.

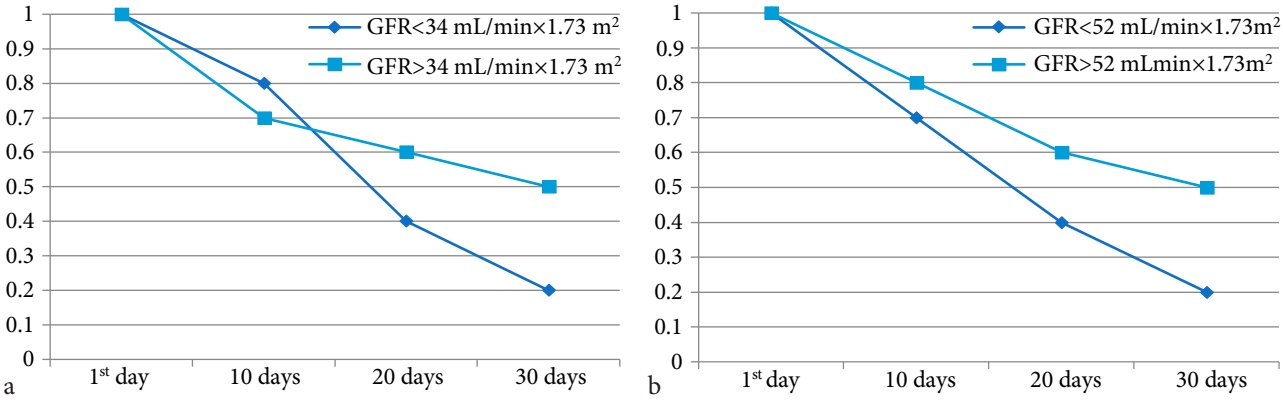

Figure 2. Comparison of survival in patients with COVID-19 in patients with threshold
Notes: a) GFR = 34 mL/min×1.73 m²; b) GFR = 52 mL/min×1.73 m². After the hospital period, patient monitoring was continued, so the time interval in the Figure comprises 30 days
Source: compiled by the author

For patients with COVID-19, important prognostic factors were age >60 years (OR 1.12; 95% CI 1.01-1.60), the presence of hypertension (OR 2.50; 95% CI 1.17-4.85), high D-dimer levels (OR 4.0; 2.02-5.20), type 2 diabetes mellitus (OR 2.75; 2.01-4.79), and high C-reactive protein levels (OR 1.94; 95% CI 0.89-3.81) (Fig. 3). For patients with the concomitant chronic coronary syndrome, age >60 years (OR 2.61; 95% CI 1.63-6.41), hypertension (OR 2.69; 95% CI 1.81-3.15), high D-dimer levels (OR 4.95; 3.15-6.80), type 2 diabetes mellitus (OR 2.15; 1.67-2.99), high ferritin (OR 3.85; 1.54-6.91) and high C-reactive protein (OR 3.01; 2.06-7.33) significantly influenced the decrease in GFR ($p < 0.05$) (Fig. 3). There was no significant effect of cholesterol level and gender on GFR in both groups. It is worth noting that elevated ferritin levels reflect the risk of renal dysfunction to a greater extent than elevated C-reactive protein levels, which is in favour of the former as a more representative laboratory prognostic marker. D-dimer, which is a fibrin degradation product, is indicative of hypercoagulability, and this indicator, as well as age over 60, was more pronounced in patients with concomitant coronary heart disease, which may be associated with chronic inflammation in the vessels and their atherosclerotic lesions.

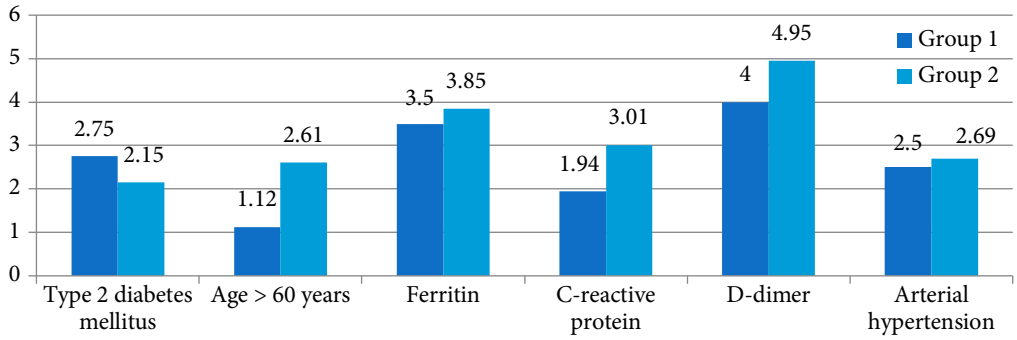

Figure 3. Odds ratio of GFR ≤ 34 mL/min×1.73 m² decrease in group 1 patients and ≤52 mL/min×1.73 m² in group 2 patients with each independent predictor)
Source: compiled by the author

At the same time, antithrombotic therapy in patients with COVID-19 without CHD had a favourable effect on the GFR (OR 0.58; 95% CI 0.31-0.97) ($p < 0.05$), but in the group with concomitant cardiovascular comorbidity, no such association was found. Thus, the clinical significance of the study is to identify the association between a decrease in glomerular filtration rate and an unfavourable prognosis of COVID-19 in patients with coronary heart disease, as well as to establish thresholds for GFR for each group, which can be used to separate patients at high risk of adverse cardiovascular events and death from all causes and cardiovascular causes. A special risk category is represented by patients with COVID-19 in combination with coronary heart disease and moderately reduced GFR ≤ 51 mL/min×1.73 m². It is necessary to consider the level of D-dimer, C-reactive protein, and ferritin to provide these patients with oxygen, low-molecular-weight heparins, glucocorticosteroids, high-dose statin therapy and timely administration of artificial lung ventilation and extracorporeal membrane oxygenation to eliminate hypoxia and thrombosis. Evaluation of the various factors that influence the improvement or deterioration of COVID-19 (including

medications) and maximising vaccination of people worldwide can play a vital role in controlling the spread of the infectious process and reducing the number of deaths.

Discussion

V. Mahalingasivam *et al.* [16] in their review study presented data from the United Kingdom that patients with a GFR of 30-60 mL/min×1.73 m^2 had a 1.3-fold higher risk of death associated with COVID-19, and in patients with a GFR <30 mL/min×1.73 m^2, this risk was 2.5 times higher than in patients with normal renal function. In this experiment, the incidence of CEP among patients in group 1 with a GFR <35 mL/min×1.73 m^2 was 3.7 times higher, which considers not only the onset of death but also the development of non-fatal cardiovascular complications, but this figure is still relatively higher. The authors noted that the lack of baseline data on renal function in the experiments creates problems in the classification of chronic kidney disease and acute kidney injury, which potentially impairs the generalisability of the results, which would be important to consider in this study.

In an experiment conducted by X. Han *et al.* in New York [17], 7.9% of hospitalised patients out of 5700 people with COVID-19 had a history of chronic kidney disease, and 9.7% of cases were fatal, which is significantly lower than the results obtained in this study. Further, the researchers cite the results of studies from China and draw attention to the fact that serum creatinine, acute kidney injury, proteinuria and haematuria were independent risk factors for mortality in COVID-19, which indicates that patients with kidney disease require increased attention and monitoring, especially for patients on haemodialysis. A meta-analysis by V. Liakopoulos *et al.* [18] demonstrated that the prevalence of CKD among patients with COVID-19 is 5.2% and is associated with a 3-fold increase in the severity of the infectious disease and a 2-fold increase in mortality.

Concerning acute kidney injury in COVID-19, according to a review study by K. Amann *et al.* [19], 20% of patients had acute renal symptoms, and 13.1% had a GFR <60 mL/min×1.73 m^2, which is also significantly less than in this study. Further, the authors, referring to the Australian registry, presented data on high overall mortality among patients with CKD and COVID-19 – 27.9% of infected dialysis patients and 6% of kidney transplant patients, which means a 1.28-fold increase in mortality compared to the control group. According to L. Yang *et al.* [20], the incidence of acute kidney injury among patients with COVID-19 is 27.17%, which increases the risk of mortality by 5.24 times and the development of severe conditions by almost 15 times. At the same time, the prevalence of CKD among patients with COVID-19 was 5.7%, which increases the risk of mortality by more than 2 times and the development of severe conditions by 1.87 times.

M. Brogan & M.J. Ross [21] note that up to 50% of patients requiring renal substitution therapy are asymptomatic, and only 47% have fever (compared to 90% in the general population), which requires increased vigilance in terms of COVID-19 infection, as well as monitoring the functional state of the kidneys. The study's author provides similar statistics, stating that the mortality rate in such patients increases by 20-30%. J.B. Wetmore [22] presented information that about 4.0% of patients on renal replacement therapy who are hospitalised for a cardiovascular event die in the hospital and another 4.5% of discharged patients die within the next 30 days. It has also been proven that not all patients with COVID-19 can be hospitalised and, therefore, are not included in trials, so the mortality rate is likely to be even higher. The scientist's study coincides with the results of this research, emphasising the fact that patients with COVID-19 in combination with various comorbidities, including coronary heart disease, have a worse tolerance of the lesions, which negatively affects the quality of kidney function.

Zh. Zheng *et al.* [23] concluded in their meta-analysis that in men over 65 years of age, hypertension, diabetes mellitus, and concomitant cardiovascular and respiratory diseases can significantly worsen the prognosis of COVID-19. The authors also noted qualitative laboratory prognostic markers, namely white blood cell count, aspartate aminotransferase, creatinine, procalcitonin, lactate dehydrogenase, high-sensitivity troponin I and D-dimer. The data obtained in this study are fully consistent with the analysed information from other sources, and it is possible to expand the range of the diagnostic programme in the future.

S. Shah & M.A. Sparks [24] also noted the role of hypertension and old age as risk factors for severe disease, and pathogenetically this is since SARS-CoV-2 penetrates host cells through the angiotensin-converting enzyme-2 receptors of the renin-angiotensin system, which in turn leads to the question of the effect of ACEIs and ARBs, which was also recorded in the present study, but was not subjected to further analysis, as it requires a separate study.

M.A. Podestà *et al.* [25] note that cardiovascular damage in patients with CKD and COVID-19 occurs in approximately 20-25% of cases, especially concerning thrombotic events, as the infectious disease is associated with a state of hypercoagulation. The authors present data with a wide range of risk rates – from 4.7 to 31%, but these cases also had a relationship with the D-dimer. P. Theofilis *et al.* [26] in their study confirm that, in addition to pneumonia and thromboembolism, renal dysfunction is a common and poor prognostic indicator associated with increased disease severity and mortality. The authors note that for the timely detection of renal damage, it is necessary to use inflammatory biomarkers not only in blood but also in urine and that urinary SARS-CoV-2 virus load may also be an early prognostic sign. However, similar findings have not been reported in other studies, which requires further discussion and study.

E.Y.M. Chung *et al.* [27] demonstrated the mortality rate among patients with CKD and COVID-19 was 32 deaths per 1000 person-weeks in their meta-analysis, which is an interesting unit of measurement that could unify patients by time of hospitalisation in subsequent studies.

According to this system, the risk of death in such patients increases 10-fold compared to people with CKD but no concomitant infection. According to R.M. May *et al.* [28], the incidence of diabetes mellitus and hypertension as clinical comorbidities was increased in patients with COVID-19 (40.4% and 72.5%, respectively), which differs from the data obtained in this study (28% and 64%, respectively).

J. Smolander & A. Bruchfeld [29] emphasise the importance of assessing the patient on admission with urine and creatinine diagnostic test strips, and subsequently, urine sedimentation and quantification of albuminuria if the results of previous tests are positive. The authors emphasise the need to continue treatment with ACEIs and ARBs, if possible.

It is also worth paying attention to the issue of post-COVID syndrome (the presence and/or persistence of symptoms not associated with any other disease 8-12 weeks after the onset of COVID-19), as the review by S. Copur *et al.* [30] notes that more than 30% of patients have symptoms of this syndrome, more than 15% require re-hospitalisation, and mortality reaches more than 6%, with cardiovascular risks and symptoms playing a key role, and this is especially true for patients with impaired renal function. Thus, the results of this study are consistent with the findings of other researchers, but COVID-19 requires a range of new qualitative studies that could highlight the issues of comorbidity, pharmacotherapy, and effective management.

Conclusions

This study found that the adverse effect of kidney damage on the course of coronavirus disease depends on the glomerular filtration rate, and it is more pronounced in patients with concomitant coronary heart disease than in patients with COVID-19 without chronic coronary syndrome. This effect is detected as early as at a GFR <59 mL/min×1.73 m^2 and is manifested in a decrease in patient survival and an increase in the number of major adverse cardiovascular events (development of acute cerebrovascular accident, non-fatal myocardial infarction, pulmonary embolism, and acute left ventricular failure > Killip class I). The survival rate of patients with CHD with and without COVID-19 during the hospital period decreases at glomerular filtration rates <52 mL/min×1.73 m^2 and <34 mL/min×1.73 m^2, respectively. The concomitant chronic coronary syndrome provokes the development of chronic renal hypoperfusion, and, accordingly, in the event of an acute infectious trigger, compensatory mechanisms fail, and among patients with an unfavourable cardiometabolic background, a decision should be made as soon as possible to conduct therapeutic interventions aimed at preserving the functional capacity of the kidneys. The independent predictors of the decrease in velocity were: type 2 diabetes mellitus, age over 60, hypertension, high levels of D-dimer, C-reactive protein and ferritin, which are consistent with studies in other countries, and it is the assessment of these factors that affect the improvement (such as low-molecular-weight heparin therapy) or worsening of COVID-19, and timely vaccination of people can play an important role in the qualitative stratification of patients into risk groups and the subsequent control of the spread of the infectious process and reduction of infectious mortality and the percentage of non-infectious complications. However, COVID-19 requires further research that could highlight the problems of comorbidities, drug interactions pathogenetic treatment, and effective management in a multidisciplinary team. One of the fundamental prospects for research on this topic may be the possibility of further analysing this sample of patients.

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Conflict of Interest

The author declares no conflict of interest.

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Порівняльний аналіз впливу швидкості клубочкової фільтрації на перебіг COVID-19 у хворих на ішемічну хворобу серця при супутній коронавірусній хворобі та без неї

Сергій Євгенович Мостовий
Кандидат медичних наук, докторант
Національний медичний університет імені О. О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-8783-3819

Анотація. Актуальність даної проблематики полягає в тому, що пандемія COVID-19 призвела до серйозних медичних наслідків, включаючи високий рівень контагіозності, розвитку хвороб, що супроводжуються ускладненням роботи нирок та серцево-судинної системи, а також підвищену смертність. Тому мета даної роботи полягала у вивченні та порівнянні впливу швидкості клубочкової фільтрації на перебіг COVID-19 у хворих на ішемічну хворобу серця та без неї. Було проведено ретроспективний аналіз 410 хворих на коронавірус, які були розподілені на 2 групи: ті, у яких була наявна хронічна ішемічна хвороба серця, і ті, у яких не було цього захворювання. Впродовж госпітального періоду (14,7 ± 5,3 діб) оцінювали комбіновану кінцеву точку – смерть від усіх причин та від серцево-судинних причин у поєднанні з основними несприятливими серцево-судинними подіями. Було визначено порогові значення швидкості клубочкової фільтрації, які асоціювалися зі зростанням частоти виникнення комбінованої кінцевої точки: для хворих на COVID-19 менше 35 мл/хв×1,73 м^2 ($p < 0,01$); для пацієнтів із ішемічною хворобою серця та COVID-19 – менше 60 мл/хв×1,73 м^2 ($p < 0,01$). Незалежними предикторами зниження фільтраційної здатності нирок у хворих 1 групи були: вік понад 65 років, наявність цукрового діабету 2 типу, високий рівень холестерину, Д-димеру, С-реактивного білка та феритину. На хворих 2 групи несприятливо впливали цукровий діабет 2 типу, артеріальна гіпертензія, високий рівень Д-димеру та С-реактивного білка ($p < 0,05$). Таку різницю було пояснено впливом проведеної терапії із точкою прикладання на антикоагулянтну та ренін-ангіотензинову систему. Це дослідження дозволить стратифікувати пацієнтів з коронавірусом в аспекті порушення ниркової функції та факторів ризику, а також визначити ефективні стратегії їх ведення в залежності від швидкості клубочкової фільтрації

Ключові слова: артеріальна гіпертензія; фактори ризику; коморбідність; летальність

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Endothelial dysfunction correction in patients with hypertension, dyslipidaemia, and decreased thyroid function

Marta Orel*
Postgraduate Student
I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine
46001, 1 Maidan Voli, Ternopil, Ukraine
https://orcid.org/0009-0007-6916-140X

Larysa Martynyuk
PhD in Medical Sciences, Associate Professor
I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine
46001, 1 Maidan Voli, Ternopil, Ukraine
https://orcid.org/0000-0001-8098-0421

Abstract. Endothelial dysfunction is considered a universal predictor of numerous diseases, development of the complications and their adverse course. The study aimed to investigate the endothelium-dependent vasodilation among patients with arterial hypertension, dyslipidemia and different functional state of the thyroid gland and feasibilities of its correction by means of hypolipidaemic and metabolic therapy. 99 patients with arterial hypertension and dyslipidemia were examined, among them were 65 hypothyroid persons (group 1) and 34 individuals with normal thyroid function (group 2). The effects of lipid-lowering combination therapy with ezetimibe and rosuvastatin or monotherapy with statins, and metabolic therapy with L-arginine aspartate during 3 months on endothelium-dependent vasodilation were studied. At the beginning of the study, the values of endothelial-dependent vasodilation in group 1 compared to those in group 2 were reliably smaller by 9.38%. After 3 months of treatment, this indicator in group 1 reliably increased by 11.11%, while 19 (29.23%) patients showed its normalization. The best values of the endothelium-dependent vasodilation was demonstrated by examinees in group 2 – the indicator reliably increased by 15.76 %, while 17 (50%) patients showed its normalization. Together, the greater increase in the percentage of endothelium – dependent vasodilation was observed among subgroups of patients that in complex treatment received combination hypolipidaemic therapy with ezetimibe and rosuvastatin, and metabolic therapy with L-arginine. The best indicators of endothelium-dependent vasodilation were demonstrated by examinees of both groups who, in addition to combination hypolipidaemic therapy, received metabolic therapy. Decreased thyroid gland function negatively affected the values of endothelium-dependent vasodilation and overweighted the possibilities of endothelial dysfunction correction in this cohort of patients. The results of the study can be applied in internal medicine clinic for complex treatment of comorbid hypertensive and hypothyroid patients

Keywords: blood pressure; lipid metabolism; hypothyroidism; ezetimibe; vasodilation; L-arginine; thyroid stimulating hormone

Introduction

Arterial hypertension (AH) is one of the leading causes of cardiovascular morbidity and mortality worldwide [1]. According to the International Society of Hypertension (ISH) over 1.5 billion people suffer from this disease [2]. AH is the cause of 10.4 million deaths annually, while in Ukraine mortality due to elevated systolic blood pressure (BP) is 552.57 per 100,000 population [3, 4]. It is predicted that the number of such patients will increase by 15-20%

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*Corresponding author

by 2025. The World Health Organization (WHO) reported that in 2019 about 10.8 million patients with AH were registered in Ukraine, among them only 14% systematically received antihypertensive therapy, about 30% – periodically [5]. STEPS Survey 2019 revealed that out of one third of the population of Ukraine with AH, 63.3% of respondents were previously unaware of their high BP and only 54.8% of these individuals, who knew, were taking antihypertensive medications [6]. Concurrently, more than 50% of patients with hypertension have additional cardiovascular risk factors, which burden the course of the disease and its prognosis and worsen the quality of life of such patients. Among them are hyperglycaemia, disorders of lipid metabolism, abdominal obesity (waist circumference of above 102 cm in men and 88 cm in women), insulin resistance as the components of metabolic syndrome, sedentary lifestyle, unhealthy diet, smoking, and some others [7].

Disturbance of the normal functioning of the vessel endothelium – endothelial dysfunction (ED), along with AH, is one of the early stages in the pathogenesis of atherosclerosis and its complications, heart failure. Furthermore, the association of AH with ED is explained by the fact that the latter can be both its cause and consequence [8]. In particular, Y. Li *et al.* [9] have demonstrated the role of ED in the development and progression of AH by reducing the release of nitric oxide (NO) and acceleration of its degradation was proven, in addition to increased activity of angiotensin – converting enzyme on the surface of endothelial cells and increased synthesis of endothelin-1 and other vasoconstrictor substances by endothelial cells in case of their dysfunction. Chronic inhibition of NO in the experiment leads to all organic outcomes of severe long-lasting AH, including atherosclerosis and vascular organ damage [10]. Conversely, according to the research of J. Goodwin [11], high BP potentiates the escalation of oxidative stress and intracellular accumulation of free radicals that adversely affect the function and cohesion of endothelial lining and is one of the pathogenetic links of ED.

Mechanisms of normalization of endothelial function in patients with AH have the objective of lowering BP, regulating lipid profile and providing additional synthesis of NO by endothelial cells. Efforts are aimed towards finding an optimal medication that will not only come up with an endothelium – protective effect, but contribute to the reverse development of ED. The study of D.V.T. da Silva *et al.* [12] revealed that among such agents are some antihypertensive drugs, including angiotensin-converting enzyme inhibitors, dihydropyridine calcium – channel blockers, β-blockers thiazide diuretics and phosphodiesterase type 5 inhibitors, sodium – glucose cotransporter – 2 inhibitors, antioxidants, NO donors and others.

The combination of two and more pathological conditions or diseases in one patient contributes to the formation of new and deepens the existing pathogenetic mechanisms of the disease. The prevalence of hypothyroidism in Ukraine is high and slowly increases, while the deficit of thyroid hormones leads to impairment of lipid metabolism and contributes to cardiovascular morbidity. There is not enough data about the functional state of the vessel endothelium in comorbid patients with hypothyroidism and arterial hypertension. The study aimed to examine the advantages of ezetimibe and L-arginine aspartate use in endothelial dysfunction correction among patients with high blood pressure, dyslipidemia and decreased thyroid gland function.

