UČESTALOST METABOLIČKIH POREMEĆAJA I HIPERTENZIJE KOD ŽENA PRE MENOPAUZE I U MENOPAUZI

ORIGINALNI RAD

ORIGINAL ARTICLE

THE PREVALENCE OF METABOLIC DISORDERS AND HYPERTENSION IN WOMEN DURING PERIMENOPAUSE AND MENOPAUSE

Sonja Smiljić[1], Srna Šapić[2], Vojkan Nestorović[1], Zvezdan Milanović[1], Mirjana Dejanović[1], Andrijana Karanović[1]

[1] Univerzitet u Prištini – Kosovska Mitrovica, Medicinski fakultet, Kosovska Mitrovica, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

[1] *University of Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia*

[2] *University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

SAŽETAK

Uvod/Cilj: Kardiometaboličke bolesti, uključujući diabetes mellitus tip 2 i hipertenziju, među vodećim su uzrocima morbiditeta i mortaliteta u Srbiji. U mlađem životnom dobu prevalenca kardiometaboličkih bolesti veća je kod muškaraca nego kod žena, ali ova prednost postepeno nestaje sa starenjem, posebno u menopauzi, i tada su žene pod većim kardiovaskularnim rizikom.

Cilj našeg istraživanja bio je da ukažemo na učestalost nepromenljivih i promenljivih faktora rizika i njihovu povezanost sa metaboličkim poremećajima i hipertenzijom kod žena pre menopauze i u menopauzi.

Metod: U ispitivanje je bilo uključeno 200 sredovečnih žena: 131 (65,5%) u perimenopauzi, koje su imale tipične znake perimenopauze duže od 6 meseci, i 69 (34,5%) žena u menopauzi, sa odsustvom ciklusa dužim od 12 meseci, starosti između 50 i 59 godina. Pacijentkinje su se javile lekaru na redovan preventivni pregled tokom decembra 2024. godine.

Rezultati: Hipertenzija je statistički značajno učestalija kod žena u menopauzi (84,1%), u odnosu na žene pre menopauze ($p < 0,001$). Žene u menopauzi su značajno češće imale metaboličke poremećaje, povećanu telesnu masu i gojaznost, i to kod 66,7% ispitanica, kao i veći obim struka kod 63,8% ispitanica ($p = 0,003$). Nivoi ukupnog holesterola, LDL-holesterola i triglicerida su bili statistički značajno viši kod žena u menopauzi u odnosu na žene pre menopauze ($p = 0,002$). Diabetes mellitus je statistički značajno učestaliji kod žena u menopauzi, gde je zastupljen kod 27% žena ($p = 0,002$). Učestalost hipotireoze je statistički značajno veća kod žena pre menopauze (14,7%) u odnosu na žene u menopauzi (4,3%) ($p = 0,027$). Ove dve grupe ispitanica nisu se značajno razlikovale u odnosu na zanimanje, porodični status i faktore rizika, kao što su sedentarne navike, navika pušenja cigareta i porodično opterećenje za oboljevanje od HTA.

Zaključak: Žene u menopauzi su značajno češće imale hipertenziju, gojaznost, dislipidemiju i diabetes melitus 2. Zato su neophodni preventivni pregledi žena u perimenopauzi i menopauzi kako bi se pravovremeni prepoznali i lečili kardiometabolički poremećaji i time sprečile teže kardiovaskularne bolesti.

Ključne reči: menopauza, hipertenzija, kardiometabolički poremećaj

ABSTRACT

Introduction/Objective: Cardiometabolic diseases, including type 2 diabetes (T2D) and cardiovascular disease, and their associated factors, such as hypertension, dyslipidemia, insulin resistance, and obesity, are among the leading causes of morbidity and mortality. At a young age, the prevalence of cardiometabolic diseases is higher in men than in women, but this female advantage gradually disappears with aging, particularly after menopause, when cardiometabolic risk factors accumulate. Our research aimed to highlight the prevalence of metabolic disorders and their association with hypertension in women during perimenopause and menopause.