Materials and Methods

The research was conducted during the period of 2019-2023 and included 99 patients with stage 2 AH who were treated in the cardiology department of the Ternopil Regional Clinical Hospital. The average age of the patients was 58.62 ± 1.12 years, among them 43 (43.43%) men and 56 (56.57%) women. The diagnosis of AH was made according to the protocol approved by the order of the Ministry of Health of Ukraine dated May 24, 2012 No. 384 [13]. Stage 2 AH was defined as systolic blood pressure (SBP) in values ≥ 140-159 mmHg and/or diastolic blood pressure (DBP) in values ≥ 90-99 mmHg and the presence of asymptomatic hypertension-mediated organ damage, and/or chronic kidney disease stage 3 while glomerular filtration rate within 30-59 mL/min, and/or diabetes mellitus without organ damage and assumed the absence of associated clinical conditions in accordance to national and European Societies of Hypertension and Cardiology (ESH/ESC 2018) requirements [14]. All patients were determined lipid profile indicators and types of dyslipidemia were established in accordance with the classification of *Fredrickson and colleagues* [15]. The functional state of the thyroid gland was evaluated in a laboratory using the enzyme-linked immunosorbent assay by determining the concentration of free thyroxine (T_4), general triiodothyronine (T_3) and thyroid-stimulating hormone (TSH) in blood serum. Normal values of the free T_4 were considered from 12 to 22 pmol/L, general T_3 from 1.3 to 3.1 nmol/L and TSH level from 0.270 to 4.20 mIU/L. Primary hypothyroidism was diagnosed when elevated TSH levels, decreased free T_4 and normal or decreased general T_3 values in blood serum. Subclinical hypothyroidism was diagnosed in the case of TSH levels from 4.21 to 10.00 mIU/L and normal values of thyroid hormones. The exclusion criteria were: stage 1 and stage 3 AH, ischaemic and/or haemorrhagic stroke, myocardial infarction in the anamnesis, diabetes mellitus, chronic kidney disease, other chronic diseases, the patient's refusal to take part or continue to participate in the study.

All examinees were divided into groups according to the functional state of their thyroid gland and methods of treatment (Table 1). Group 1 involved 65 (65.65%) individuals with reduced thyroid function, among them were 34 (34.34%) patients with primary hypothyroidism and 31 (31.31%) patients with subclinical hypothyroidism, who previously received levothyroxine replacement therapy in the dosage of 25-50 mcg daily for the purpose of normalizing the thyroid function. Group 2 included 34 (34.34%) individuals with arterial hypertension with normal thyroid

function. Examinees of both groups were randomly divided into 4 subgroups and each of them was prescribed distinctive treatment. Patients in all subgroups received hypolipidaemic therapy with rosuvastatin; in subgroup 1, individuals were additionally prescribed ezetimibe and metabolic therapy, in subgroup 2 patients received combination lipid-lowering therapy with ezetimibe, and in subgroup 3 – metabolic therapy, besides statins. All examinees received antihypertensive and antiplatelet medicines according to approved national protocol [13].

Table 1. Distribution of patients into groups in accordance to the functional state of their thyroid gland and methods of treatment

Group	Characteristics
1, n = 65	*Patients with arterial hypertension and reduced thyroid function*
1.1, n = 16	Combination: ezetimibe 10 mg + rosuvastatin 10 mg 1 tablet once daily, L-arginine aspartate oral solution 1 measuring spoon (5 mL) 4 times daily
1.2, n = 16	C ombination: ezetimibe 10 mg + rosuvastatin 10 mg 1 tablet once daily
1.3, n = 16	Rosuvastatin 20 mg 1 tablet once daily, L-arginine aspartate oral solution 1 measuring spoon (5 mL) 4 times daily
1.4, n = 17	Rosuvastatin 20 mg, 1 tablet once daily
2, n = 34	*Patients with arterial hypertension and normal thyroid function*
2.1, n = 9	Combination: ezetimibe 10 mg + rosuvastatin 10 mg 1 tablet once daily, L-arginine aspartate oral solution 1 measuring spoon (5 mL) 4 times daily
2.2, n = 8	Combination: ezetimibe 10 mg + rosuvastatin 10 mg 1 tablet once daily
2.3, n = 9	Rosuvastatin 20 mg 1 tablet once daily, L-arginine aspartate oral solution 1 measuring spoon (5 mL) 4 times daily
2.4, n = 8	Rosuvastatin 20 mg, 1 tablet once daily

Source: compiled by the authors

Functional state of vascular endothelium was determined by non-invasive technique of the endothelium-dependent vasodilation (EDV) of the brachial artery (BA) evaluation by the method proposed by D.S. Celermajer *et al.* [16] before and after 3 months of prescribed treatment. All examinees underwent a cuff test while by means of Doppler ultrasound examination the initial diameter (D0) of the BA and diameter of the BA on the fifth minute after distal occlusion of the blood flow (D1) were determined. The response of the vessel endothelium was evaluated as the ratio of the difference between the diameter of the BA on the fifth minute of test and the initial diameter of the BA to its initial diameter:

$$EDV = \frac{(D_1 - D_0)}{D_0} \times 100\%, \quad (1)$$

where *EDV* – endothelium – dependent vasodilation; D_0 – initial diameter of the BA; D_1 – diameter of the BA on the fifth minute of distal occlusion of the blood flow.

An increase in the BA diameter of less than 8-10% when performing a cuff test was considered a manifestation of ED. Statistical analysis of the obtained data was carried out using MS Excel 2016. The results of the study are presented in the form of arithmetic mean values with the error of the mean square deviation of the sample (M ± m). The probability of data differences in groups was determined using the reliability coefficient P, which was estimated based on Student's t test. The difference in indicators was considered statistically reliable at $P < 0.05$. The strength and direction of the linear relationship between variables was measured by Pearson's pairwise correlation coefficient (R). The study was conducted on the basis of informed consents in accordance with the requirements of bioethics in compliance with the provisions of the e Helsinki Declaration [17].

Results and Discussion

The mean age of the patients in group 1 was 61 ± 1.38 years, and in group 2, it was 54.06 ± 1.73 years (P = 0.003). There was found no reliable difference in the age of patients between different subgroups of each group. TSH level among patients with AH and hypothyroidism prevailed this indicator among those with normal thyroid function on 3,25 mIU/mL (5.66 ± 0.35 mIU/mL against 2.41 ±v0.18 mIU/mL respectively, P = 0.000).

The study found that the mean value of EDV in patients with AH and decreased thyroid function at the beginning of the study was reliably lower compared with this indicator among patients with AH and normal thyroid function by 9.38% (6.67 ± 0.07% against 7.36 ± 0.13%, P = 0.000) (Fig. 1). According to the results of cuff test among group 1 before and 3 months after the prescribed treatment, the mean value of EDV reliably increased by 11.11% and was 7.41 ± 0.12% (P = 0.000).

The highest indicators of EDV among patients with AH and decreased thyroid function were observed in subgroup 1.1, who, in addition to standard complex treatment, received lipid-lowering combination therapy with ezetimibe and rosuvastatin, and L-arginine aspartate (Table 2). The increase in the percentage of EDV in this subgroup was 16.49%. Together, the reliable improvement of EDV among individuals in subgroup 1.3 by 13.18% was noted, who received therapy with rosuvastatin and L-arginine.

Among patients in subgroups 1.2 and 1.4, who were administered ezetimibe and rosuvastatin, or monotherapy with rosuvastatin without L-arginine, the increase in the percentage of EDV was rather smaller – 8.51% and 6.19% respectively. Normalization of ED was observed among 10 (15.39%) patients in subgroup 1.1 and among 3 (4.62%) and 6 (9.23%) examinees in subgroups 1.2 and 1.3 respectively. No patient in subgroup 1.4 with AH and reduced thyroid function showed normalization of EDV value while taking rosuvastatin.

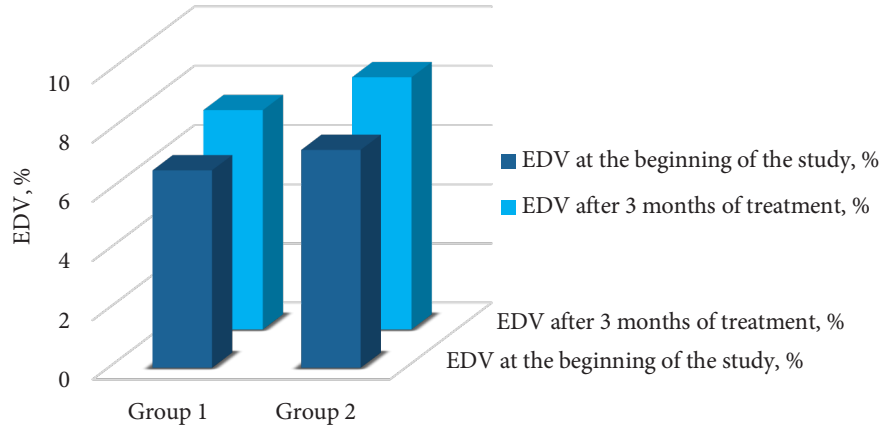

Figure 1. The mean values of EDV in patients with decreased and normal thyroid function, %
Source: compiled by the authors

Table 2. EDV in patients with AH and decreased thyroid function before and after treatment (M ± m)

Group	EDV at the beginning of the study, %	EDV after 3 months of treatment, %
1.1	6.95 ± 0.14	8.09 ± 0.23* P = 0.000
1.2	6.46 ± 0.17	7.01 ± 0.22* P = 0.000
1.3	6.83 ± 0.15	7.73 ± 0.25* P = 0.000
1.4	6.46 ± 0.10	6.86 ± 0.14* P = 0.000

Notes: * marked indicators are significantly different from the data at the beginning of the study (P < 0.05)
Source: compiled by the authors

The best measures of EDV of the BA were demonstrated by examinees with AH and normal thyroid function. The mean value of EDV in this group of patients significantly increased by 15.76% and was 8.52 ± 0.17% (P = 0.000). Especially, there was noted reliable improvement of EDV by 20.19% in subgroup 2.1 (Table 3). The value of EDV in subgroup 2.3, while taking rosuvastatin and L-arginine, reliably increased by 17.32%, and in subgroups 2.2 and 2.4 among patients, who were administered either combination of ezetimibe and rosuvastatin, or monotherapy with rosuvastatin, by 13.26% and 11.85% respectively. Normalization of ED was observed in 5 (55.56%) individuals in subgroup 2.1, 5 (62.5%) examinees in subgroup 2.2 and among 4 (44.44%) and 3 (37.5%) patients in subgroups 2.3 and 2.4 respectively.

Table 3. EDV in patients with AH and normal thyroid function before and after treatment (M ± m)

Group	EDV at the beginning of the study, %	EDV after 3 months of treatment, %
2.1	7.58 ± 0.33	9.11 ± 0.42* P = 0.000
2.2	7.62 ± 0.26	8.63 ± 0.37* P = 0.000
2.3	6.93 ± 0.28	8.13 ± 0.29* P = 0.000
2.4	7.34 ± 0.19	8.21 ± 0.27* P = 0.001

Notes: * marked indicators are significantly different from the data at the beginning of the study (P < 0.05)
Source: compiled by the authors

The correlation analysis revealed strong negative reliable correlations of EDV with the age of patients (R = -0.6877, P = 0.000) and TSH levels (R = -0.5111, P = 0.000), and weak negative correlations with duration of hypertension (R = -0.1987, P=0.049) and body mass index (R = -0.2074, P = 0.039) among examinees of all groups.

While the primary objective of statin therapy in managing hypertensive patients is traditionally focused on lipid reduction, this study has unveiled a noteworthy improvement in endothelium-dependent vasodilation (EDV) of the brachial artery (BA) following a 3-month course of rosuvastatin in all examined patients. Furthermore, the research by V. Serhiyenko & A. Serhiyenko [18] suggests that the positive impacts of statin therapy on the vascular wall and blood flow stem from an augmentation in the expression of endothelial NO-synthase. This augmentation leads to increased nitric oxide release, enhancing vasodilation in coronary and peripheral arteries, along with the suppression of local inflammation and stabilization of atherosclerotic plaques. The pleiotropic effects of statins on the endothelium encompass a reduction in endothelin-1 synthesis, suppression of angiotensin-1 and tissue plasminogen activator receptors, increased expression of plasminogen activator inhibitor, coupled with a reduction in oxidative stress. These actions collectively enhance neovascularization and reendothelialization processes, inhibit endothelial cell apoptosis, and confer antithrombotic and anti-ischaemic properties [19].

Concurrently, the perspective of Y. Higashi [20] emphasizes the need for more specific and adequate methods to evaluate endothelial function, particularly in patients with dyslipidemia, considering the close association observed between endothelial dysfunction, disturbances in lipid metabolism, and their potential role in cardiovascular complications. Another lipid-lowering agent, ezetimibe, has demonstrated an ability to improve vascular endothelial function. However, the mechanisms underlying this effect remain incompletely understood. It is considered that the reduction of the risk of adverse cardiovascular events when using ezetimibe is a result of blocked activity of cholesterol transport protein Niemann-Pick C1 – Like 1 at the level of the villi of small intestine mucous membrane, which leads to suppression of intestinal absorption and reducing the inlet of low – density lipoproteins (LDL), oxidized LDL and oxysterol, that come with food, into the liver [21]. According to the studies of M. Vavlukis and A. Vavlukis [22] this sequentially leads to the activation of the LDL receptors on the surface of hepatocytes and is accompanied by an increased clearance of the LDL cholesterol from the blood. While this study revealed the highest increase in the percentage of EDV among patients who received combination lipid-lowering therapy with ezetimibe and rosuvastatin compared to patients who received monotherapy with statins, the research of V. Serhiyenko & A. Serhiyenko [23] found that the use of ezetimibe can reduce the levels of LDL cholesterol by 10-18%. In combination with statins, it decreases the level of triglycerides by 10%, insignificantly affects the level of high-density lipoprotein cholesterol in blood, contributes to the regression of atherosclerotic plaques, and improves vasodilation.

Shifting focus to L-arginine, a conditionally essential amino acid serving as a substrate for NO synthase, it catalyses the synthesis of NO by endothelial cells. Oral L-arginine selectively enhances EDV in individuals with impaired endothelial function, reducing the aggregation and adhesion of thrombocytes and monocytes to the endothelial wall, and limiting the synthesis of endothelin-1. Several studies have showcased the beneficial effects of L-arginine use in patients with arterial hypertension, ischaemic heart disease, and atherosclerosis, impacting not only endothelial function but also normalizing blood pressure levels, lipid metabolism, LDL oxidation processes, and decreasing markers of cell adhesion and pro-inflammatory cytokines in blood serum. L-arginine has also demonstrated positive effects on the proliferation of vascular smooth muscle cells and an overall enhancement in the quality of life for such patients [24, 25].

Nevertheless, there remains a scarcity of data regarding the outcomes of hypolipidaemic and metabolic therapy in individuals with arterial hypertension and an impaired functional state of their thyroid gland. This study identified the most substantial increase in the percentage of EDV among hypertensive patients who received a combination of lipid-lowering therapy with ezetimibe and rosuvastatin, alongside metabolic therapy involving L-arginine. This increase amounted to 16.49% among individuals with decreased thyroid function and 20.19% among those with normal thyroid function. Additionally, a robust negative correlation was observed between EDV and TSH levels across all examined patients. These findings underscore the potential interplay between metabolic factors, thyroid function, and the efficacy of combined therapeutic approaches in hypertensive individuals.

Conclusions

Both, arterial hypertension and decreased thyroid gland function, negatively affect the state of the vessel endothelium. While the conducted study aimed to discover the changes of endothelium-dependent vasodilation among patients with hypertension and different thyroid gland function, as well as prospects of its correction, it revealed significantly lower indicators among those with hypothyroidism. Moreover, the study found that decreased levels of thyroid hormones not only had a negative impact on the values of endothelium-dependent vasodilation in hypertensive patients, but burdened the possibilities of endothelial dysfunction correction in this cohort of examinees The mean values of endothelium-dependent vasodilation among patients with hypothyroidism were reliably lower compared with those among patients with arterial hypertension and normal thyroid function both before and after the prescribed treatment – 6.67 ± 0.07% against 7.36 ± 0.13% (P = 0.000) and 7.41 ± 0.12% against

8.52 ± 0.17% (P = 0.000) respectively. The greater increase in the percentage of endothelium-dependent vasodilation indicators was observed among patients of both groups that received lipid-lowering combination therapy with ezetimibe and rosuvastatin, and metabolic therapy with L-arginine aspartate. The use of combination hypolipidaemic and metabolic therapy in the complex treatment of patients with arterial hypertension, dyslipidemia and decreased thyroid function contributed to the reliable improvement of endothelial-dependent vasodilation by 16.40% (P = 0.000). Concomitantly, the strong negative reliable correlation of endothelium-dependent vasodilation with the level of thyroid stimulating hormone was found among all examined individuals (R = -0.5111, P = 0.000). Further studies concerning the effects of the proposed schemes of treatment on lipid metabolism and cardiovascular risk factors modification among patients with AH, depending on the functional state of the thyroid gland, are expected.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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Корекція ендотеліальної дисфункції у пацієнтів із гіпертензією, дисліпідемією та зниженою тиреоїдною функцією

Марта Андріївна Орел

Аспірант
Тернопільський національний медичний університет ім. І. Я. Горбачевського МОЗ України
46001, майдан Волі, 1, м. Тернопіль, Україна
https://orcid.org/0009-0007-6916-140X

Лариса Петрівна Мартинюк

Кандидат медичних наук, доцент
Тернопільський національний медичний університет ім. І. Я. Горбачевського МОЗ України
46001, майдан Волі, 1, м. Тернопіль, Україна
https://orcid.org/0000-0001-8098-0421

Анотація. Ендотеліальна дисфункція вважається універсальним предиктором багатьох захворювань, розвитку їх ускладнень та несприятливого перебігу. Метою роботи було дослідити ендотелій-залежну вазодилятацію плечової артерії у хворих на артеріальну гіпертензію та дисліпідемію із різним тиреоїдним статусом та можливості її корекції із застосуванням гіполіпідемічної та метаболічної терапії. Обстежено 99 осіб із артеріальною гіпертензією та дисліпідемією, серед них 65 пацієнтів із зниженою функцією щитоподібної залози (група 1) та 34 пацієнти із нормальним тиреоїдним статусом (група 2). Вивчено вплив гіполіпідемічної терапії із застосуванням комбінації езтимібу та розувастатину або монотерапії статинами, а також метаболічної терапії із використанням L-аргініну аспартату протягом трьох місяців на ендотелій-залежну вазодилятацію. Показник ендотелій-залежної вазодилятації у групі 1 на початку дослідження був вірогідно меншим від даного показника у групі 2 на 9,38 %. Через 3 місяці призначеного лікування показник ендотелій-залежної вазодилятації у групі 1 достовірно покращився на 11,11 %, водночас у 19 (29,23 %) осіб спостерігали його нормалізацію. Найкращі показники ендотелій-залежної вазодилятації продемонстрували обстежені групи 2 – середній показник вірогідно зріс на 15,76 %, а його нормалізацію продемонстрували 17 (50 %) пацієнтів. Більший приріст відсотка ендотелій-залежної вазодилятації спостерігався у підгрупах пацієнтів, які отримували у складі комплексної терапії комбіновану гіполіпідемічну терапію езетимібу та розувастатину, та метаболічну терапію із застосуванням L – аргініну. Найкращі показники ендотелій-залежної вазодилятації продемонстрували обстежені обох груп, які, окрім комбінованої гіполіпідемічної терапіїї, додатково отримували метаболічну терапію. Гіпотиреоїдний статус пацієнтів негативно впливав на показники ендотелій-залежної вазодилятації та обтяжував можливості корекції ендотеліальної дисфункції у даній когорті осіб. Результати дослідження можуть бути використані у клініці внутрішніх хвороб у комплексному лікуванні хворих із коморбідною патологією – артеріальною гіпертензією та гіпотиреозом

Ключові слова: кров'яний тиск; обмін ліпідів; гіпотиреоз; езетиміб; вазодилятація; L-аргінін; тиреотропний гормон

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Regulation of oxidative stress and lipid peroxidation induced by epinephrine: The corrective role of L-Glutamic acid

Nataliya Salyha*
PhD in Biological Sciences, Senior Researcher
Institute Biology of Animals National Academy of Agrarian Sciences of Ukraine
79034, 38 V. Stusa Str., Lviv, Ukraine
https://orcid.org/0000-0003-0592-407X

Abstract. Oxidative stress is related to the development of metabolic and chronic diseases. Mitigation and prevention of the oxidative stress influence remain one of the most pressing issues in biology and medicine. The objective of the research was to examine and compare the role of the glutamic acid, both individually and in combination with pyridoxine, in mitigating the oxidative stress effects elicited by epinephrine. Biochemical methods (determination of the activity of antioxidant enzymes, alanine and aspartate aminotransferases, lipid peroxidation products) and statistical methods were used in the research. The findings indicate that the additional use of L-glutamic acid, both individually and in combination with pyridoxine, allows the body to reach control values or approach them to a greater extent than in groups of animals that did not receive these substances. In particular, such data were found for the following indicators: restored glutathione, lipid hydroperoxides (third experimental group), glutathione peroxidase, thiobarbituric acid reactive substances (second and third experimental groups), superoxide dismutase (spleen, liver, brain), catalase (liver, brain). In contrast, in the first experimental group, which only experienced stress, the activity of superoxide dismutase (spleen, brain, and liver) and catalase (brain, liver, and lungs) decreased compared to the control and the second and third experimental groups. When modelling epinephrine-induced oxidative stress, L-glutamic acid, both individually and in combination with pyridoxine, demonstrated a mitigating effect on the oxidant-antioxidant imbalance, which is a key factor in the level of oxidative stress. The research has shown the potential application of L-glutamic acid for mitigating and protecting the body during states accompanied by oxidative stress

Keywords: activity; biochemical reactions; damage; antioxidant enzymes; rats

Introduction

Oxidative stress, its impact on the human and animal body, and the search for substances with antioxidant properties are among the priority areas of biology and medicine. In particular, the modern lifestyle significantly contributes to the onset of oxidative stress. According to T.R. Kıran *et al.* [1], oxidative stress is an imbalance between the production of free radicals on one hand and antioxidant protection on the other. Stress is one of the factors that lead to damage to organs and systems and the development of diseases. H. Qi *et al.* [2] have investigated that prolonged exposure to oxidative stress can cause structural defects in deoxyribonucleic acid (DNA), as well as functional changes in certain enzymes and cellular structures, consequently leading to cell death.

Amino acids have different antioxidant activities. L-glutamic acid (L-Glu) can protect the body due to its many properties, including antioxidant properties. The L-glutamic amino acid is the main metabolic centre in many organisms [3, 4]. Besides its role in synthesis of protein, it is involved in a variety of processes. L-Glu is a precursor for other amino acids, including L-aspartate, L-alanine, L-proline and L-ornithine. And most importantly, this amino acid, together with L-cysteine and L-glycine, is the synthesis precursor of reduce glutathione (GSH). GSH maintains

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*Corresponding author

redox homeostasis in the cell and protects against oxidative damage. J. Kumar *et al*. [5] have hypothesized that L-Glu may enhance the antioxidant status and affect the concentration of neurotransmitters. The positive effect of glutamic acid, both alone and in combination with other substances, has also been established in the treatment of nutritional deficiencies [6, 7]. L.A. Ponomarenko *et al*. [8] found that the use of drug based on glutamic acid in the basic therapy of patients with gastroenterological pathology has increased the level of reduced glutathione and normalized lipoperoxidation processes. The results obtained by P.H. Tsai *et al.* [9] revealed that glutamine consumption reduces the expression of genes associated with oxidative stress, and increases antioxidant potential in diabetic rats. D.H. Tran *et al.* [10] propose the existence of a cystine/glutamate antiporter system, wherein intracellular glutamate is expelled to facilitate the uptake of cystine. These researchers also demonstrated that with an increase in oxygen concentration, the uptake of L-glutamic acid by endothelial cells increases. As noted by K. Stach *et al.* [11], pyridoxine (Pyr) or vitamin B6 is a highly significant compound for cellular metabolism. M. Parra *et al.* [12] indicate that Pyr is an extremely important cofactor for numerous biochemical reactions occurring in the cell. Summarizing the above, oxidative stress contributes to the development of diseases and mitigating its consequences remains one of the most urgent problems. Thereby, the aim of the research was to investigate the markers of the antioxidant system and lipid peroxidation under conditions of oxidative stress caused by epinephrine.

Materials and Methods

The studies were conducted using 40 adult Wistar rats (180-200 g) which were kept on the standard diet of the vivarium of the Institute of Animal Biology. The research was conducted in 2020. The rats were kept at the temperature of 22 ± 2°C, the humidity of 50 ± 5% and a 12-h light/12-h dark cycle. Rats (10 animals per group) were divided into 4 groups: three experimental (EG) (Exp.1, Exp.2, Exp.3) and Control (CG). The experiment duration was 24 hours. Three groups of rats (first, second, and third) were administered epinephrine intraperitoneally (2 mg/kg). Then, the rats of the second group were injected with the L-Glu (750 mg/kg), the third experimental group was injected with L-Glu (750 mg/kg) and Pyr (0.430 mg/kg). Rats of the control group – the appropriate amount of saline. Blood and tissues were collected after decapitation of animals under thiopental anaesthesia. The blood samples were centrifuged at 3000×g for 15 min; the tissue samples were homogenized, then centrifuged at 15000×g for 15 min.

Glutathine peroxidase activity (GPx, EC 1.11.1.9) was controlled by the glutathione restoration rate in the nicotinamide adenine dinucleotide phosphate (NADPH) presence [13]. The activity of glutathione reductase (GR, EC 1.6.4.2) was determined by the method of catalysis of NADPH-dependent reduction of the oxidised glutathione (GSSG) and reported as μmol NADPH/min/mg protein [13]. The activity of superoxide dismutase (SOD, EC 1.15.1.1) was defined by the level of inhibition of the rate of nitroblue tetrazolium-reduction. The catalase activity (CAT, EC 1.11.1.6) was defined by formation of a stable complex of molybdenum salts and hydrogen peroxide [13]. The level of reduced GSH was quantified by reactions between the SH groups of GSH and 5,'5'-dithio-bis (2-nitrobenzoic acid) [13]. The content of lipid hydroperoxide (LOOH) was counted as the difference between the control and the experimental values and the content of products reacting from thiobarbituric acid (TBARS) based on the interaction between thiobarbituric acid and malonic aldehyde and represented as nmol of TBARS/mL [13]. The concentration of *aspartate aminotransferase (ASAT)* and alanine *aminotransferase (ALAT)* were investigated in the blood plasma by using a biochemical analyser "Humalyzer 2000" (Germany). Experimental data were processed by methods of variation statistics using OriginPro 8 software. To determine differences between sample means, the Student's t-test was used. Differences with a P value of less than 5% ($P < 0.05$) were considered significant. Research conducted as per the principles of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" [14] and the Law of Ukraine No. 3447-IV "On Protection of Animals from Cruelty" [15].

Results

Glutathione has a fundamental role against oxidative stress and oxidative damage [16]. The increase in the content of reduced glutathione in the red blood cells (RBC) of rats of the 1st and 2nd groups in comparison with CG was found (Fig. 1(A)). It is worth mentioning the content of the above tripeptide in the L-Glu/Pyr group did not undergo significant changes. GR activity was significantly reduced in animals of all EG (Fig. 1(B)).

The GPx activity in RBC was significantly higher in animals of the first EG in relation to the CG (Fig. 2(A)). Instead, GPx activity did not change in the animals of the 2nd EG and 3rd EG that received additional the above-mentioned substances. The activity of the studied enzyme in animals of the second and third groups was probably lower than in animals of the first EG. No changes in catalase activity were observed in any of the EG of animals (Fig. 2(B)). The decrease in GH may be the lack of reduced NADPH coenzymes formed in the pentose phosphate cycle. It is difficult to explain the prolonged activation of GPx in the animals of the first EG, which was almost 5 times higher compared to the second and third EG that received additional L-Glu and Pyr. Moreover, catalase activity did not change in any of the EG of animals compared to the control. Such changes can be interpreted as mobilisation of the body to overcome the effects of oxidative stress. It can be assumed that this occurred after a previous decrease in this indicator.

The key regulatory systems of the organism include the antioxidant protection system, which regulates the level of free radicals and peroxides formed in biochemical reactions involving reactive oxygen species. The antioxidant

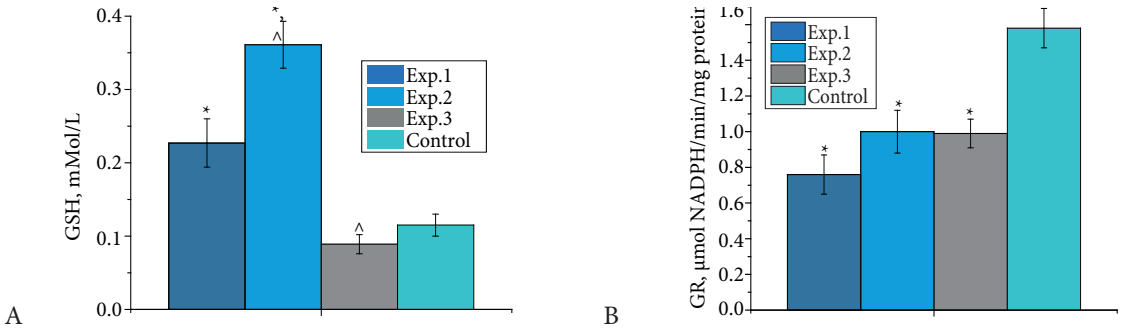

Figure 1. Influence of L-Glu and L-Glu/Pyr on GSH content and GR activity in rat RBCs
Notes: A — GSH content in rat red blood cells under the influence of L-Glu and L-Glu/Pyr. B – GR activity in rat red blood cells under the influence of L-Glu and L-Glu/Pyr. * – differs significantly from the CG ($P < 0.05$). ^ – differs significantly from the 1st EG ($P < 0.05$)
Source: compiled by the author

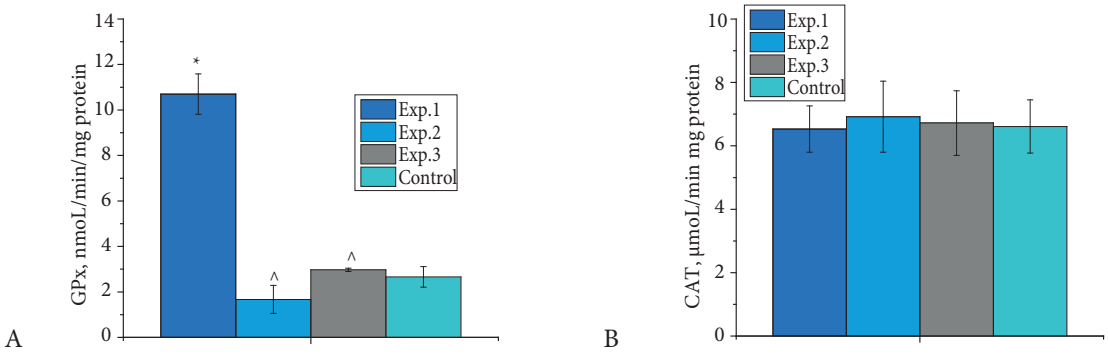

Figure 2. Influence of L-Glu and L-Glu/Pyr on GPx and CAT activity in rat RBCs
Notes: A — GPx activity in rat red blood cells under the influence of L-Glu and L-Glu/Pyr. B – CAT activity in rat red blood cells under the influence of L-Glu and L-Glu/Pyr. * – differs significantly from the CG ($P < 0.05$). ^ – differs significantly from the 1st EG ($P < 0.05$)
Source: compiled by the author

defence system prevents the development of uncontrolled reactions, in particular, lipid peroxidation reactions. Intensification of free radical processes is a universal mechanism of cell damage. This research has shown an intensification of lipid peroxidation in the first and second EG exposed to stress. It is worth noting the increase in the LOOH content in the first and second groups by 65.5% and 43.6%, respectively, and the content of TBARS in 2 times in animals of the first group of animals compared to the control (Fig. 3(A, B)).

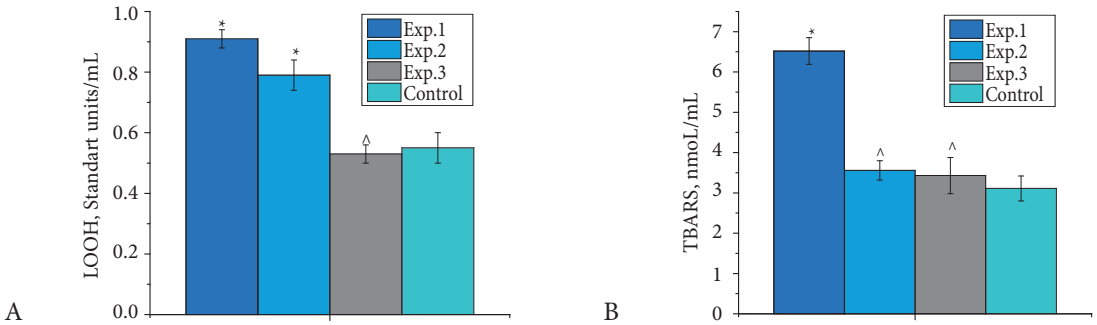

Figure 3. LOOH and TBARS content in rat blood plasma under the influence of L-Glu and L-Glu/Pyr
Notes: A — LOOH content in rat blood plasma under the influence of L-Glu and L-Glu/Pyr. B – TBARS content in rat blood plasma under the influence of L-Glu and L-Glu/Pyr. * – differs significantly from the CG ($P < 0.05$). ^ – differs significantly from the 1st EG ($P < 0.05$)
Source: compiled by the author

The antioxidant defence system in body tissues prevents the development of lipid peroxidation reactions. SOD provides dismutation of the superoxide radical, which is a precursor of the hydroxide radical. The results obtained indicate that superoxide dismutase activity in kidney tissue was higher in animals of the first and second EG compared to control (Fig. 4(A)). This can be explained by the activation of antioxidant enzymes in response to stress. It should be noted that the increase in SOD activity was most pronounced in animals of the first and second EG compared to the CG. Superoxide dismutase activity in spleen tissues was significantly reduced in animals of the first EG by 31.6% compared to the CG. This confirms the data on the antioxidant and membrane-stabilising effects of L-Glu. Lower superoxide dismutase activity was observed in the brain and liver tissues of rats of the first EG injected with epinephrine without the above amino acids compared to the CG. The SOD activity in lung and myocardial of all EG was at the level of the CG. CAT activity in brain and liver tissues was significantly lower by 60.5% and 38.8%, respectively, in animals of the first EG that received epinephrine (Fig. 4(B)). In the animals of the 2nd EG and 3rd EG, which received glutamic acid and glutamic acid in combination with Pyr, CAT activity was at the control level. The amount of catalase in a cell is sufficient to prevent a small amount of H_2O_2 from causing potential toxicity. When analysing catalase activity in lung tissue, it should be noted that this indicator decreased in animals of the first and second EG by 19% and 16.4%, respectively, compared to the CG of rats.

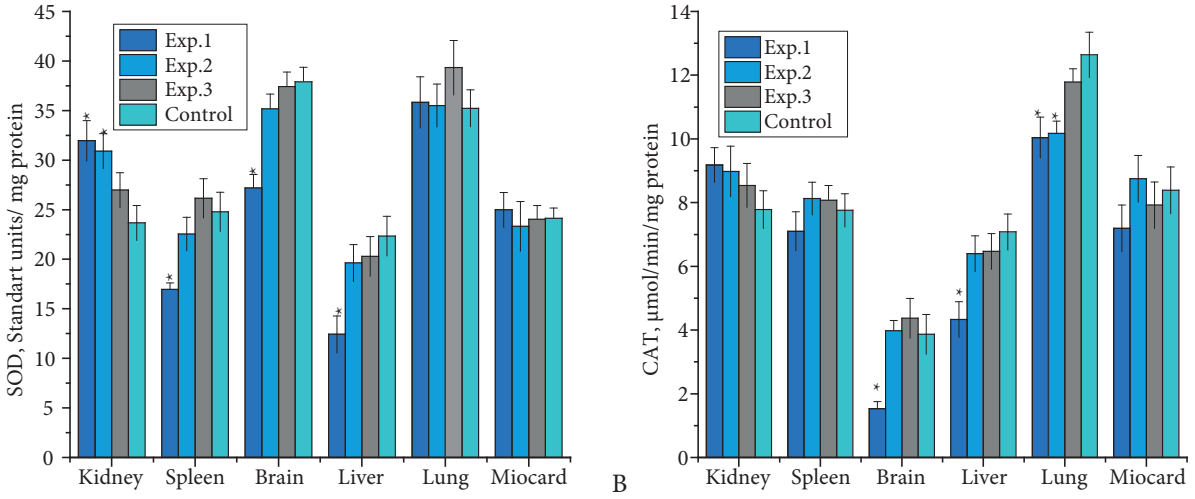

Figure 4. SOD and CAT activity in various rat tissues under the influence of L-Glu and L-Glu/Pyr
Notes: A — SOD activity in rat tissues under the influence of L-Glu and L-Glu/Pyr. B – CAT activity in rat tissues under the influence of L-Glu and L-Glu/Pyr. * – differs significantly from the CG ($P < 0.05$), ^ – differs significantly from the 1st EG ($P < 0.05$)
Source: compiled by the author

The protein level metabolism in the body is indicated by the intensity of reamination processes, which are characterized by the activity of two aminotransferases. Due to the increased biosynthesis of proteins in the organism of rats, the activity of transamination reactions increases. ALAT catalyses the reaction between L-alanine and 2-oxoglutarate, which converts them to L-glutamate and pyruvic acid salt. As can be seen (Table 1), the activity of ALAT in blood plasma did not significant changes. ALAT activity was higher in the first EG of rats, but these data were not significant.

Table 1. Aminotransferase activity in rat blood plasma under the influence of L-Glu and L-Glu/Pyr

Groups	ASAT (U/mL)	ALAT (U/mL)
EG 1	1.57± 0.12*	0.31± 0.03
EG 2	1.03± 0.01	0.29± 0.02
EG 3	0.96± 0.01	0.23± 0.03
Control	0.96± 0.02	0.26± 0.02

Notes: * – differs significantly from the CG ($P < 0.05$)
Source: compiled by the author

As for ASAT (Table 1), which catalyses the reaction between L-aspartate and 2-oxoglutarate, as a result of which they are converted to L-glutamate and oxaloacetate, a significantly higher activity of this aminotransferase was found in animals of the first EG by 1.6 times compared to the control. Elevated levels of ASAT under stress are

considered a sign of mitochondrial stimulation and a marker of tricarboxylic acid cycle activity. The results summing, the additional use of L-glutamic acid, both alone and in combination with pyridoxine, had a positive effect on the body of animals. This was established based on the analysis of most of the studied parameters, the values of which were close to the CG of animals.

Discussion

The effect of the test substances on free radical processes in the blood of rats were investigated. A correlation between oxidative stress indicators and the enzymes' activity was found. The decrease of the GR activity and increase in GPx activity in animals of the first EG exposed to experimental stress may be due to compensatory reactions occurring in the organism in response to the effects of experimental stress. The data obtained by W. He *et al.* [17] also indicate that Glu reduces oxidative stress through direct antioxidant effects and significantly changes the activity of investigated enzymes. SOD and CAT activity in animal tissues also underwent changes under stress, in particular, a reduced content of SOD (spleen, brain, and liver) and CAT (brain, liver, and lungs) of the first EG was found compared to the CG. The SOD activity decrease in first EG of rats is probably due to the depletion of the antioxidant capacity and formation of free radical oxidation products. This is probably due to the adaptive response of superoxide dismutase as a substrate-dependent enzyme to stress. It is worth pointing out that SOD is involved in the scavenging of superoxide generated by electron transport chain complexes. It is worth noting that superoxide dismutase activity in myocardial and lung tissue of all EG was at the level of the CG. This suggests that under conditions of oxidative stress, the antioxidant system is mobilised.

The animals which were injected with L-Glu and Glu/Pyr, respectively, differed favourably. The investigated antioxidant enzymes' activity in the above-mentioned groups were more similar to the data in the CG of rats. Z. Liu *et al.* [18] suggest that there are complex interactions between reactive oxygen species and different types of antioxidants to restore redox balance. This may be associated with the fact that, among other things, the membrane-stabilizing and antioxidant properties of the amino acid which was used in these studies. Pyr is the coenzyme in the conversion of homocysteine to cysteine, which supports GSH biosynthesis. Pyr is a powerful antioxidant, which stores are quickly depleted under stress. Deficiency of Pyr leads to alterations in the many aminoacids metabolism, including glutamate. L-Glu plays the key role in the metabolic processes of many organisms, including nitrogen uptake, amino acid biosynthesis and cofactor production. It can be assumed that this may be due to the fact that glutamic acid is a synthesis precursor of reduced glutathione. G. Lian *et al.* [19] results indicate that glutamine catabolism leads to de novo GSH synthesis. A number of authors also point to the ability of the glutamic acid to reduce the effects of oxidative stress in both plants and animals by regulating the level of antioxidant enzymes [20-22]. J. Fardus *et al.* [20] assume that L-Glu pretreatment mitigated oxidative damage due to keeping ionic homeostasis and raising the activity of antioxidant enzymes (ascorbate peroxidase and catalase).

Other researchers have found that feeding of glutamine can effectively improve immune status by increasing the antioxidant capacity of the experimental animals [21]. The findings are consistent with a number of researchers who have concluded that L-Glu has antioxidant properties [23-25]. The antioxidant properties of glutamic acid are primarily related to the fact that this amino acid is a precursor of numerous biologically active substances, such as reduce glutathine, poly-glutamine phosphate cofactors, pyrimidine and purine nucleotides, some amino acids, in particular, alanine, aspartate, proline, arginine. This is also with the results of this work. In particular, S. Mahdavifard *et al.* [24] established that the use of the aforementioned amino acid led to the normalisation in the level of glutathione in the animals of the EG compared to the control. H. Zhang *et al.* [25] point to the glutamic acid ability to inhibit lipid peroxidation and increase antioxidant capacity. The above-mentioned authors suggest and assume that Glu reduces oxidative stress through direct antioxidant action and increased antioxidant enzyme activity. Based on their own research, authors K. Grucza *et al.* [26] also consider that an increase in GSH levels in the body can be achieved with the help of glutamic acid supplements. The use of the aforementioned amino acid led to the normalisation by the amount of GSH in the animals of the third EG compared to the CG of investigated animals. In the modelling of oxidative stress induced by epinephrine, there is a mitigating effect of glutamic acid, both alone and in combination with pyridoxine on the oxidant-antioxidant imbalance, which is the main factor in the degree of oxidative stress. L-glutamic acid in combination with pyridoxine and L-glutamic acid individually reduce oxidative stress by intensification of the antioxidant enzymes activity and inhibiting lipid oxidation. Moreover, L-Glu/Pyr has a more significant effect than L-Glu. The aforementioned amino acid, by restoring the oxidant-antioxidant balance, participating in protein metabolism, had a positive effect on the body of rats under stress.

Conclusions

When studying and comparing the role of L-glutamic acid individually and in conjunction with Pyr in mitigating the effects of the epinephrine-induced oxidative stress, a change in oxidative stress markers was detected. The results obtained indicate that the supplementary use of L-Glu and L-Glu/Pyr allows the organism to achieve the control level values or approach them to a greater extent than in animals that did not receive the above substances. In particular, such data were found for the following indicators: GSH, LOOH (third EG), GPx, TBARS (second and third EG), SOD (spleen, liver, brain), CAT (liver, brain).

In contrast, the activity of SOD and CAT in the studied tissues also changed under the influence of stress. In particular, in animals of the first EG, a decrease in the content

of SOD (spleen, brain, and liver) and CAT (brain, liver, and lungs) were found compared to the control and the second and third EG. In animals treated with L-Glu and L-Glu/Pyr, no changes in these parameters were found compared to the CG. It was found that the superoxide dismutase activity in the lung and myocardial tissues was at the level of the CG in all study groups. These studies have shown the possibility of using L-Glu to mitigate and defend the body in conditions accompanied by oxidative stress. Further scientific studies are recommended to extensively investigate the possible relationships among various antioxidant markers under the influence of oxidative stress and the role of amino acids in these processes. These investigations will provide more insights into the interaction of the body's antioxidant systems and determine how amino acids affect these systems under stress conditions. This can be of significant importance in the development of new methods for the prevention and treatment of diseases associated with oxidative stress.

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None.

Conflict of Interest

The author declares no conflict of interest.

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Регуляція оксидативного стресу та пероксидного окиснення ліпідів, індукованих адреналіном: коригуюча роль L-глутамінової кислоти

Наталія Омелянівна Салига

Кандидат біологічних наук, старший науковий співробітник
Інститут біології тварин Національної академії аграрних наук України
79034, вул. Василя Стуса, 38, м. Львів, Україна
https://orcid.org/0000-0003-0592-407X

Анотація. Окислювальний стрес асоціюється з розвитком метаболічних та хронічних захворювань. Пом'якшення та запобігання наслідків оксидативного стресу залишається однією з найактуальніших проблем біології та медицини. Метою дослідження було вивчити та порівняти роль L-глутамінової кислоти як окремо, так і в комбінації з піридоксином у пом'якшенні наслідків оксидативного стресу, спричиненого епінефрином. У роботі використовували біохімічні методи (визначення активності антиоксидантних ензимів, аланін- та аспартатамінотрансфераз, вмісту продуктів пероксидного окиснення ліпідів) та статистичні методи. Отримані результати свідчать, що додаткове застосування L-глутамінової кислоти, як окремо, так і у комплексі з піридоксином дозволяє організму вийти на рівень контрольних значень або наблизитися до них більшою мірою, ніж у групах тварин, які не отримували вищезазначені речовини. Зокрема, такі дані були виявлені щодо наступних показників: відновлений глутатіон, гідропероксиди ліпідів (третя дослідна група), глутатіонпероксидаза, продукти реакції з тіобарбітуровою кислотою (друга і третя дослідні групи), супероксиддисмутаза (селезінка, печінка, мозок), каталаза (печінка, мозок). На відміну від цього, у першій дослідній групі, яка зазнавала лише дії стресу, активність супероксиддисмутази (селезінка, мозок і печінка) та каталази (мозок, печінка і легені) знижувалася порівняно з контролем та другою і третьою дослідними групами. При моделюванні оксидативного стресу, індукованого епінефрином, відзначається пом'якшувальний вплив L-глутамінової кислоти як окремо, так і в комбінації з піридоксином на оксидантно-антиоксидантний дисбаланс, що є основним чинником рівня оксидативного стресу. Дослідження показали можливість застосування L-глутамінової кислоти, з метою пом'якшення та захисту організму при станах, що супроводжуються оксидативним стресом

Ключові слова: активність; біохімічні реакції; пошкодження; антиоксидантні ензими; щури

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Dupuytren's contracture treated with collagenase *Clostridium histolyticum*

Martina Vidova Ugurbas*
Doctor of Medicine, Associate Professor
Pavol Jozef Šafárik University in Košice
04 180, 2 Srobarova Str., Kosice, Slovak Republic
https://orcid.org/0000-0003-4620-6031

Abstract. Treatment of Dupuytren's contracture improves the quality of life of patients, but standard open fasciectomy surgery is traumatic and requires long-term rehabilitation. The study aimed to determine whether injectable treatment with collagenase preparations was effective in comparison with open fasciectomy. Forty patients were examined. Of these, 15 were treated with *Clostridium histolyticum* collagenase preparations (the main group), and 25 underwent limited fasciectomy (the control group). In 11 (73.3%) patients of the main group, restoration of mobility of the affected joints was achieved after the first injection, in 3 (20%) – after the second, and in 1 (6.7%) – after the third. Patients in the main group remained able to work after treatment and did not require rehabilitation; the function of the upper limb was fully restored on the day of intervention. During the observation period, 12 (80%) patients in the main group were concerned about dry skin at the intervention site, and 5 (33.3%) patients were concerned about itching and discolouration of the skin at the intervention site. In 25 (100%) patients of the control group, joint mobility was fully restored. The ability to use the hand after surgery in patients of the control group was limited for 6 (4.5; 10) days. All patients in the control group required rehabilitation to relieve stiffness and restore the functional capabilities of the hand. The period of disability in these patients lasted 16 (12; 24.5) days. 11 (44%) patients had complaints of pain or discomfort in the intervention area during the follow-up, and 24 (96%) patients were bothered by itching. Satisfaction with the choice of treatment method in the main group was more frequent compared to the control group. Relapses during the observation period were absent in both groups. Thus, the efficacy of *Clostridium histolyticum* collagenase preparations are comparable to the results of surgical treatment. Minimally invasive treatment is optimal for patients with mild disease, as well as for those who have a low risk of contracture recurrence. The results of this study can be useful for surgeons when choosing the optimal method of treating Dupuytren's contracture

Keywords: palmar fibromatosis; minimally invasive intervention; hand surgery; open fasciectomy; clinical trial; patient management

Introduction

Dupuytren's contracture is a chronic connective tissue disease. This pathology occurs as a result of fibrous changes in the palmar fascia, a layer of connective tissue that covers the tendons on the palm side of the hand. These changes lead to shortening and tightening of the fascia, which in turn limits the mobility of the fingers. According to an epidemiological study by N. Salari *et al.* [1], the prevalence of Dupuytren's contracture in European countries is approximately 10%. In the initial stage of the disease, patients complain of nodule-like formations on the palmar surface of the hand. Such nodules are not painful and do not limit the mobility of the limb. However, the disease gradually progresses, and the nodules turn into fibrous bands, which causes a flexion contracture. Most often, contractures are formed on the fourth or fifth finger, but there are also cases of multiple contractures. Although pain in patients with this pathology is not common, the contracture significantly impairs their quality of

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*Corresponding author

life, as it limits their ability to perform daily activities, including self-care and work capacity [2].

The aetiology of the disease is not known for certain. H. Ruettermann *et al.* [3] in a literature review conclude that about 80% of cases of Dupuytren's contracture are associated with a genetic predisposition. Other risk factors include diabetes mellitus, liver disease, and epilepsy. According to a study by J.N. Aleksandar *et al.* [4], among patients with diabetes mellitus, the risk is increased by factors such as age, duration of the disease, poor blood glucose control and hypokalaemia. L. Murínová *et al.* [5] note that Dupuytren's contracture can be an occupational disease if it develops after prolonged work with vibrating tools. Alcohol consumption is also a significant risk factor for the development of pathology, unlike smoking [6, 7].

The treatment of Dupuytren's contracture is complex. It is difficult to slow down the development of the pathology even with timely diagnosis. According to the R. Sanjuan-Cervero [8], physiotherapy is not effective, but radiotherapy and corticosteroid injection therapy can slow the formation of the contracture, reduce patient discomfort, and reduce the likelihood of future surgical treatment. However, further research is needed to prove the effectiveness of these methods. According to the British Medical Journal guidelines, updated in 2023, patients with one or more Dupuytren's nodules are recommended to be actively monitored with the recommended frequency of visits to the doctor every 6 months. A more active approach to treatment is indicated for patients with Dupuytren's contracture who have a functional impairment [9]. Minimally invasive treatments (injections of *Clostridium histolyticum* collagenase, needle aponeurotomy, or percutaneous fasciotomy) are recommended for patients with a range of motion of up to 30°. In patients with more severe extension disorders, open fasciectomy may also be used.

According to H. Ruettermann *et al.* [3], limited open fasciectomy is the "gold standard" for the treatment of Dupuytren's contracture, as it allows for restoring hand function in the vast majority of cases. After limited fasciectomy, the incidence of contracture recurrence is lower than after needle aponeurotomy or percutaneous fasciotomy. The disadvantage of this method is high tissue trauma during the operation, which leads to a long period of disability and requires rehabilitation. Injectable therapy with *Clostridium histolyticum* collagenase preparations is much less traumatic, so patients recover faster after this treatment and do not require long-term rehabilitation. However, the effectiveness of this treatment compared to invasive methods requires further study [8].

Thus, Dupuytren's disease significantly worsens the quality of life of patients and causes economic losses for the state, and etiological treatment and prevention are impossible due to the multifactorial nature of the pathology. Standard surgical methods of treatment have significant drawbacks, but for the routine use of minimally invasive treatment, it is necessary to investigate whether it is effective in comparison with traditional invasive methods. The study was aimed at comparing the treatment of Dupuytren's contracture with *Clostridium histolyticum* collagenase preparations and open fasciectomy.

Materials and Methods

The study was conducted at the Department of Plastic, Reconstructive and Aesthetic Surgery of the Louis Pasteur University Hospital, which is part of the Faculty of Medicine of Pavol Jozef Šafárik University, Kosice, Slovakia. The study period was from January 2021 to May 2023.

The study included 40 patients, of whom 23 (57.5%) were men and 17 (42.5%) were women. The age of the patients was 56 (46.5; 69) years. The main group included 15 patients (9 (60%) men and 6 (40%) women), their age was 53.5 (44; 69.5) years. In 8 (53.3%) patients, the extension limitation did not exceed 50°, which characterised a relatively early stage of Dupuytren's contracture, and in the remaining 7 (46.7%) patients, the limitation was more pronounced and exceeded 50°.

Patients in the main group received injectable treatment with enzyme preparations isolated from the bacterium *Clostridium histolyticum*. *Clostridium histolyticum* collagenase contains two classes of enzymes: AUX-I and AUX-II. Collagenase class I (AUX-I) cleaves the end fragments of the collagen chain, respectively, and collagenase class II (AUX-II) cleaves the inner segment of this chain. In all cases, the drug was injected into the most proximal part of the fibrous cord. It was extremely important to prevent skin contact with the drug, as this could lead to damage to the skin. In the case when two joints (metacarpophalangeal and proximal interphalangeal) were involved in the pathological process on one finger, the drug was initially injected only into the metacarpophalangeal joint. This approach made it possible to achieve extension of the affected finger in both joints at once, while reducing trauma to the hand tissues, which, although minimal, still occurs even with a sparing approach to treatment.

The inclusion criteria were as follows: the presence of Dupuytren's contracture of the second degree or higher, which was assessed as restriction in the extension of the metacarpophalangeal and/or proximal interphalangeal joints of at least one finger of the upper limb (excluding the thumb), with patients having restriction in the extension of at least one finger, while the presence of Dupuytren's nodules alone was not a reason for inclusion in the study; age over 18 years; consent to participate in the study.

The study excluded patients with severe Dupuytren's contracture (extension limitation of more than 135°), as well as patients with concomitant musculoskeletal pathology, including osteoarthritis, gout, rheumatoid or gouty arthritis, ankylosing spondylitis, neuromuscular pathology of the hand; pregnant women; bleeding patients and those who are constantly taking anticoagulants. The study also did not include patients with previous surgical interventions on the affected hand, whether as a result of Dupuytren's contracture treatment or for any other

reason, as well as those who had already received treatment with *Clostridium histolyticum* collagenase. Patients with diabetes mellitus were also excluded from the study, as differential diagnosis of Dupuytren's contracture and diabetic hyperpathia may be difficult in some cases. Instead, a history of trauma to the affected hand or a hereditary factor was not considered a criterion for excluding patients from the study.

The choice of treatment method (surgical or injection) for each patient was determined by the doctor based on the recommendations of the British Medical Journal, as well as considering the individual characteristics of the patient [9]. Factors such as the presence of contraindications to surgery (severe somatic pathology, drug allergies), age, and the patient's preference for treatment were considered. Patients decided on the treatment method after receiving detailed information about the benefits and risks of each method.

Before use, the *Clostridium histolyticum* collagenase preparation in the amount of 0.58 mg was diluted in 0.25 or 0.2 mL of saline (respectively, for metacarpophalangeal and proximal interphalangeal joints), after which it was injected into the affected joint. The drug remained at the injection site for 24 hours, after which, using local anaesthetics, the patient was allowed to extend the finger, which was accompanied by the destruction of the contracture. The injection therapy with *Clostridium histolyticum* collagenase preparations, followed by breaking the contracture and releasing one or more fingers, was performed in the manipulation room or directly in the doctor's office. The surgical intervention involved open fasciectomy and was performed in the operating room.

After treatment, all patients were followed up for 12 months. Initially, monitoring of the patient's clinical condition immediately after the intervention took place daily and for patients who received injection therapy lasted several days, as the treatment was outpatient, while for those patients who received surgical treatment – from a week, as these patients were hospitalised. During the follow-up, the following methods were used to assess the patient's condition: collection of complaints and anamnesis data (including information on the duration of disability), assessment of the patient's objective status, including local status, and measurement of the degree of restriction in finger extension.

Data were collected, tabulated using MS excel and later presented as percentages and proportions. The design of this study was approved by the University Biomedical Ethics Committee and agreed with the legal department and medical law specialists. The study complied with the basic bioethical standards, such as the principle of autonomy of research participants, the absence of harm to them, the existence of research benefits for society that outweigh the possible risks to patients participating in the study, as well as the principle of justice and non-discrimination [10]. All patients agreed to the processing of personal data and gave voluntary informed consent to participate in the study.

Results

The technique of injecting *Clostridium histolyticum* collagenase into the affected tendon cord includes three stages and is shown in detail in Figures 1-3. The doctor performing the intervention makes only one puncture of the skin and then directs the drug in different directions, changing the angle of the needle.

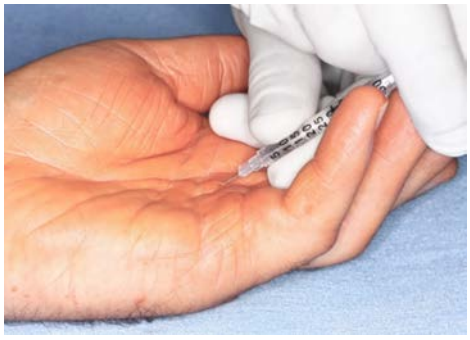

Figure 1. Injection of *Clostridium histolyticum* collagenase into the fibrotic ligament, the beginning of the intervention
Source: photographed by the author

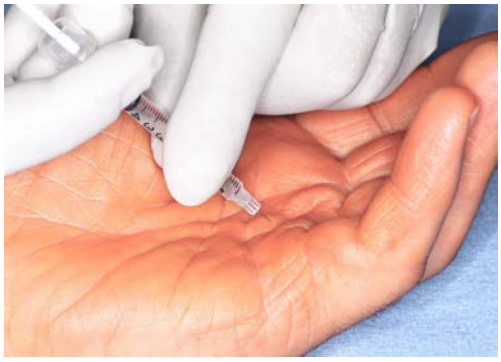

Figure 2. Injection of *Clostridium histolyticum* collagenase into the fibrotic ligament, a continuation of intervention
Source: photographed by the author

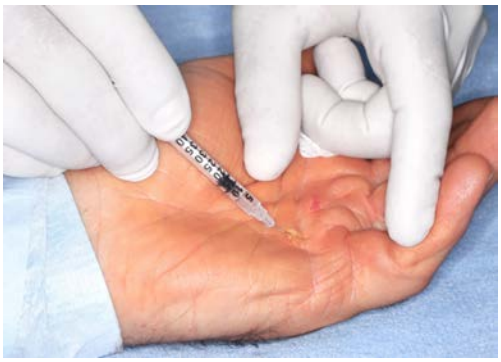

Figure 3. Injection of *Clostridium histolyticum* collagenase into the fibrotic ligament, end of the intervention
Source: photographed by the author

As mentioned earlier, the procedure for breaking the Dupuytren's contracture was performed the day after the injection using local anaesthesia. The technique of local anaesthesia and the positive results of the treatment of Dupuytren's contractures of four fingers are shown in Figures 4 and 5.

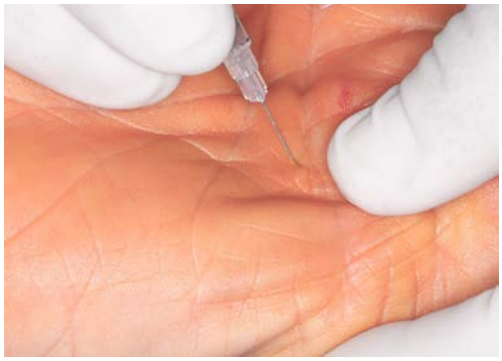

Figure 4. Use of local anaesthesia the day after the injection of *Clostridium histolyticum* collagenase
Source: photographed by the author

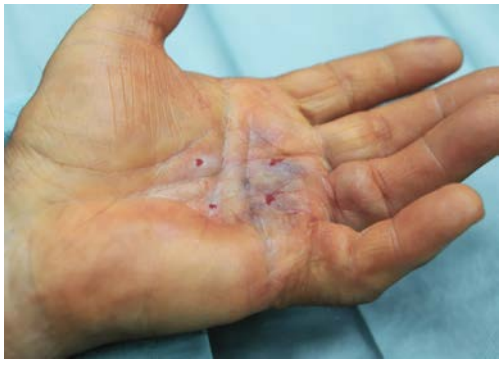

Figure 5. Palm surface of the hand after treatment of Dupuytren's contracture of the index, middle, ring fingers and little finger with collagenase of *Clostridium histolyticum*
Source: photographed by the author

In 11 (73.3%) patients of the main group, the first and only injection of *Clostridium histolyticum* collagenase demonstrated its effectiveness, which allowed to break the fibrous cord and achieve freedom of movement in the affected finger or several fingers. However, for 4 (26.7%) patients, the initial application of *Clostridium histolyticum* collagenase was ineffective and did not allow for the complete release of one or more fingers. All patients who failed the first treatment attempt were offered a second intervention at intervals of at least 4 weeks, to which all patients agreed.

Repeated intervention was performed using an identical methodology and was effective in 3 out of 4 patients who did not achieve the desired treatment result during the initial intervention. The patient whose contracture rupture was not possible after the second injection was offered a third session of injection therapy. He agreed that the treatment was performed 4 weeks later and was successful: the patient fully regained freedom of movement in the affected joint. In the early postoperative period, patients quickly regained the ability to use the limb undergoing the intervention. The pain in the projection of the ruptured contracture, although disturbing, was well relieved by taking non-steroidal anti-inflammatory drugs. Within one to two days after rupture of the fibrous cord, the pain decreased to the extent that it did not require painkillers. In 6 (40%) patients, oedema of the hand undergoing the intervention was observed. The swelling was mild and disappeared in a few days.

Patients regained the functionality of their upper limbs almost immediately after contracture correction. They did not need rehabilitation measures or long-term medical supervision. The patients' work capacity was preserved, so they could resume their jobs after treatment. The course of the postoperative period after the second and third injection therapy sessions did not differ from that after the first session. After the second and third injections, the pain was moderate in all cases and resolved after taking non-steroidal anti-inflammatory drugs. Swelling of the hand was observed in 1 patient after the second injection of *Clostridium histolyticum* collagenase preparations. The control group included 25 patients (including 14 (56%) men and 11 (44%) women), the age of the study participants in this group was 57 (48; 73.5) years). Patients in the control group underwent surgical treatment by limited open fasciectomy.

Limited fasciectomy was performed using regional anaesthesia, including brachial plexus block. To access the contracture, zigzag incisions were made along the natural palmar and finger folds. This approach provided adequate access to the aponeurosis while preventing unnecessary tissue trauma. The limited fasciectomy involved the removal of only those tissues that were macroscopically assessed as pathological during the operation, in contrast to open dermofasciectomy, when the entire palmar aponeurosis is removed regardless of the degree of damage. After the surgery, the wound remained open without the use of skin grafts for closure. This approach reduced postoperative pain and improved early recovery of hand function. During the operation, complications such as nerve and vascular damage are possible, although extremely rare (1-2%). Intraoperative complications are associated with the formation of compacted bands at the site of fascial bundles. Some tapes can distort neurovascular structures, creating a risk of damage during surgical procedures.

Early postoperative complications, which occur more frequently (up to 20% of cases), are haematoma formation and wound infection [3]. The patients who participated in this study did not have any complications both during surgery and during the rehabilitation period. The absence of complications was facilitated by careful observance of septic and antiseptic rules during surgery, careful planning of the course of operations and development of their techniques, prophylactic use of antibiotics perioperatively and careful monitoring of the wound with regular treatment with antiseptic and healing agents. However, despite the

absence of complications, all patients in the control group experienced pain in the operated hand, swelling and inability to use the upper limb in the early postoperative period. Discomfort symptoms decreased after taking non-steroidal anti-inflammatory drugs, elevating the limb, and applying cold to it, but the effectiveness of these drugs was temporary and did not affect functional impairment. The need for painkillers in patients of the control group persisted for about a week. The operated limb was fixed in a functional position in the early postoperative period, which ensured 45-70° flexion in the metacarpophalangeal joints and extension in the proximal and distal interphalangeal joints. The duration of the hand immobilisation period in patients of the control group was 6 (4.5; 10) days.

In the first few days after surgery, patients were referred for a consultation with a physiotherapist to develop an individual rehabilitation plan. Early start of rehabilitation is extremely important, as it allows for the fastest possible restoration of the function of the operated limb, preservation of the range of motion achieved during the operation, and prevention of stiffness. At the same time, the load should be gentle, as excessive exercise can slow down tissue regeneration and healing. Patients are also advised to temporarily limit driving and to keep the arm elevated even at rest. All patients who participated in the study were subsequently followed up. Patients in the main group did not have any visual damage to the skin after the puncture sites healed, and no pain or swelling was observed. During the survey, it was found that the quality of life after treatment improved in all 15 (100%) patients of the main group. Since the patients' preferences were considered when choosing a treatment method, they were asked during the follow-up examination whether they regretted their choice. All 15 (100%) patients were satisfied with their choice. 9 (60%) patients would recommend this method to their relatives if necessary, and 6 (40%) patients were undecided at the time of the examination. During the entire observation period, no relapses were recorded in the main group.

After treatment with *Clostridium histolyticum* collagenase preparations, there is a risk of developing several serious complications. First of all, it is a tendon rupture that requires repeated surgical intervention for reconstruction. No tendon ruptures were observed in the patients of this study. The risk of bleeding during this intervention is minimal, provided that the patient has no haematological pathology and does not take anticoagulants. On the contrary, antiplatelet medication is safe and does not increase the risks of the procedure. The second, but no less important, is algodystrophy, which is also known as Zudeck's syndrome, complex regional pain syndrome type I or reflex sympathetic dystrophy. Patients with algodystrophy suffer from pain, hypersensitivity of the hand skin to any stimuli, pale skin or its hyperaemia, dryness and itching, swelling, and muscle weakness.

During the examination in the dynamics, 12 (80%) patients in the main group complained of dry skin in the area of the palm where the puncture was performed, while 5 (33.3%) patients had minor skin discolouration and itching. However, these symptoms decreased over time and were well-corrected with the use of skincare products. Thus, there were minor trophic disorders, and such a serious complication as Zudeck's syndrome was absent in these patients during the observation period. In 17 (68%) patients of the control group, there were complaints of periodic discomfort in the intervention area. Swelling of the operated hand was observed in 11 (44%) patients and itching in the postoperative wound area in 24 (96%) patients. 21 patients reported complaints of stiffness in their movements after stopping rehabilitation activities or improper exercise. During the survey, all 25 (100%) patients in the control group had improved quality of life. However, only 8 (32%) were ready to recommend limited fasciectomy to their relatives in case of need, 12 (48%) patients were undecided, and 5 (20%) said they would not recommend this intervention to anyone. When asked about satisfaction with the choice of treatment method, 11 (44%) patients were dissatisfied. Disability in patients of the control group was 16 (12; 24.5) days.

When the postoperative wounds had healed, patients in the control group were concerned about the formation of postoperative scars, associated cosmetic defects and a feeling of tightness in the skin. However, in all cases, the functional effect achieved by the treatment was maintained. Thus, the recovery of patients after treatment with *Clostridium histolyticum* collagenase preparations was relatively rapid, and no serious complications were recorded. In contrast, recovery after surgical treatment was more difficult and lengthier.

Discussion

Over the past 10 years, a significant amount of data has been collected on various treatments for Dupuytren's contracture. Several literature reviews with meta-analyses were conducted to systematise this information. All of these reviews confirm the effectiveness of treatment with *Clostridium histolyticum* collagenase preparations compared to placebo.

In particular, M. Brazzelli *et al*. [11] conducted a meta-analysis of the results of five randomised clinical trials involving 493 patients. After treatment with *Clostridium histolyticum* collagenase preparations, the extension limitations caused by contracture were significantly reduced compared to the placebo group. It is clear that the number of side effects from the use of active drugs was higher than in the placebo group, but most of these symptoms were not serious. Out of 493 patients, only 4 (0.8%) experienced serious complications of the procedure: three cases of tendon rupture and one case of complex regional pain syndrome. This study did not directly compare *Clostridium histolyticum* collagenase preparations with placebo. However, the absence of serious complications confirms the meta-analysis data, which indicates that such complications are extremely rare and account for less than 1%. The clinical efficacy of injectable therapy with *Clostridium histolyticum* collagenase preparations is also confirmed by other systematic reviews of the literature with meta-analyses [12, 13].

E. Soreide *et al.* [14] analysed 20 clinical trials involving a total of 1584 patients to compare the effectiveness of three treatments for Dupuytren's contracture: percutaneous needle aponeurotomy, limited fasciectomy, and injection therapy with *Clostridium histolyticum* collagenase. The researchers concluded that injection therapy was better tolerated by patients compared to surgical treatments. However, it was found that patients treated with *Clostridium histolyticum* collagenase products had a significantly higher recurrence of Dupuytren's contracture compared to those who underwent percutaneous needle aponeurotomy. The authors also noted a higher incidence of adverse events after injection therapy compared to percutaneous needle aponeurotomy, although the incidence of adverse events compared to open fasciectomy was not investigated. The effectiveness in restoring the functional capabilities of the hand was approximately the same for all methods. Similar findings were obtained in a more recent meta-analysis by D. Obed *et al.* [15]. They also indicated a higher incidence of complications after the use of *Clostridium histolyticum* collagenase preparations compared to percutaneous needle aponeurotomy, although they did not investigate this in comparison with open fasciectomy. Among the side effects of treatment, local pain and swelling at the site of intervention were most often noted. Such symptoms were also noted in the study under review, but they did not pose a serious problem for patients, as they were short-lived and mild, especially in comparison with open fasciectomy, which is much more traumatic than percutaneous needle aponeurotomy.

Only two meta-analyses directly compared open fasciectomy and injection therapy with *Clostridium histolyticum* collagenase preparations. T.B. Cooper *et al.* [16] analysed 17 scientific publications that included 2142 joints in 1784 patients. The researchers concluded that both methods are equally effective. However, surgical treatment is accompanied by a significantly higher risk of complications, although it is associated with a lower likelihood of contracture recurrence.

R. Liechti *et al.* [17] analysing the results of 11 studies involving 1051 patients, also noted a higher likelihood of recurrence of Dupuytren's contracture after injection therapy compared to open fasciectomy. According to their results, the use of *Clostridium histolyticum* collagenase preparations increase the likelihood of contracture recurrence by 5 times compared to invasive intervention. Despite this, the data of R. Liechti *et al.* [17] indicate that the clinical efficacy of open fasciectomy is superior to injection therapy, although the data of the current study do not support this opinion.

A high relapse rate after injection therapy has been found in other studies. According to the results of the meta-analysis A.B. Sandler *et al.* [12], the probability of recurrence of Dupuytren's contracture within the next two years after injection therapy is about 23%. M. Brazzelli *et al.* [11] note that eight years after the use of *Clostridium histolyticum* collagenase preparations, recurrence is observed in 100% of cases. According to S. Nann *et al.* [18], the highest probability of contracture recurrence is observed between 2 and 5 years after the intervention. In this study, it was not possible to assess the recurrence rate due to the short follow-up period. However, the information on complications is consistent with the observations obtained in this study.

In terms of financial costs, therapy with *Clostridium histolyticum* collagenase preparations is more cost-effective than open fasciectomy, as highlighted by the findings of A.V. Fitzpatrick *et al.* [19]. The researchers acknowledge that in the case of severe contracture with severe functional impairment, invasive intervention is still a rational choice rather than injection therapy. On the other hand, M. Brazzelli *et al.* [11] believe that for patients with moderate functional impairment, injection therapy with *Clostridium histolyticum* collagenase preparations is both clinically and economically feasible.

A meta-analysis conducted by C.R. Wong *et al.* [20] investigated the treatment of recurrent Dupuytren's contracture. The researchers analysed 12 studies involving 311 patients who had undergone various treatments, such as percutaneous needle aponeurotomy, injections of *Clostridium histolyticum* collagenase drugs, fasciotomy or fasciectomy, and suffered from recurrent contracture formation. The study showed that none of these approaches is effective enough to treat recurrent Dupuytren's contracture. Therefore, given that none of the existing methods are ideal for preventing recurrence, it is important to find a treatment that minimises the likelihood of contracture recurrence. Currently, open fasciectomy is considered the most effective in preventing recurrence, but it has its drawbacks. Therefore, stratifying patients according to the risk of Dupuytren's contracture recurrence is a logical approach. Patients with a low risk of recurrence may be offered injection therapy, while patients with a high risk should be recommended for surgery.

The causes and risk factors for recurrence in patients with Dupuytren's contracture are not yet well understood. In 2018, an article by S. Hindocha [21] described the diathesis of Dupuytren's disease. Scientists have identified several phenotypic features that are associated with a more severe course of the disease, its faster development, and a higher likelihood of relapse after treatment. Among these features were a burdened family history, bilateral lesions, ectopic manifestations of Dupuytren's contracture, onset of pathology at the age of less than 50 years, and male gender. L. Geoghegan *et al.* [22] conducted a large meta-analysis that analysed 51 studies with a total of 54 491 patients. They confirmed that these phenotypic features are indeed associated with an increased risk of disease recurrence, although they do not affect the severity of the disease. Clinicians should consider these risk factors when providing patients with recommendations for the treatment of Dupuytren's contracture.

Conclusions

The study found that the treatment of Dupuytren's contracture with *Clostridium histolyticum* collagenase preparations is no less effective than open fasciectomy. The study demonstrated that even in cases where it is not possible to break the

fibrous cord after the first injection, the probability of clinically successful treatment with the second and third injections is high. According to the study, recovery after the use of *Clostridium histolyticum* collagenase preparations is much faster than after open fasciectomy. Patients do not need rehabilitation and do not lose their ability to work, which is especially important for young and middle-aged patients. In terms of cost-effectiveness, injection treatment is also superior to surgery, except in cases of severe Dupuytren's contracture, which was not the subject of this study. The study showed that after injection therapy, patients are significantly more satisfied than those who underwent surgery.

Since injection therapy involves a certain amount of tissue trauma caused by the rupture of the fibrous cord, pain and swelling of the hand are inevitable. However, the study confirmed that the duration of these symptoms is limited to a few days, and their severity is much less compared to pain and swelling after a full-fledged surgical intervention, such as open fasciectomy. According to the study, prolonged wound healing and cosmetic defects that occur after open fasciectomy are significant disadvantages of surgical treatment. A significant disadvantage of injection therapy is the higher recurrence rate of Dupuytren's contracture compared to open fasciectomy surgery. The highest risk of contracture recurrence is between two and five years after treatment. These data somewhat limit the possibilities of widespread use of *Clostridium histolyticum* collagenase preparations.

A promising area for further research is the identification of risk factors for the recurrence of Dupuytren's contracture. Preliminary data indicate that patients without a family history of contractures, with the onset of the disease in old age and with unilateral lesions have a lower risk of recurrence. In addition, it is necessary to find methods to prevent recurrence of Dupuytren's contracture after treatment.

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None.

Conflict of Interest

The author declares no conflict of interest.

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Контрактура Дюпюїтрена, що лікується колагеназою *Clostridium histolyticum*

Мартіна Відова Угурбаш
Доктор медицини, доцент
Університет Павла Йозефа Шафарика в Кошице
041 80, вул. Шробарова, 2, м. Кошице, Словацька Республіка
https://orcid.org/0000-0003-4620-6031

Анотація. Лікування контрактури Дюпюїтрена покращує якість життя пацієнтів, але стандартна відкрита фасціектомія є травматичною і вимагає тривалої реабілітації. Метою дослідження було визначити ефективність ін'єкційного лікування препаратами колагенази порівняно з відкритою фасціектомією. Обстежено сорок пацієнтів. З них 15 лікували препаратами колагенази *Clostridium histolyticum* (основна група), а 25 піддалися обмеженій фасціектомії (контрольна група). У 11 (73,3 %) хворих основної групи відновлення рухливості уражених суглобів досягнуто після першої ін'єкції, у 3 (20 %) – після другої і в 1 (6,7 %) – після третьої ін'єкції. Пацієнти основної групи залишалися працездатними після лікування і не потребували реабілітації; на день втручання функція верхньої кінцівки повністю відновилася. Сухість шкіри в місці втручання за період спостереження турбувала 12 (80 %) пацієнтів основної групи, свербіж та зміна кольору шкіри в місці втручання – 5 (33,3 %). У 25 (100 %) хворих контрольної групи повністю відновилася рухливість суглобів. Можливість користуватися рукою після операції у пацієнтів контрольної групи була обмежена протягом 6 (4,5; 10) днів. Усі пацієнти контрольної групи потребували реабілітації для зняття скутості та відновлення функціональних можливостей кисті. Термін непрацездатності у цих пацієнтів тривав 16 (12; 24,5) діб. 11 (44 %) пацієнтів під час спостереження скаржилися на біль або дискомфорт у ділянці втручання, 24 (96 %) пацієнтів турбував свербіж. Задоволеність вибором методу лікування в основній групі була більшою, ніж у контрольній. Рецидивів за період спостереження в обох групах не було. Таким чином, ефективність препаратів колагенази *Clostridium histolyticum* порівнянна з результатами хірургічного лікування. Малоінвазивне лікування оптимально для пацієнтів з легким перебігом захворювання, а також для тих, у кого низький ризик рецидиву контрактури. Результати цього дослідження можуть бути корисними хірургам при виборі оптимального методу лікування контрактури Дюпюїтрена

Ключові слова: долонний фіброматоз; малоінвазивне втручання; хірургія кисті; відкрита фасціектомія; клінічне дослідження; ведення пацієнтів

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Pharmacological and morphological features and socioeconomic aspects of cannabidiol: A literature review

Oles-Pylyp Hasiuk*
Doctor of Medicine, Senior Laboratory Assistant
Danylo Halytsky Lviv National Medical University
79010, 69 Pekarska Str., Lviv, Ukraine
https://orcid.org/0009-0007-9456-4526

Abstract. The relevance of detailed analysis of the available scientific research on the effects of cannabidiol on the human body is determined by the growing popularity of the non-psychoactive substance in cannabis products as a medicine. The research aimed to collect and systematise information about the positive and negative effects of cannabidiol, as well as the possibilities of its use in medicine. An analysis of 3375 scientific articles, publications and reports was conducted, of which 68 were selected that best met the terms of the request. The collected data was summarised and presented in a structured format. The results of the review indicate the remarkable pharmacological potential of cannabidiol, which can be used as a promising therapeutic agent in various medical fields. In the studies reviewed, cannabidiol showed anticonvulsant and antiepileptic effects, as well as a positive impact on drug substitution programmes. However, the possibility of negative reactions and potentially harmful effects of cannabidiol was also noted: it can lead to the development of psychological and physical dependence; increases the risk of physiological disorders, including the impact on spermatogenesis and disruption of the female microflora; affects behaviour and leads to developmental abnormalities. The effects of cannabidiol on the human body are still not well understood, and its distribution in the absence of sufficient legal regulation may pose a risk to the health and safety of consumers. Understanding all aspects of cannabidiol use will ensure proper management of its use and development of the relevant legislative framework, as well as facilitate further research and development of new drugs based on this plant extract

Keywords: cannabis; toxicology; law; epilepsy; chronic pain; generalised anxiety disorder

Introduction

Cannabidiol, as one of the active cannabinoids in cannabis plants, is finding more and more applications in medicine, but its potential benefits and impact on various aspects of human functioning remain a subject of debate in scientific circles. Data on cannabinol is contradictory, and its legality and safety are being questioned globally. Understanding the potential risks, side effects and interactions with other medicines is critical to ensuring the safety and efficacy of cannabidiol in clinical practice.

Many studies have already been conducted on the effects of cannabidiol on the human body. Since 2018, Ukrainian scientists have been actively working on this issue and have reached certain conclusions. For example, G.V. Zaychenko & P.V. Simonov [1] investigated the positive properties of cannabinoids associated with the activation of CB2 receptors. Activation of CB2 receptors had a cardioprotective effect, reduced cerebral ischaemia, suppressed inflammation, oxidative-nitrosative stress and cell death, slowed the progression of atherosclerosis and had a nephroprotective effect. By contrast, activation of CB1 receptors in vascular and cardiac tissues contributed to the development of cardiovascular disease through oxidative and nitrosative stress and protein kinase activation. B. Hinz & R. Ramer [2] also demonstrated the probable carcinogenic properties of cannabinoids, which showed carcinogenic effects both when used alone and in combination with

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*Corresponding author

other anticancer drugs. The authors noted that this area required further study. O. Sulaieva *et al.* [3] also found that CB2 receptors may be involved in the malignant transformation and progression of non-small cell lung cancer (NSCLC). However, some issues remained unexplored. For example, data on the effects of cannabidiol on the nervous system and its potential role in the treatment of mental and neurological diseases are limited.

Regarding the market of cannabinoids, and cannabidiol in particular, in Ukraine, scientists N. Aliekperova *et al.* have written [4]. Their study noted serious prospects for the development of the cannabidiol market in Ukraine. The authors pointed out that interest in cannabidiol products was growing, and this could create new opportunities for the development of the medical and pharmaceutical industries. According to the researchers, the Ukrainian market had significant potential for the production and consumption of cannabidiol-based products, including oils, creams, and other medicines. The authors also stressed that the development of the cannabidiol market could have a positive impact on the country's economy, providing new jobs, attracting investment, and stimulating the development of industries related to the production of cannabidiol products.

N. Aliekperova *et al.* [5] also studied the attitudes of Ukrainian pharmacists towards the legalisation of medical cannabis and cannabidiol-based products. The study showed that only half of the professionals supported the legalisation of these products. Other participants in the experiment expressed some doubts and reservations related to the safety, dosage, and quality of cannabidiol products. The safety of this plant extract has already been the subject of debate, and in some cases, its effectiveness has been questioned [6]. This indicated the need for further research to determine the efficacy and safety of cannabidiol in medicine. The purpose of this study was to review the pharmacological profile of cannabidiol and its effects on various body systems, as well as to consider possible mechanisms of action of this compound, especially in the context of the treatment of mental and neurological diseases.

In this study, a literature review of relevant scientific sources and publications was conducted through a systematic analysis of scientific sources to identify trends, develop key findings, and formulate scientific recommendations. Scientific databases such as PubMed, Google Scholar, Scopus, and Cochrane Database of Systematic Reviews were used to collect relevant scientific publications. The search for scientific sources was conducted using keywords related to the research topic, such as "cannabidiol", "cannabidiol toxicity", "cannabidiol treatment", "cannabidiol side effects", "cannabidiol pharmacy", "cannabidiol prevalence", "cannabidiol harm", "cannabidiol therapeutic properties", "cannabidiol marketing", "cannabidiol legal status".

The selected scientific sources were read in detail, critically comprehended, and analysed to collect information related to the research topic, and the quality of the sources was assessed, including verification of the authors' credibility, research methodology and availability of substantiated evidence. Key aspects, conclusions and recommendations related to the topic were identified. Data from scientific sources were organised and summarised for further analysis. Information from the sources obtained was systematised, summarised, and presented in the literature review.

Analysis of Chemical, Pharmacodynamic and Pharmacokinetic Features and Properties of Cannabidiol

Active research on cannabidiol began in 2016. The main topics investigated included cannabidiol's properties, its interaction with various drugs, pharmacological profile, health effects, etc (Fig. 1).

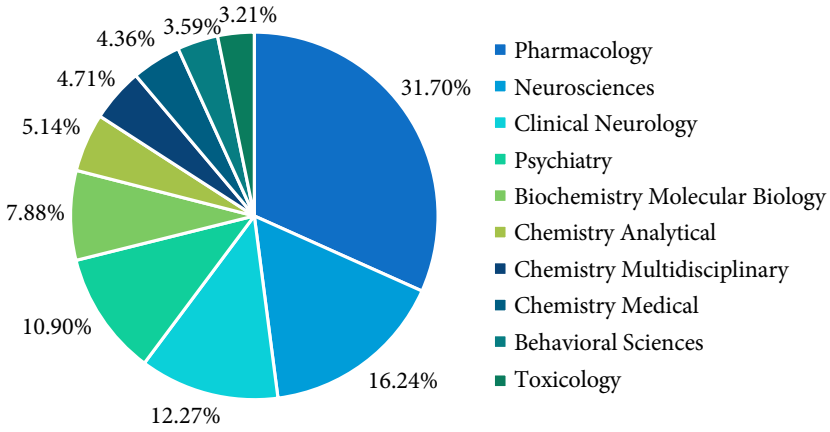
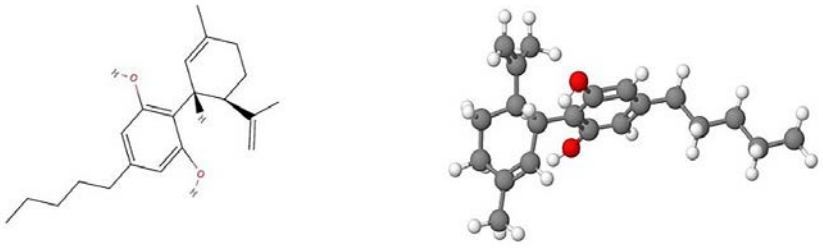


Figure 1. Visualisation of research areas on the effects of cannabidiol
Source: compiled by the author based on [7]

The results showed that cannabidiol was a complex research object that was studied concerning various aspects of health and disease. However, it was evident that the harmful effects and toxicity of cannabidiol were not sufficiently studied (only 3.21%), and therefore further research was needed [7].

The cannabis plant, "marijuana", or "cannabis" has been used for many years as a medicine to relieve pain and

seizures. Cannabis contains approximately 540 naturally occurring compounds, including more than 100 that have been identified as phytocannabinoids due to their common chemical structure [3]. The predominant psychotropic component is Δ9-tetrahydrocannabinol (Δ9-THC), while the main non-psychoactive ingredient is cannabidiol (CBD). These compounds are partial agonists or antagonists of the prototypical cannabinoid receptors, CB1 and CB2. Δ9-THC and CBD can act as analgesics, antiemetics, anti-inflammatory agents, anticonvulsants, and as protective agents against neurodegeneration. However, there has been a lack of well-controlled, randomised clinical trials to provide evidence of the effectiveness of Δ9-THC or CBD as therapeutic agents, as well as to fully understand their effects on the human body. The legalisation of cannabis for medicinal and recreational use in some regions would allow for the necessary research on its pharmacokinetics and pharmacology [8]. Particular attention has been paid to the non-psychoactive substance in cannabis products – CBD. CBD was first isolated from cannabis extracts by R. Adams *et al.* in 1940 [9]. Cannabidiol is a cyclohexene substituted with a methyl group at position 1, a 2.6-dihydroxy-4-pentylphenyl group at position 3, and a prop-1-en-2-yl group at position 4 (Fig. 2).



a b

Figure 2. Molecular structure of cannabidiol
Notes: a – structural model; b – 3D model of a structure
Source: [10]

At room temperature, cannabidiol is a colourless crystalline solid [11]. In the industry, cannabidiol can be produced in dry form, oil, capsules, and supplements. M. Premoli *et al.* [12] report that cannabidiol has a low ability to bind to the CB1 and CB2 cannabinoid receptors, although it acts as an agonist/antagonist of these receptors. The main effect of CB1 and CB2 receptor antagonism is to reduce the binding capacity of tetrahydrocannabinol (THC) and its related isomers [13]. T. Bosquez-Berger *et al.* [14] also studied its ability to exhibit partially antagonistic properties to serotonin receptors. Cannabidiol is also an allosteric opioid receptor modulator. The pharmacological effects of CBD may include peroxisome proliferator-activated receptor (PPARγ) agonism, inhibition of voltage-dependent cation channels, and intracellular calcium release [15].

L.J. Martin *et al.* found [16] that cannabidiol has a multifaceted pharmacology due to its ability to bind to cholesterol on the cell membrane. The oral bioavailability of cannabidiol in humans is approximately 6%, while its inhalation bioavailability ranges from 11 to 45% (average 31%) [17]. The half-life of CBD is 18-32 hours [18]. Studies conducted by G. della Rocca *et al.* [19] showed that when CBD was taken in capsule form, the peak concentration (Cmax) was reached 4-5 hours after ingestion. But if CBD was consumed in the form of oil, the Cmax was reached much faster – in 1-2 hours. At the same time, the use of oil provided a higher bioavailability of CBD compared to capsules. Cannabidiol was absorbed more rapidly by inhalation than by ingestion (maximum concentration – Tmax – was 5 minutes, respectively) [20]. Plasma CBD concentrations showed a nonlinear increase with dose and 6.5% bioavailability at a dose of 3000 mg. The absorption of CBD increased threefold with a high-fat meal, indicating the accumulation of CBD in body fat tissue. CBD is not able to be absorbed in the oral epithelium or absorption is limited, instead, the main absorption of the substance occurs in the gastrointestinal tract [19]. Cannabidiol is metabolised in the liver and intestine by cytochrome P450 enzymes CYP2B6, CYP2C19, CYP2D6, CYP2J2 and CYP3A4, as well as by isoenzymes UGT1A7, UGT1A9 and UGT2B7, forming various metabolites [21]. CBD metabolism is very complex, especially in hepatocytes (Fig. 3).

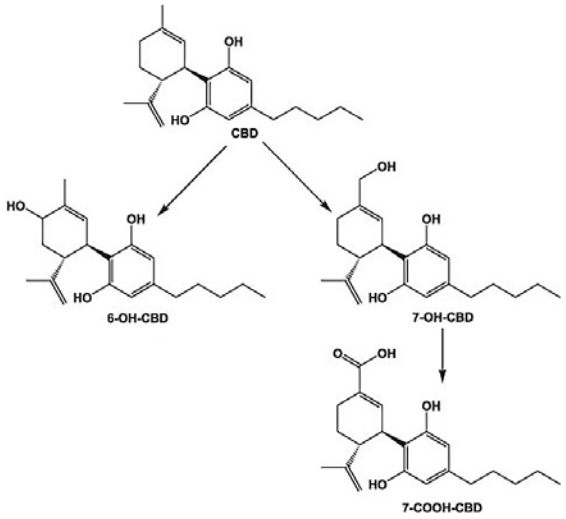


Figure 3. CBD metabolism in a liver
Notes: CBD – cannabidiol

The main human metabolite is 7-carboxycanabidiol (7-COOH-CBD; ~90% of all measured in plasma) [22], as well as 6α- and 6β-hydroxyisomers and derivatives hydroxylated on the alkyl side chain with subsequent glucuronidation. In general, Q. Rao *et al.* [23] identified 24 CBD metabolites in the liver. The main concern with 7-COOH-CBD was its reactive acyl glucuronide. CBD is excreted from the body in faeces (84%) and also in urine (8%) [24]. This indicates that the main route of elimination of CBD is through the intestine, which may affect the efficiency of its pharmacokinetics and the possibility of accumulation in the body with prolonged use.

Cannabidiol interacts with a variety of neurotransmitter systems, including serotonin and opioid receptors, which can affect a variety of aspects of neural activity and body physiology. Regarding serotonin receptors, some studies indicate that CBD can interact with 5-HT1A receptors, which are responsible for controlling mood, sleep, and other mental functions [6, 12, 24]. This may partially explain the anxiolytic (anti-anxiety) and antineuropathic properties of CBD. Experiments [13, 15, 17] have demonstrated the effect of CBD on other serotonin receptors, which can affect various aspects of mood and mental state. Regarding opioid receptors, there is some evidence to suggest that CBD may interact with the body's opioid systems. Studies have shown that CBD can affect the activity of opioid receptors, causing a reduction and presentation of pain [17, 18]. However, the mechanisms of this interaction are not yet fully understood and require further study. In general, the interaction of cannabidiol with these neurotransmitter systems shows that CBD can have a complex effect on nervous activity, mood, pain, and other physiological processes in the body [6].

Allosteric modulation of opioid receptors opens up interesting opportunities for the development of new approaches to the management of pain and other conditions associated with the opioid system. This could lead to an increase in the effectiveness of opioid therapy, providing more intense analgesia with lower doses of opioids. As noted by R.A. Vlad *et al.* [24], it is possible to reduce side effects associated with opioid therapy, such as constipation and respiratory depression. Allosteric modulators can slow down the development of opioid tolerance, make opioid therapy more individualised, and reduce the risk of psychological and physiological dependence. Allosteric modulation of opioid receptors can affect biological systems in various ways. According to studies [23, 24], this process can lead to an increase in the analgesic effect of opioid drugs and provide more effective pain control. At the same time, it is possible to reduce the dose of opioids, which can reduce the risk of side effects and the development of drug tolerance. Another important aspect is the ability of allosteric modulation to minimise the adverse effects associated with opioid therapy, such as respiratory depression and constipation. Additionally, the use of allosteric modulators may reduce the risk of opioid dependence due to the ability to achieve the desired effect at lower doses. Cannabidiol is one of the main non-psychoactive components of cannabis. It interacts with various receptors and neurotransmitter sys tems, exhibiting potential therapeutic properties. Cannabidiol is metabolised in the liver to form various metabolites and is primarily excreted in the faeces. Studies of the pharmacokinetics and pharmacodynamics of cannabidiol are important for understanding its effects and developing optimal patterns of use.

Legal Status, Prevalence and Potential Impacts of Cannabis

The legal status of CBD varies by country and jurisdiction. In some countries, such as Canada and some US states, legislation has allowed the use of marijuana and its constituents, including CBD, as a medicinal product [25]. In the European Union, CBD was classified as a "novel food substance", which meant that it had to be registered and approved before being used in food [26]. In many other countries, such as Australia, Japan, and Singapore, CBD has not yet been legal, regardless of its use as a medicinal product or in food [27]. Some countries only allow the use of CBD if it contains less than 0.2-0.3% of the psychoactive substance found in marijuana (THC) [25]. Internationally, CBD is not under the control of the United Nations (UN) on Narcotic Drugs and Psychotropic Substances because it has no psychoactive properties and does not cause a narcotic effect [27]. On 7 April 2021, the Ukrainian government legalised the use of isolated cannabidiol [28]. Thus, the legal status of CBD has been constantly changing, and different countries have taken different approaches to regulating its use.

CBD-based products were distributed across European countries with different legal statuses. The expected effect of CBD use depended on social status. For example, people with lower incomes reported improved well-being and reduced anxiety and stress [27]. At the same time, the use of cannabidiol by people with a higher level of education was associated with a desire for increased concentration and headache relief [27]. Thus, it could be argued that CBD products were widespread among different segments of the population. This was facilitated by the availability and variety of products. The main way of distributing CBD was through the Internet (64%), where it was easy to order and deliver goods without proper age verification, and the number of stationary sales shops and pharmacies was also increasing, with a 17% share of sales, with the rest of the turnover carried out by shadow and unregistered outlets [29]. In most countries, the laws governing the use of CBD were not clear, thus turning it into an unregulated sector [30]. Despite a ruling by the Court of Justice of the European Union stating that CBD was not a drug, its status remained unclear [31]. Part of the reason for the tightness of the legal framework was due to insufficient research on the effects of CBD-based products on the human body, which created room for further research and a phased study of the effects of CBD in different population groups. The main regions of distribution of cannabidiol were North America and Europe, and to a lesser extent Latin America, Asia, the Middle East, and Africa (Fig. 4).

Figure 4. Global cannabis market outlook for 2024

Source: [32]

The first innovative companies for the industrial production and distribution of cannabis products received a total of $128.5 million in investment [32]. The investment market in this sector continued to grow. A recent report by the Centre for Medical Cannabis estimated that 8-11% of European adults have tried CBD for various purposes [33]. The size of the global cannabidiol market in 2023 was estimated at USD 9.4 billion (Fig. 5).

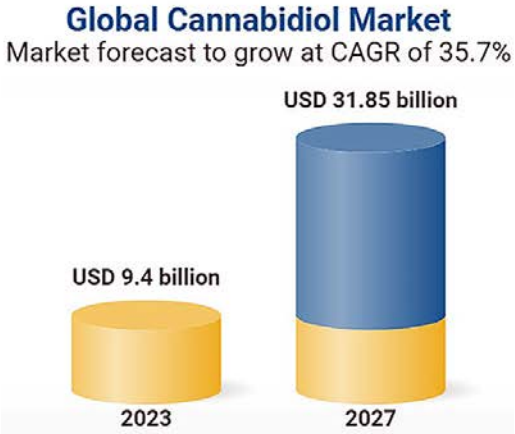


Figure 5. Global market value and revenue forecast for 2027

Source: [34]

The scientific community has shown interest in the chemical compound cannabidiol due to its positive effects and neuroprotective properties in several neurodegenerative diseases, including amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, and Alzheimer's disease [10]. According to the findings of R. Kaufmann *et al.* [35], improved well-being was highlighted as the main reason for CBD use among a relatively healthy population. Reduced anxiety, improved sleep, and reduced stress were also described as the most expected effects of CBD. This study included a sample of 469 in patients who were treated as inpatients. Overall, 33.3% of patients reported using CBD, with the most common uses being to reduce anxiety (52.4%), improve insomnia symptoms (33.3%), and reduce pain (23.8%). The majority of patients (61.9%) said that CBD use did not affect their substance dependence, but some (16.7%) reported that CBD use helped them reduce their use of other substances [36].

CBD has also been used in treatment programmes for other drugs and alcohol addiction [37]. As CBD has demonstrated many therapeutic effects in neural circuits involved in the development of drug addiction and drug-seeking behaviour, it has become a promising candidate for the treatment of substance abuse disorders. Studies have shown that CBD reduced the drive to obtain amphetamine and prevented its recurrence in rats

that had previously been trained to find amphetamine independently [38]. In addition, it was found that CBD modulated D1- and D2-receptor levels in the mesocorticolimbic areas of the rat brain. This indicated that CBD could be a potential treatment for drug addiction, in particular, to prevent the recurrence of drug seeking [39]. As a result of the experiment by K. Nouri *et al.* [40] proved that cannabidiol reduced intrusive drug-seeking thoughts using dopaminergic receptors in the nucleus accumbens. The results also indicated the potential benefit of CBD to reduce inflammation in people with cocaine use disorder. The interaction between cannabidiol and the CB1 receptor could be an important factor in the treatment of cocaine dependence. A CB1 receptor antagonist could reverse the effectiveness of CBD in reducing cocaine seeking [41]. Y. Qian *et al.* [42] found that cannabidiol reduced cocaine withdrawal symptoms and craving, and improved cognitive function and mood in mice. The possibility of using cannabidiol and its analogues as an alternative treatment for pain and prevention of opioid abuse in rats [43], gambling and behavioural addiction [44] has also been identified. A recent double-blind, randomised study by R.M. Vitale *et al.* [38] reported the effect of reducing cravings and drug-induced anxiety in people with heroin use disorder. The legal status of cannabidiol varies in different countries and jurisdictions. CBD-based products are common among different segments of the population. Cannabidiol is being researched as a potential remedy for a variety of conditions, including anxiety, insomnia, pain, and the treatment of drug and alcohol addiction.

Cannabidiol Toxicity and Side Effects: A Review of Studies on the Effects on the Body

A significant claim is that cannabidiol can alter the liver metabolism of other drugs, making them ineffective or toxic [42]. Cannabidiol both metabolises and inhibits the cytochrome P450 enzyme pathway, in particular CYP2C19 and CYP3A4. Cannabidiol has been reported to cause significant increases in the serum levels of other drugs metabolised through this pathway, such as macrolide antibiotics [39]. Given that other common medications are also metabolised through this pathway, the greatest danger of cannabidiol may not have been its direct side effects, but rather the inhibition of metabolic pathways in the liver, which could have caused significant drug interactions. The concomitant use of cannabidiol and methadone led to a marked increase in serum methadone levels, most likely due to cannabidiol-induced inhibition of the CYP isoenzyme [45]. Studies have shown that the simultaneous use of cannabidiol and antibiotics in rats increased the area under the concentration-time curve (AUC) of the antibiotic, indicating an increase in its bioavailability [46]. In addition, cannabidiol reduces the excretion of the antibiotic from the blood plasma, which could lead to an increase in the toxicity of this drug.

In clinical trials of the only certified cannabidiol-based drug (EPIDIOLEX), using the maximum recommended maintenance doses, significant increases in liver to body weight (LBW), plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin were observed. CBD increased the ratio of LBW, ALT, AST, and total bilirubin [45]. Hepatotoxicity gene expression arrays showed that CBD differentially regulated more than 50 genes, many of which were associated with oxidative stress responses, lipid metabolism pathways, and drug-metabolising enzymes [46]. CBD has also shown clear signs of hepatotoxicity, possibly of a cholestatic nature. The involvement of numerous pathways related to lipid and xenobiotic metabolism has raised serious concerns about potential drug interactions as well as the safety of CBD itself [47]. Another study demonstrated an interaction between cannabidiol and plasma biological parameters [48], where the average daily dose of CBD was 50.3 mg, and the prevalence of elevated ALT was 9.1%, AST 4.0%, alkaline phosphatase 1.9%, and total bilirubin 1.7%.

Women might have a higher risk of side effects and other responses to CBD therapy compared to men [49]. Subsequent studies have also noted an effect on spermatogenesis. Thus, treatment with 0.5 μM CBD significantly reduced sperm concentration [50]. Mice exposed to CBD showed a decrease in the size of the seminiferous tubules, a narrowing of the diameter of the tubular lumen in these tubules, and a reduction in the height of the seminiferous epithelium. In an experiment conducted by R.K. Carvalho *et al.* [51], sperm DNA damage worsened, the activity of the antioxidant enzyme SOD in sperm decreased, the percentage of motile elements decreased significantly, and more abnormal shapes were found. Another study reported that oral administration of 30-300 mg/kg body weight/day of CBD for 90 days caused a decrease in testicular size and inhibition of spermatogenesis [47]. 30 mg/kg body weight/day of CBD administered orally for 34 consecutive days, followed by a 35-day recovery period, caused a decrease in Sertoli cells, abnormal sperm morphology, and decreased plasma testosterone levels. Z. Pandelides *et al.* [50] found the effect of CBD on the development of Dario fish. It was noted that cannabidiol had a significant effect on larval behaviour and developmental abnormalities. During development, CBD caused significant adverse effects at both the cellular and tissue levels of the organism. Based on the molecular changes observed in this study, the authors identified the main pathways of CBD toxicity, such as binding of Cnr1, Cnr2 and/or PPAR receptors and alteration of metabolic pathways (e.g., retinol) (Fig. 6). The oral route of administration of CBD products is one of the most common. CBD can transform in the acidic environment of the stomach to THC. This conversion was found in studies with gastric fluid modelling (Fig. 7). CBD is a compound rich in pharmacological interactions. The most commonly reported results are neurological, carcinogenic and drug interactions (Fig. 8).

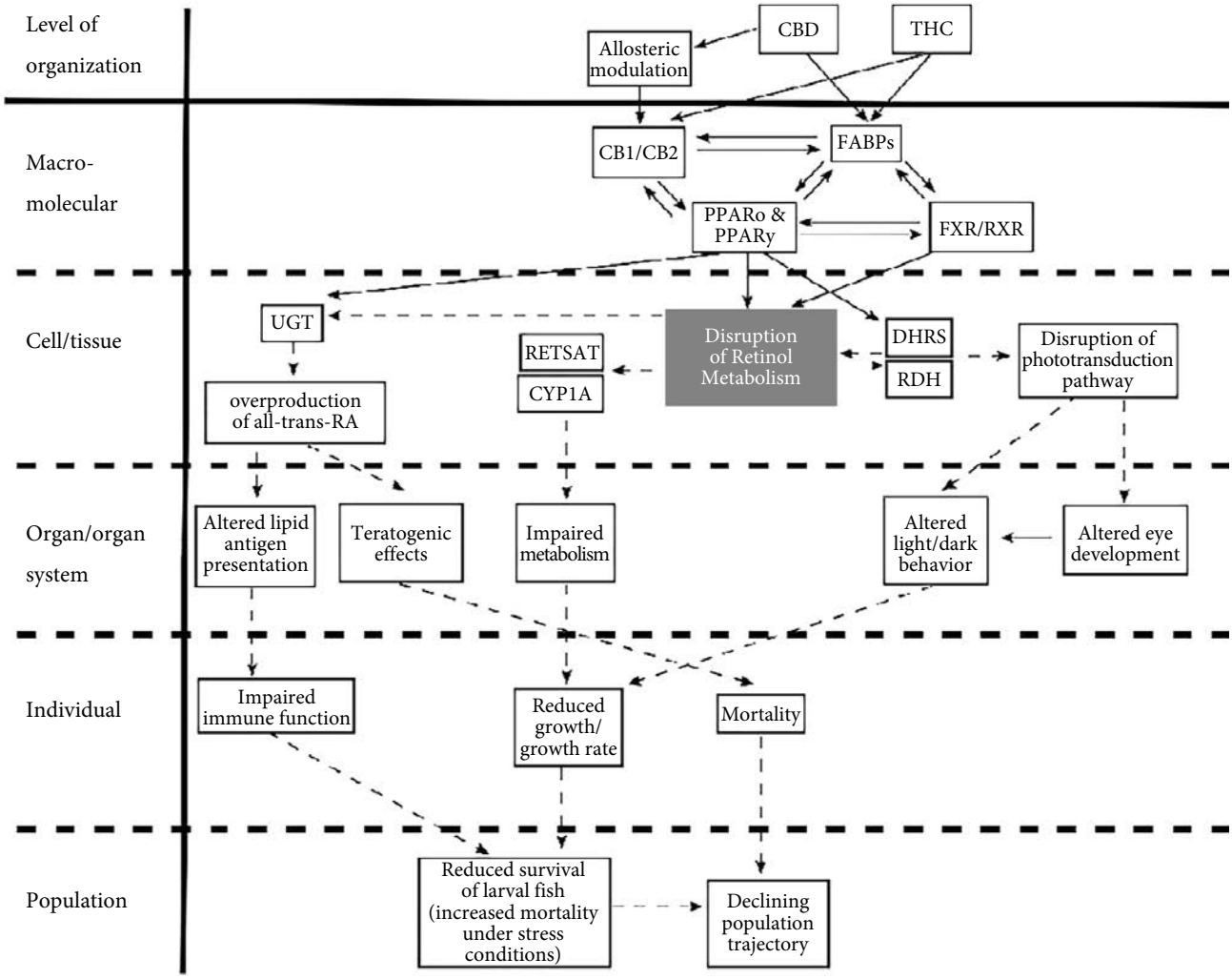


Figure 6. Potential adverse effects of cannabinoid toxicity

Notes: continuous lines with arrows indicate known linkages, while dashed lines with arrows represent likely pathways of adverse effects; CBD – cannabidiol; THC – tetrahydrocannabinol; CB1/CB2 – cannabinoid receptors; FABP – fatty-acid-binding proteins; PPAR – peroxisome proliferator-activated receptors; FXR/RXR – farnesoid X receptor/retinoid X receptor; UGT – UDP-glucuronosyltransferase; RETSAT – retinol saturate; CYP1A – cytochrome P450 1A; DHRS – dehydrogenase; RDH – retinol dehydrogenase

Source: [52]

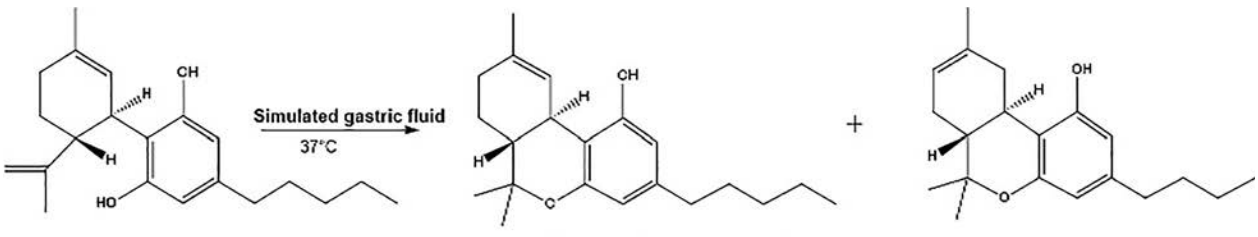


Figure 7. Psychoactive products of acid-catalysed cyclisation of cannabidiol in the presence of simulated gastric fluid at 37°C

Source: [53]

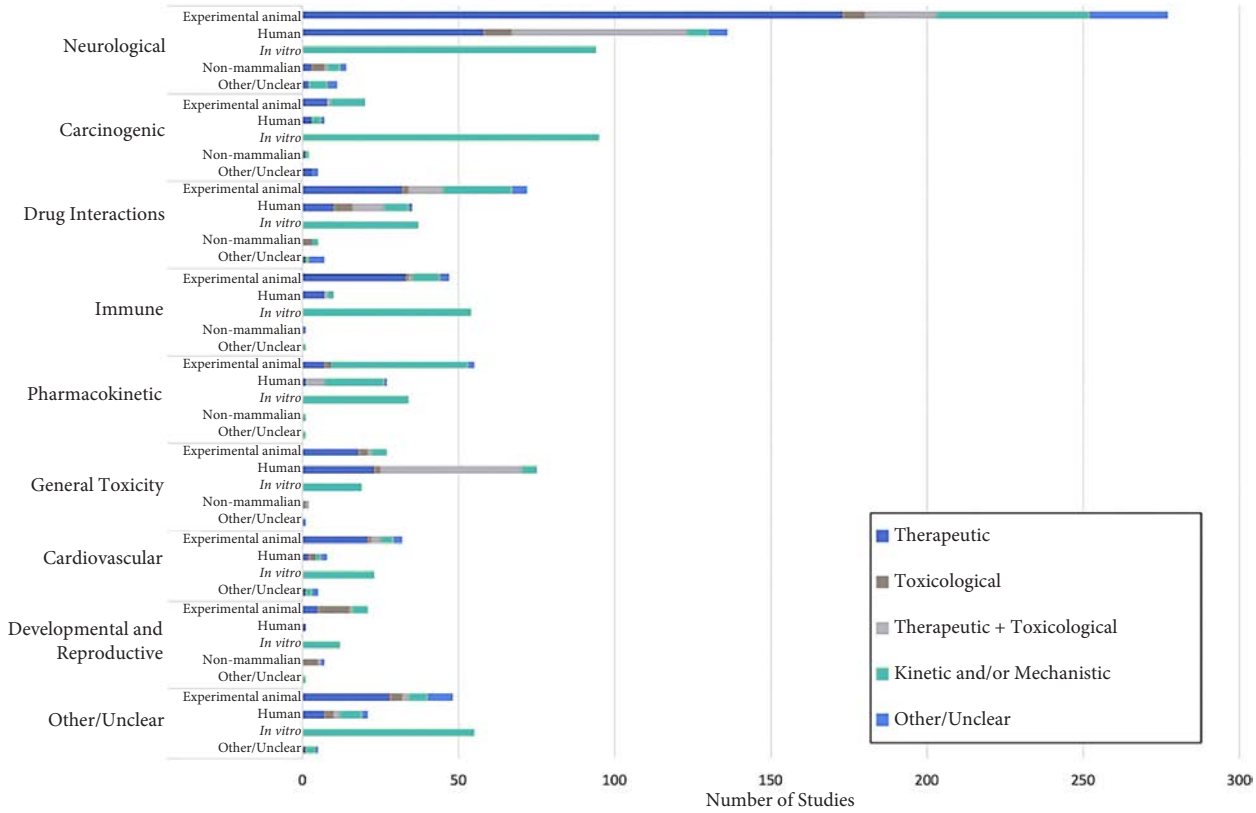


Figure 8. Studies on the safety of cannabidiol

Source: [54]

Cannabinoids have been linked to multiple types of cancer. The use of cannabidiol plant material and liquid extracts has been associated with an increased risk of prostate cancer [55]. Testicular cancer was found to be most strongly associated with cannabis exposure. The area under the cumulative exponential E-Value curve for tobacco, alcohol use disorders (AUD), cannabis, THC, cannabidiol, cannabichromene, cannabinol, and cannabigerol was 34, 32, 13, 0, 103, 58, 25, 31, indicating that cannabidiol was most involved in carcinogenesis [56]. Another effect of CBD was observed in the excretory system. Participants without chronic kidney disease (CKD) who consumed cannabidiol had a faster decline in glomerular filtration rate [57]. Despite its anti-inflammatory properties, B. Carmona-Hidalgo *et al.* [58] found that CBD worsened diabetic nephropathy and led to an earlier end-stage renal disease in a mouse model.

To exploit the full potential of cannabidiol's therapeutic value, pharmaceutical companies have been working to create new forms of cannabinoids with reduced side effects and toxicity. One of them was a method of producing a new cannabinoid, 8.9-dihydrocannabidiol (8.9-DHCBD). The antibacterial and antioxidant properties of the substance were studied. The results of the study showed that 8.9-DHCBD had strong antibacterial activity against some strains of bacteria that are pathogenic to humans, as well as significant antioxidant activity. The authors of the article argued that 8.9-DHCBD could have potential applications as a new natural antibiotic and antioxidant [59].

On the other hand, it is worth noting that most of the statements about the positive and beneficial effects of using CBD-based products have avoided the issue of the effects on the body and the consequences of use. J.A. Crippa *et al.* [60] have proposed CBD as a promising therapeutic tool to overcome several clinical problems. Since 2001, more than two hundred clinical trials have focused on the use of CBD for the treatment of seizures, cancer, post-traumatic stress disorder, and other health problems [61]. The evidence of a positive effect on anxiety, depression, sleep disorders or other psychological conditions is limited and contradictory and was mostly based on subjective testimonies of the subjects [62]. It is also worth noting that according to the European Food Safety Authority (EFSA) statement on the safety of cannabidiol as a novel product, based on an assessment of the available data, there are uncertainties in the data on the safety of cannabidiol as a novel product [63].

CBD and CBD-containing products have been growing quantitatively in markets around the world, yet despite their high popularity among consumers, knowledge about the negative effects of CBD-containing products remained limited. Accumulating evidence indicated that CBD when administered in clinically relevant doses or over a long period, had a significant potential for hepatotoxicity, as well as for interactions with various conventional medications [64]. The US Food and Drug Administration (FDA), while acknowledging the potential benefits of CBD, also argued that questions remained about its safety, including the

potential for liver damage [65]. Another significant claim was that cannabidiol could alter the liver metabolism of other drugs, making them ineffective or toxic [66].

Among natural extracts from cannabis plants, synthetic analogues of CBD have also gained popularity on the market and have been actively used in e-cigarettes. Numerous cases in 2012 linked synthetic cannabinoids to acute kidney injury [67, 68]. In particular, nephrotoxicity could be associated with an effect on proximal tubular mitochondrial function. Renal biopsies in such cases most often demonstrated acute tubular necrosis, with some cases of acute interstitial nephritis [67]. In the context of e-cigarettes used to heat CBD oil, an important aspect is the prevalence of E-cigarette or Vaping Use-Associated Lung Injury (EVALI). This syndrome has a significant association with the use of vaping products with cannabidiol, in particular CBD. The study selected seventeen international cases from 13 countries for analysis [68]. Countries outside the US had more men in the cohorts (76% compared to 58-83%), and the average age of patients from these countries was slightly higher (31 years compared to 27, 19, and 27 years). The use of nicotine/flavoured e-liquids was more common among patients outside the US (100% vs. 58-67%), and the use of cannabinoid-based products was less common (24% vs. 78-92%) [68]. Cannabidiol has potential side effects and toxicity. It can interact with other drugs, inhibiting their metabolism in the liver. Hepatotoxicity, nephrotoxicity, and reproductive toxicity of cannabidiol have been observed. Its conversion to psychoactive substances in the stomach and its association with certain types of cancer is a concern. However, evidence for positive effects is often contradictory and limited.

Conclusions

Cannabidiol, as one of the active cannabinoids contained in cannabis plants, is gaining increasing recognition in medical practice. However, its potential benefits and effects on various aspects of human body functioning continue to be the subject of debate in scientific circles. In this study, the main focus was on a thorough analysis of the therapeutic properties of cannabidiol, as well as the study of possible negative effects and toxicity associated with its use. Additionally, the relevance of CBD as a chemical compound in the modern global market was studied and the main areas of its application were identified. The data obtained in the course of the study revealed a significant interest of the scientific community in this complex compound.

The features and properties of cannabidiol as one of the main components of cannabis, which affects the body through interaction with receptors and neurotransmitter systems, have been studied. It has a complex metabolism in the liver and is mainly excreted in the faeces. Cannabidiol affects serotonin and opioid receptors, which opens up prospects for the treatment of pain and other conditions. Even though CBD-based products have been legalised by regulators in the United States and Europe, there have been legitimate concerns about possible negative effects on the body. There was considerable ambiguity in the views and opinions on cannabidiol. At the same time, it is important to note that its use as a therapeutic agent is widespread in neurology, psychiatry, addiction medicine and palliative care. After analysing the results, some major concerns were identified about the possible negative effects of cannabidiol on the body. The main ones included the issues of hepatotoxicity, possible carcinogenicity, impact on reproductive health, possible adverse reactions, and possible interaction with other medicines. It is important to note that at the time of the study, information on the impact of cannabidiol on certain body systems, such as the excretory, immune, and cardiovascular systems, remained insufficiently studied.

Further scientific research is needed to fully unlock the potential of cannabidiol and objectively assess its benefits and risks. Topics for further research may include an analysis of the comprehensive effects of cannabidiol on the body and a general overview of its mechanism of action. Particular attention should be devoted to the interaction of cannabidiol with other drugs and its effect on various body systems. It is important to note that the effective and safe use of cannabidiol can play an important role in improving the quality of life of patients, but this requires in-depth study and proper regulation of its use in medical practice.

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Conflict of Interest

The author declares no conflict of interest.

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Фармако-морфологічні особливості та соціально-економічні аспекти канабідіолу: огляд літератури

Олесь-Пилип Ігорович Гасюк
Доктор медицини, старший лаборант
Львівський національний медичний університет імені Данила Галицького
79010, вул. Пекарська, 69, м. Львів, Україна
https://orcid.org/0009-0007-9456-4526

Анотація. Через зростаючу популярність непсихоактивної речовини продуктів коноплі як лікувального засобу, необхідно було провести детальний аналіз наявних наукових досліджень з теми впливу канабідіолу на людський організм. Метою цього огляду був збір та систематизація інформації про позитивні та негативні впливи канабідіолу, а також про можливості його використання в медицині. Проведений аналіз 3375 наукових статей, публікацій і звітів, з яких відібрано 68 тих, що найбільше відповідали умовам запиту. Зібрані дані були узагальнені і представлені в структурованому форматі. Отримані результати огляду вказують на значний фармакологічний потенціал канабідіолу, який може використовуватися, як перспективний терапевтичний засіб у різних медичних сферах. В розглянутих дослідженнях канабідіол виявляв протисудомний, протиепілептичний ефект, а також позитивний вплив в програмах заміни наркотичних речовин. Проте також було відзначено можливість негативних реакцій та потенційно шкідливого впливу канабідіолу: може призводити до розвитку психологічної та фізичної залежності; підвищує ризик розвитку фізіологічних порушень, зокрема вплив на сперматогенез та порушення жіночої мікрофлори; впливає на поведінку та призводить до відхилень у розвитку. Дія канабідіолу на організм людини досі залишається недостатньо вивченою, а його розповсюдження в умовах недостатнього законодавчого регулювання може чинити ризик для здоров'я та безпеки споживачів. Розуміння всіх аспектів використання канабідіолу забезпечить належне управління його використанням і розвитком відповідної законодавчої бази, а також сприятиме подальшому вивченню та розробці нових препаратів на основі даного рослинного екстракту

Ключові слова: канабіс; токсикологія; право; епілепсія; хронічний біль; генералізований тривожний розлад

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Hemodynamic features of pregnant women with atrial septal defect in the third trimester of pregnancy: A literature review

Serhii Nakonechnyi*
PhD in Medical Sciences, Associate Professor
Zaporizhzhia State Medical and Pharmaceutical University
69035, 26 Maiakovsky Ave., Zaporizhzhia, Ukraine
https://orcid.org/0000-0002-1087-9659

Iryna Sokolovska
PhD in Medical Sciences, Assistant Professor
Zaporizhzhia State Medical and Pharmaceutical University
69035, 26 Maiakovsky Ave., Zaporizhzhia, Ukraine
https://orcid.org/0009-0008-2487-1675

Iryna Hanzhyi
Doctor of Medical Sciences, Professor
Zaporizhzhia State Medical and Pharmaceutical University
69035, 26 Maiakovsky Ave., Zaporizhzhia, Ukraine
https://orcid.org/0009-0008-2490-5222

Abstract. Due to the decline in mortality rates among children with heart disease, a significant number of such children have reached reproductive age. However, since knowledge about the impact of pregnancy on haemodynamics in women with heart disease is limited, this study is extremely relevant. The study aimed to provide a comprehensive review of current scientific sources and consolidate the knowledge gained on haemodynamic features in pregnant women with atrial septal defects. Several methods were used in the study: analysis, including comparative analysis, synthesis, bibliography, systematisation, and categorisation. A two-stage approach in the form of a systematic literature review was also used. The complex haemodynamic changes that occur in pregnant women, both in normal and pathological conditions, in particular in pregnant women with atrial septal defect, are considered. The question is specified as to why hemodynamic changes become most significant in the third trimester of pregnancy, their impact on the course of pregnancy, and the outcome of labor completion. The topic of acute and chronic complications of atrial septal defect and modern principles of their prevention and treatment are covered. Special attention is paid to the methods of correction of this heart defect, considering their advantages, disadvantages and possible complications. The experience of perinatal centres in several European countries in managing pregnancies in women with cardiovascular disease, in particular with atrial septal defects, is reviewed. Gaps in knowledge about the prevalence of these defects and risk factors were filled. The study addressed the lack of a comprehensive view of this problem: from pathophysiological basis and epidemiology to treatment and modification of risk factors. The study is of great practical value for healthcare professionals, as it can serve as a basis for the development of preventive programmes and other interventions for pregnancies of women with congenital cardiovascular disease

Keywords: congenital malformations; gestation; cardiovascular complications; risk factors; open oval window; pulmonary hypertension

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*Corresponding author

Introduction

Maternal and child health is one of the most important aspects of health care, both at the individual and population levels, as it largely shapes the health of the nation. In this context, congenital malformations (CM) are of particular importance, which is directly related to the significant share of this group of pathologies in the structure of morbidity and mortality in the neonatal period. Healthcare professionals often consider the CM issue in the short term, neglecting the long-term consequences, such as the development of chronic diseases and a deterioration in quality of life. Congenital heart disease (CHD) accounts for the largest share of the CM structure, including pathologies that are accompanied by a violation of the integrity of the heart chambers, such as atrial septal defects (ASD). Modern methods of early diagnosis and treatment can largely avoid the consequences in the short term, which leads to a reduction in neonatal mortality. This allows a significant proportion of patients to reach reproductive age. It is during this period that the long-term CM consequences, including CHD, come to the fore, which causes the problem of pregnancy management with this comorbidity, as gestation is a significant risk factor for decompensation of heart disease. The main problem with past studies on this topic was their narrow focus, with researchers looking at the problem from a particular part of it, such as epidemiology or pathophysiological aspects of haemodynamic changes. As scientific materials were accumulated, it became necessary to form a comprehensive and comprehensive view of the problem.

This issue was discussed by Ukrainian researchers on several occasions. As such, V. Yaroslavskyi & Yu. Tsysar reviewed the general theoretical basis of the problem, superficially touching upon the epidemiology and clinical CHD manifestations [1]. Hemodynamic changes during pregnancy in healthy women and those with CHD were also highlighted, especially in the third trimester of pregnancy, as this period is characterised by the greatest hemodynamic changes. S. Triska *et al.* highlighted the practical aspects of pregnancy management in women with CHD, also devoting a separate paragraph to acquired heart disease [2]. The authors emphasised the importance of risk stratification in all pregnant women, and the order and stages of their hospitalisation in healthcare facilities, depending on the identified risk group. I. Kravchuk *et al.* focused on the impact of acquired heart disease on pregnancy, particularly in women with thrombophilia, leaving aside aspects of congenital heart disease [3]. Scientists have noted that haemodynamic disorders that occur in pregnant women with heart disease significantly increase the risk of complications such as weakness of labour, bleeding, and newborn asphyxia. In particular, the study found that thromboembolic complications were the most dangerous. V. Kryvetskyi *et al.* noted that some CHD, even despite advances in modern diagnostic technologies, may remain undetected for long periods, especially in the case of ASD, as some types of this defect are not accompanied by significant haemodynamic disorders in physiological conditions [4]. In some cases, ASD is manifested during pregnancy, due to increased haemodynamic changes in the third trimester of pregnancy. T. Shevchenko *et al.* emphasise that computed tomography is the most optimal method for the effective diagnosis of ASD, although this method is not as widely used in this area as, for example, ultrasound methods [5]. It is important to note that this method has certain limitations in terms of availability and a certain group of contraindications, which also leads to the predominant use of other methods of instrumental research to detect ASD. This, in turn, can lead to undiagnosed haemodynamically insignificant defects. Late detection of ASD can pose risks to pregnancy.

Thus, given the medical and social significance of this problem, the aim of this study is a comprehensive review of the literature and consolidation of existing knowledge on the features of haemodynamics in pregnant women with ASD, especially in the third trimester of gestation and clinical manifestations of the identified disorders. Additional tasks include studying the epidemiology of CHD, its impact on the course of pregnancy and identifying the main risk factors associated with this group of pathologies. A detailed study of this problem can be used to develop optimal approaches to the management of pregnancy and childbirth in women with ASD, improving the quality of their lives and the health of their children.

An extensive and exhaustive scientific literature search was conducted using the analysis and bibliographic method in biomedical scientific and practical resources, including Science Direct, CINAHL, PubMed, Cochrane Library, Web of Science, Ovid, JSTOR, Psychology Database, and EMBASE. Various combinations of keywords and phrases related to the issue of ASD and risk factors, such as "atrial septum", "pregnancy", "haemodynamics", "developmental pathology", "newborns", "risk factors", and others, were used. The search covered scientific materials published in the period from 2018 to 2023, including both basic researches, for which a wider time frame was chosen, and current scientific publications. To refine the focus of the research, the results of this search were adjusted to focus on scientific articles published in journals specialising in biomedicine, leaving aside the socio-economic aspect of the topic. Studies were analysed that comprehensively covered both the issues of ASD and haemodynamic changes in pregnant women in normal and pathological conditions. As a result of this work, more than 100 scientific papers were analysed. Subsequently, 47 of the best scientific papers were selected using exclusion criteria. The main directions for further research were outlined using the synthesis method. The same methods were used to systematise and classify the collected information. The systematisation and categorisation methods resulted in a structured data system that greatly simplified the analysis and interpretation of information on ASD and related risk factors. In addition to the above, the study used a two-stage approach based on the proven bibliographic and analytical methods proposed by S.K. Boell & D. Cecez-Kecmanovic [6]. The application of this allowed for a comprehensive aggregation, systematisation, classification, and analysis of sources on the issue.

Congenital Heart Defects: Defect Variants, Clinical Manifestations, Risk Factors and Diagnostic Methods

According to the study by N. Khudoykulova, congenital heart disease is one of the most common anomalies in newborns, occurring in the range of 4 to 10 cases per 1000 live births [7]. Among the most common congenital heart defects are the following: interventricular septal defects, atrial septal defects, transposition of the great vessels, patent ductus arteriosus, and Phalo group defects. Among patients with congenital heart defects, 47% are detected during prenatal screening in a maternity hospital or other healthcare facility, and 93% of cases are detected before the age of 1 year. 60-65% do not survive the first year of life due to the lack of necessary surgical correction, as highlighted in their work by T. Protsak & K. Khovanets [8]. The structure of congenital heart defects includes congenital stenosis of the aortic mouth, coarctation of the aorta, Fallot's group defects, atrial septal defect, patent ductus arteriosus, and ventricular septal defect, as shown in Figure 1. Thus, ASD is one of the most common heart defects and, given the high prevalence of this group, CM in general [9].

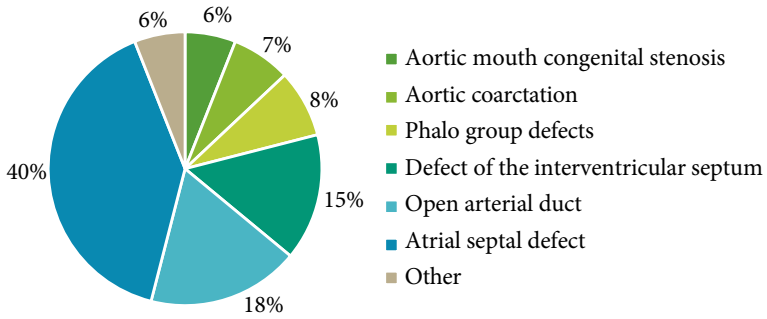

Figure 1. Congenital heart disease nosological structure
Source: Compiled by the authors based on [8, 9]

There are four different types of atrial septal defects, although only two of them are of significant practical importance in the context of pregnancy. The most common of these is a secondary defect, which is located only at the level of the foramen ovale and is usually found in adult patients. Primary atrial septal defect, in turn, accounts for only 15-20% of all cases and is usually detected in childhood. This type of ASD is often combined with congenital mitral valve insufficiency, which continues to progress over time despite correction in childhood. This is accompanied by the development of decompensated mitral insufficiency, which was noted by C. Frescura & G. Thiene [10].

Given the high prevalence and medical significance of both developmental disorders in general and congenital heart diseases in particular, scientists continue to focus on the factors that contribute to the development of these pathologies. This issue covers a wide range of risk factors, from genetically determined to iatrogenic. As such, B.D. Gelb highlighted the topic of genetic determination of CHD and emphasised the use of modern genetic achievements as both early diagnosis of these malformations and prevention of their development [11]. The issue of the drug effect on the risk of developing birth defects was investigated by X. Wen *et al.* [12] and N. Mallah *et al.* [13], focusing on the use of macrolides and opioid analgesics, respectively. Such studies and the implementation of their results in medical practice may help to avoid iatrogeny. Researchers also paid attention to the maternal somatic state as a risk factor for congenital heart disease. Z. Liang *et al.* examined the impact of obstetric and gynaecological pathology on the risk of developing CHD in the example of endometriosis, the researchers emphasised the need for detailed diagnosis and subsequent correction of reproductive system pathologies during pregnancy planning [14]. According to N.Z. Costa *et al.* [15] and M.J. de Ramírez-Altamirano *et al.* [16], environmental factors, in particular chemicals such as agropesticides and heavy metals, are risk factors for the development of CHD in some cases.

J.O. Seyi-Olajide *et al.* highlighted the importance of developing and implementing screening programmes for the early diagnosis of CHD [17]. The researchers noted that there is a certain gap between the quality of such programmes in high-, middle- and low-income countries. In middle- and low-income countries, the primary early CHD diagnosis tool is ultrasound, which requires neither significant material resources nor significant qualifications of medical personnel. At the same time, as noted by Y. Xia *et al.* noted that in high-income countries, modern screening programmes tend to use innovative diagnostic methods, such as the identification of biomarkers in pregnant women's blood [18].

Hence, CHD is the most common group of congenital malformations, with ASD taking the leading place among them. The ASD structure is not homogeneous and consists of four types, the most common of which is a secondary atrial septal defect, which is characterised by late diagnosis. ASD can also be combined with other heart defects, the most significant of which is congenital mitral valve insufficiency. The combination of these defects can lead to the development of decompensated mitral insufficiency. Given the medical and social significance of CHD, several studies have

been conducted on the factors of development of this group of pathologies, identifying a wide range of factors, from genetic to iatrogenic. The most common method of diagnosing CHD, including ASD, is ultrasound diagnostics. However, in high-income countries, innovative methods such as the detection of specific biomarkers in pregnant women's serum are being integrated into screening programmes.

Physiological Changes in the Cardiovascular System During Pregnancy

The woman's body undergoes significant changes during pregnancy that are not related to the CHD. The increase in blood volume in the bloodstream, mainly due to plasma, is positively correlated with gestational age, which peaks in the third trimester. This causes the development of gestational haemodilution, which is accompanied by changes in placental circulation due to a decrease in blood viscosity. Also, heart failure is quite common, which is caused by the inability of the heart muscle to adapt to the increased volume of the bloodstream, which significantly affects the placental circulation. Anaemia in combination with increased oxygen demand of the heart muscle can lead to a mismatch between the demand and blood supply, which can aggravate the existing phenomena of ischaemia in the form of exacerbation or manifestation of coronary heart disease, as highlighted in the study by M. Konovalova & N. Mykhailovska [19]. There is an increase in cardiac output of up to 50% in the third trimester, which is associated with an increase in left ventricular end-diastolic volume. The stroke volume and heart rate are also positively correlated with gestational age. These changes are not uniform; a significant increase in both indicators can be observed during the first 8 weeks of gestation, after which their levels do not change significantly over 20 weeks, as noted by N.H. Troiano [20]. Remodelling of cardiac activity begins in the first weeks of pregnancy and is associated with an increase in left ventricular end-diastolic volume. J. Ren *et al.* noted that in physiological pregnancy, both systolic and diastolic blood pressure decrease [21]. Pressure indicators undergo the greatest changes in the second trimester of pregnancy. There is also reason to believe that changes occur at the level of the vascular bed: venous blood volume and vein distension increase, basal oxygen consumption increases by about 50 mL/min, which is due to increased lung ventilation. Changes in respiratory parameters are associated with the central effect of progesterone, increased angiotensin II levels, and changes in blood osmolarity, as demonstrated by R.M. Sima *et al.* [22]. Some extracardiac factors, such as the position of the pregnant woman in space, also affect cardiac output. Thus, uterine enlargement can lead to a decrease in cardiac output by compressing the vena cava and aorta when the pregnant woman is in the supine position. This compression leads to a decrease in venous return and a 20-30% decrease in cardiac output. In the supine position, a woman may develop hypotension syndrome in the later stages of pregnancy. On the other hand, cardiac output is optimal when a woman is on her side. Childbirth also contributes to an increase in cardiac output. In the first hour after birth, cardiac output increases by about 22%. As noted by Z.N. Pascual & M.D. Langaker, within 2-4 weeks after delivery, the index gradually decreases and returns to normal levels approximately 6 weeks after birth [23]. During pregnancy, the ratio of the activity of the coagulation and anti-coagulation systems of the blood is also disturbed, with the dominance of the former, as studied in detail by B.B. Warren *et al.* [24]. This is primarily due to an increase in the concentration of such coagulation factors as VII, VIII, IX, X, and XII. At the same time, fibrinolysis is inhibited by a decrease in the concentration of protein S, which ultimately leads to the inhibition of fibrinolysis. These changes lead to the development of hypercoagulability and a natural increase in the risk of thrombotic and thromboembolic complications, and this risk persists for 6 weeks after delivery.

A study conducted by M. Bester *et al.* [25] demonstrated that pregnant women undergo a significant restructuring of the autonomic nervous system, characterised by a decrease in the tone of the parasympathetic and an increase in the tone of the sympathetic nervous systems. These changes lead to changes in heart rate variability, which is a sensitive marker of the functioning of the autonomic nervous system. In addition, in pregnant women, there is a decrease in the reactivity of the autonomic nervous system, which can negatively affect the implementation of adaptive mechanisms of the cardiovascular system during pregnancy, which is especially dangerous for pregnant women with CHD.

As such, pregnancy is accompanied by significant changes in the cardiovascular system. Hemodynamic changes are characterised by an increase in blood volume, cardiac output, and heart rate. The increase in blood volume is caused by hypervolaemia, which occurs mainly due to an increase in the amount of plasma. The increase in cardiac output is due to an increase in left ventricular end-diastolic volume, and the increase in heart rate is a compensatory response to the increase in blood vessel volume. Cardiac remodelling, which is characterised by an increase in the mass of the left ventricle and its chambers, also occurs as a result of the heart's adaptation to increased stress. A shift in haemostasis towards hypercoagulation due to an increase in the concentration of blood coagulation factors and a decrease in fibrinolysis activity. This shift is physiologically caused by the prevention of bleeding during labour. Changes in autonomic regulation, characterised by a weakening of parasympathetic and strengthening of sympathetic influences, occur due to an increase in the level of catecholamines produced by the adrenal glands. In women with CHD, the above changes can lead to decompensation of cardiac pathology and the development of pregnancy complications, as discussed in the next section.

Clinical and Haemodynamic ASD Complications in Pregnant Women

Sometimes, due to minor and nonspecific clinical manifestations in the form of fatigue and impaired exercise

tolerance, ASD is not diagnosed for a long time. Uncorrected ASD is accompanied by the movement of blood along a pressure gradient from the left atrium to the right atrium, which causes an enlargement of the right atrium and, subsequently, the right ventricle. This can also lead to the development of secondary tricuspid valve failure, as noted by V.T. Binh *et al.* [26]. These haemodynamic changes are significantly exacerbated in the third trimester of pregnancy when the volume of circulating blood increases by approximately 50%. Almost half of patients with late-diagnosed ASD suffer from heart rhythm disturbances, which in some cases may be the main manifestation of the pathology. Given the phenomenon of left-to-right shunting and turbulent blood flow due to heart rhythm disturbances, the risk of thromboembolic events is significant. In some cases, ASD is diagnosed only after the onset of complications, such as acute cerebrovascular accident, which is based on the phenomena of paradoxical embolism, as described in detail by V. Muroke *et al.* [27]. P. Sjöberg *et al.* noted that during pregnancy, patients with uncorrected ASD have a 4-5% increased risk of cardiac arrhythmias due to increased circulating blood volume and additional stretching of the heart chambers [28]. In addition, physiological tachycardia in the second half of pregnancy, given the already existing arrhythmia, can lead to severe paroxysmal arrhythmias. Given the increased activity of the anti-clotting and inhibition of the fibrinolytic blood systems that progress during pregnancy, the risk of paradoxical embolism through the left-to-right shunt increases significantly in the third trimester of gestation. This risk, depending on the stage of pregnancy, is 2-5%.

Uncorrected ASD is often accompanied by the development of chronic pulmonary circulatory disorders. It has been proven that 6-35% of patients develop pulmonary hypertension as a result of left-to-right shunting due to the presence of a connection between both atria. It is especially important that the development of pulmonary hypertension only initially depends on the phenomena of left-to-right shunting. Subsequently, as morphological, and functional changes in the pulmonary vessels progress, hypertension continues to exist regardless of certain cardiac circulatory events. Thus, timely surgical intervention is aimed at preventing the development of severe pulmonary hypertension, as emphasised by C.J. Cool *et al.* [29]. This condition is associated with an increased risk of disability and death. According to the study by E.A. Bradley & A.N. Zaidi, prevention of the progression of morphological changes in medium and small calibre pulmonary vessels is the main predictor for surgical correction of ASD, although in the presence of advanced pulmonary hypertension, correction of ASD may not affect the severity and progression of secondary disease [30]. A. Potapchuk *et al.* [31] and E. Kadirogullari *et al.* [32] concluded that modern advances in early diagnosis, especially with the use of ultrasound methods, have significantly improved the prognosis of patients with pulmonary hypertension, in particular, due to ASD. In turn, H.F. Qiu *et al.* [33] and J.H. Seol *et al.* [34] examined the problem through the prism of heart surgery and found that modern surgical interventions have reduced the percentage of patients with pulmonary hypertension in the postoperative period compared to previous years.

Pulmonary hypertension is accompanied by dilation of the pulmonary artery, which can lead to compression of the coronary vessels. In most cases, the left main coronary artery, which originates from the left coronary leaflet of the aortic valve and divides into the left circumflex artery and the left anterior descending artery along its path, is compressed. This is especially important as these arteries supply the myocardium of the left ventricle and atrium. The clinic of left main coronary artery compression resembles that of acute coronary syndrome, which significantly complicates differential diagnosis and can lead to ineffective care. This complication is especially relevant in pregnancy, especially in the third trimester, when in the case of pulmonary hypertension with overflow of the bloodstream, the pulmonary artery is particularly enlarged, as discussed by R.D. Zwijnenburg *et al.* [35]. Pulmonary hypertension, especially its resistant forms, is a contraindication to pregnancy due to obstetric and cardiac complications. For women who do become pregnant, premature termination of pregnancy is recommended, as emphasised by various groups of researchers, such as M. Ladouceur *et al.* [36] and A. Shevchenko & Yu. Krut [37].

According to S. Malakhova *et al.*, most women with ASD have an optimal pregnancy outcome, except for those diagnosed with pulmonary hypertension [38]. In this context, it is important to compare pregnancy outcomes in women who have undergone correction of ASD and those who have not. In the first case, a higher risk of eclampsia and pre-eclampsia, low birth weight, and intrauterine death was found compared to the general population, which is associated with insufficient placental blood supply due to the presence of left-to-right shunting, aggravated by haemodynamic changes in the third trimester of pregnancy. In turn, those women who were surgically treated for this reason did not have significant differences from the average population, although an increased risk of heart rhythm disorders was found, which is directly related to the fact of cardiac surgery.

It is also necessary to emphasise that risk stratification is particularly important in the context of pregnancy in women with ASD, as they are more vulnerable to common risk factors. As noted by M. Khara *et al.*, attention should be paid to the presence of comorbidities, in particular gestational diabetes [39]. N. Loia *et al.* [40] recommended a set of pregravid preparation measures to avoid hypovitaminosis and other nutritional conditions, and fetotoxicity and teratogenicity of some drugs used to treat pulmonary hypertension, in particular in women with ASD, as emphasised by O. Aleksieiev [41].

Given all of the above, some important aspects should be emphasised. In general, ASD is not a particularly dangerous heart defect; a significant proportion of people can live for decades without ever knowing they have this pathology. Nevertheless, ASD has a formidable complication, as this

defect, like other diseases and conditions accompanied by changes in haemodynamics, is prone to gradual progression. In this case, this complication is pulmonary hypertension. Pregnancy is a physiologically complex and multifaceted process that causes changes in almost all organs and systems of the body, several of which are associated with haemodynamics, leading to a worsening of disorders in women with ASD. Haemodynamic disorders peak in the third trimester of pregnancy. These changes during this period can lead to placental circulatory disorders, although pregnancy is usually optimal in women with ASD. The most dangerous changes in haemodynamics occur when a pregnant woman with ASD develops pulmonary hypertension, in which case termination of pregnancy is recommended.

Thus, the above material demonstrates that ASD, although one of the least haemodynamically significant heart defects, nevertheless leads to left-to-right blood shunting, which is very difficult to diagnose due to nonspecific and vague clinical manifestations. During pregnancy, a woman's body undergoes several changes, including those directly related to haemodynamics: an increase in circulating blood volume due to plasma, haemodilution, a tendency to thrombosis and fibrinolysis disorders. These changes develop gradually, reaching their peak in the third trimester of pregnancy. These metamorphoses can exacerbate haemodynamic disorders in women with uncorrected ASD, which carries a risk of placental circulatory disorders. In turn, women who have undergone surgical correction are only more likely to develop heart rhythm disorders. In general, women with ASD have an optimal pregnancy outcome, except for the development of the most dangerous complication of ASD, pulmonary hypertension.

Experience of Perinatal Centres in Managing Pregnancy in Women with Congenital Cardiovascular Disease

Besides, some other aspects of the problem deserve further attention, such as the impact on the haemodynamics of morphologically similar defects that are also associated with the atrial septum, the most up-to-date recommendations for the management of this pathology and consideration of information from perinatal centres in some European countries. The most pathogenetically similar heart defect to ASD is the patent foramen ovale (PFO). B. Zhang *et al.* noted that PFO is a defect that occurs in approximately 25% and is a preserved opening through which left-to-right shunting occurs in the foetal period [42]. PFO, as well as ASD, usually does not cause serious haemodynamic disorders, although they are more severe in patients with the first pathology. L. Chen *et al.* note that hemodynamic changes during pregnancy, especially in the third trimester, are accompanied by a deepening of pathological changes caused by left-to-right shunting in the case of PFO, which is accompanied by an increased risk of heart failure and placental circulatory failure [43]. The most dangerous and, at the same time, the most common complication of the PFO is the development of paradoxical embolism and, as a result, ischaemic stroke. Given the changes in the coagulation system during pregnancy, the risk of acute cerebrovascular disorders is particularly high during this period. Thus, the authors recommend that the defect be corrected during pregnancy planning, especially if there is a history of acute cerebrovascular disorders. In the case of an uncorrected defect, prophylactic aspirin use is recommended starting from the second trimester of pregnancy to reduce the risk of thrombosis. Thus, PFO and ASD are defects with a common location, a common type of bypass surgery, and a similar effect of pregnancy on the course of pathology. In both cases, haemodynamic changes become significant only in the third trimester of pregnancy, remaining insignificant in normal conditions. Both pathologies are characterised by a mild clinical course, the most dangerous manifestation of which is complications, for PFO – acute cerebrovascular accident, and for ASD – pulmonary hypertension. This material, unlike the present study, also does not provide information on haemodynamic changes in pregnant women, both in physiological conditions and in cases of pathology.

An exhaustive analysis of the clinical course and treatment strategies for ASD was done by M. Brida *et al.* [44]. The authors emphasise that the current paradigm in the treatment of ASD is the surgical correction of the defect before the age of 25, which allows both to avoid the development of pulmonary hypertension or thromboembolic complications and to leave time for pregnancy planning. The procedure is performed both with the help of a catheter and directly surgically. Recent advances have significantly improved the catheter-based procedure, and this method of intervention is now the preferred method for most patients with ASD. This procedure has a smaller range of potential complications, lower risk, shorter postoperative period, and faster recovery. The procedure is carried out under the careful supervision of additional examination methods: ultrasound or X-ray. In modern conditions, many instruments based on permanent materials are used, but the latest in this field is plastic surgery by implantation of biological implants capable of controlled degradation and gradual replacement with cardiac tissue. In turn, surgical intervention is used in cases where it is impossible to perform defect repair using a catheter. It is usually performed in the case of massive defects, and the intervention is carried out with the help of a heart-lung machine, using a midline sternotomy approach. The procedure is highly effective, with a mortality rate of less than 1% and a 7% risk of complications. Nevertheless, in the postoperative period, there is a risk of developing heart rhythm disturbances due to the disruption of the structure of the cardiac conduction system and the occurrence of postoperative scars. Thus, the aforementioned material confirms the recommendations made in this study regarding the need to correct the defect before pregnancy. The present work is strictly practically oriented to the field of cardiac surgery and therefore omits several aspects demonstrated in this study, in particular, an exhaustive analysis of haemodynamic changes and the impact of these changes on the foetal condition.

The issue of changes in haemodynamics caused by cardiovascular disease during pregnancy and their potential impact on the course of pregnancy was studied by European scientists. W. Drenthen *et al.* examined data from perinatal centres in the Netherlands and Belgium, focusing on risk factors that may be caused by cardiovascular disease, including ASD, in pregnant women [45]. The researchers found cardiovascular complications in 7.6% of pregnant women, with heart failure and rhythm disturbances predominating; eclampsia (12%) and pre-eclampsia (4.1%) prevailed among obstetric complications that occurred in 24% of cases; neonatal complications occurred in 25% of paradigms, with preterm birth and birth of underweight children predominating; neonatal mortality was 4%. Danish researchers led by S. Udholm *et al.* studied the course of pregnancy in women with ASD and found that although the perinatal outcomes of the pathology in women with the disorder and the control group were similar, women with ASD had a threefold higher risk of developing pre-eclampsia [46]. A significant proportion of women with ASD used artificial insemination methods. J. Roos-Hesselink *et al.* in a multicentre study analysed information on 5739 cardiovascular disease-associated pregnancies from around the world, including the Netherlands, Belgium, Norway, and the United Kingdom [47]. 60% of pregnant women had cardiovascular disease, and these patients, in particular those with ASD, were at high risk. Among them, 11% of pregnancies were accompanied by the development of heart failure, and 16% in the early postpartum period. Foetal pathology was observed in at least 21% of cases, more than half of which were premature births; caesarean section was used in 9% of cases, 16% of which were for cardiac reasons, more than half of which were due to pulmonary hypertension.

As such, these studies complement the material on the risks associated with the cardiovascular system CM, their causes, and consequences in the example of perinatal centres in Europe. These studies were mostly strictly epidemiological, omitting several issues: the pathophysiological basis of the pathological process, and methods of its diagnosis and correction, which is demonstrated in this material.

Conclusions

Congenital defects of the cardiovascular system are the most common and socially significant among congenital malformations, and one of the most common is congenital atrial septal defect. Based on the data of many studies, it can be stated that under normal conditions, this defect does not lead to significant haemodynamic disorders and is manifested only in the case of a prolonged uncorrected course with the development of pulmonary hypertension or in the case of complex multisystemic changes, as in pregnancy. Changes in systemic haemodynamics in pregnant women are positively correlated with gestational age, reaching their peak in the third trimester of pregnancy. Changes in the form of an increase in total blood volume, a tendency to thrombosis and fibrinolysis aggravate the haemodynamic disorders inherent in congenital atrial septal defect by left-to-right shunting. These changes are clinically manifested by thromboembolic complications, heart failure, and placental circulatory disorders, although most women have an optimal pregnancy and delivery.

The most serious complication of a defect that has not been corrected for a long time is the development of pulmonary hypertension, which is especially dangerous during pregnancy and is a direct indication of its termination. In the case of pulmonary hypertension caused by atrial septal defect, this condition directly depends on cardiac haemodynamics only at the initial stages of its development. In the case of a long course, morphological and functional changes in the pulmonary vessels persist and progress regardless of the correction of the heart wall defect.

The current paradigm in the treatment of this defect is atrial septal defect repair, which reduces the risk of significant haemodynamic disorders during pregnancy. The most modern method in this area is balloon surgery with the use of biological implants. Surgical interventions in this regard should be performed when planning a pregnancy under the age of 25, which helps to avoid undesirable consequences in the third trimester of pregnancy or during childbirth. Interventions are recommended to be performed using balloon plastics, as this minimises the risk of developing cardiac arrhythmias in the future. Nevertheless, large defects can currently be corrected only with the help of full-fledged surgery.

The experience of perinatal centres in Europe in managing pregnancy in women with congenital cardiovascular disease in general and atrial septal defects, in particular, is also considered. Due to the pathogenetic and morphological similarities, additional attention was also paid to the issue of pregnancy in women with an open oval window. Further research in this area should be aimed at solving the problem of pregnancy in women with uncorrected atrial septal defects complicated by pulmonary hypertension.

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Conflict of Interest

The authors declare no conflict of interest.

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Особливості гемодинаміки вагітних з дефектом міжпередсердної перетинки у III триместрі вагітності: огляд літератури

Сергій Юрійович Наконечний

Кандидат медичних наук, доцент
Запорізький державний медико-фармацевтичний університет
69035, просп. Маяковського, 26, м. Запоріжжя, Україна
https://orcid.org/0000-0002-1087-9659

Ірина Сергіївна Соколовська

Кандидат медичних наук, асистент
Запорізький державний медико-фармацевтичний університет
69035, просп. Маяковського, 26, м. Запоріжжя, Україна
https://orcid.org/0009-0008-2487-1675

Ірина Юріївна Ганжий

Доктор медичних наук, професор
Запорізький державний медико-фармацевтичний університет
69035, просп. Маяковського, 26, м. Запоріжжя, Україна
https://orcid.org/0009-0008-2490-5222

Анотація. У зв'язку зі зниженням показника смертності серед дітей з вадами серця, значна кількість таких дітей досягли репродуктивного віку. Однак, оскільки знання щодо впливу вагітності на гемодинаміку у жінок із серцевими вадами обмежені, дане дослідження є вкрай актуальним. Метою роботи був всебічний огляд сучасних наукових джерел та консолідація отриманих знань щодо особливостей гемодинаміки у вагітних з дефектами міжпередсердної перетинки. Під час проведення дослідження було використано ряд методів: аналіз, зокрема порівняльний, синтез, бібліографія, систематизація та категоризація. Також було залучено двоетапний підхід у вигляді систематизованого огляду літератури. Розглянуто комплекс гемодинамічних змін, що виникає у вагітних, як у нормі, так і при патології, зокрема у вагітних з дефектом міжпередсердної перетинки. Конкретизоване питання, чому гемодинамічні зміни набувають найбільшого значення у III триместрі вагітності, їх вплив на перебіг вагітності та результат завершення пологів. Висвітлено тему гострих та хронічних ускладнень дефекту міжпередсердної перегородки та сучасні принципи їх попередження та лікування. Окрему увагу приділено методам корекції зазначеної вади серця з урахуванням їх переваг, недоліків та можливих ускладнень. Розглянуто досвід перинатальних центрів ряду країн Європи у веденні вагітностей у жінок з вадами серцево-судинної системи, зокрема з дефектами міжпередсердної перетинки. Заповнено прогалини у знаннях щодо розповсюдженості даних вад та факторів ризику. Під час проведення дослідження вирішено проблему відсутності всебічних поглядів на дану проблему: від патофізіологічних основ та епідеміології, до лікування та модифікації факторів ризику. Дослідження має широку практичну цінність для медичних працівників, так як воно може слугувати основою для розробки профілактичних програм та інших інтервенцій щодо вагітностей жінок з вродженими вадами розвитку серцево-судинної системи

Ключові слова: вроджені вади розвитку; гестація; серцево-судинні ускладнення; фактори ризику; відкрите овальне вікно; легенева гіпертензія

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