Method: The study included 200 middle-aged women: 131 (65.5%) perimenopausal women who had experienced typical perimenopausal signs for more than 6 months, and 69 (34.5%) menopausal women with absent menstrual cycles for more than 12 months, aged 50-59 years. The patients visited their physician for a routine preventive examination in December 2024.

Results: Hypertension was statistically significantly more common in women in menopause (84.1%) compared to premenopausal women ($p < 0.001$). Women in menopause had significantly higher rates of metabolic disorders, increased body mass and obesity, with 66.7% of the participants affected, as well as a larger waist circumference in 63.8% of the participants ($p = 0.003$). Menopausal women had statistically significantly higher levels of triglycerides, LDL cholesterol, and total cholesterol than premenopausal women ($p = 0.002$). Among women going through menopause, diabetes mellitus was statistically substantially more prevalent, affecting 27% of them ($p = 0.002$). Premenopausal women had a statistically significantly greater prevalence of hypothyroidism (14.7%) than did menopausal women (4.3%) ($p = 0.027$). These two groups of participants did not differ significantly in terms of sedentary habits, smoking, or family history of hypertension.

Conclusion: Type 2 diabetes, obesity, dyslipidaemia, and hypertension were all substantially more common in menopausal women. Preventive screenings are therefore crucial for women going through menopause and perimenopause to promptly detect and treat cardiometabolic disorders and prevent more serious cardiovascular diseases.

Keywords: menopause, hypertension, cardiometabolic disorder

Autor za korespondenciju:
Sonja Smiljić
Medicinski fakultet, Univerzitet u Prištini – Kosovska Mitrovica
Anri Dinana b.b, 38220 Kosovska Mitrovica, Srbija
Elektronska adresa: sonja.smiljic@med.pr.ac.rs

Corresponding author:
Sonja Smiljić
Faculty of Medicine, University of Priština – Kosovska Mitrovica
bb Anri Dinana Street, 38220 Kosovska Mitrovica, Serbia
E-mail: sonja.smiljic@med.pr.ac.rs

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UVOD

Kardiometaboličke bolesti, uključujući diabetes mellitus tip 2 i hipertenziju, su među vodećim uzrocima morbiditeta i mortaliteta u Srbiji. U mlađem životnom dobu, prevalenca kardiometaboličkih bolesti je veća kod muškaraca nego kod žena, ali ova prednost postepeno nestaje sa starenjem, posebno u menopauzi, i tada su žene pod većim kardiovaskularnim rizikom. Iako je reproduktivno starenje karakteristično za oba pola, faze reproduktivnog starenja su bolje opisane kod žena. Estrogeni su prototip ženskih hormona i u godinama pre menopauze ispoljavaju punu aktivnost. Menopauza je faza života u kojoj se dešava ne samo pad estrogena i relativni višak androgena već i brojne psihofiziološke promene koje su posledica hormonskog disbalansa [1].

Očekivano je da će u 2025. godini širom sveta biti preko 1 milijarda žena u menopauzi [2]. Žene se ćešće suočavaju sa neadekvatnom dijagnostikom i terapijom kardiovaskularnih bolesti u poređenju sa muškarcima. Čak i kada su kod žena prisutni tradicionalni kardiovaskularni faktori rizika, lekar im ne pridaje adekvatnu važnost što dovodi do lošijeg ishoda bolesti. Hipertenzija je češća među ženama i nosi dvostruko veći rizik od mortaliteta u poređenju sa muškarcima [3]. Žene sa dijabetesom imaju veći rizik od ishemijske bolesti srca, i to za 3 do 7 puta u odnosu na muškarce kod kojih je samo 2 do 3 puta veći rizik ako boluju od diabtes mellitus tip 2 [4]. Diabetes mellitus tip 2 je potvrđen kod jedne od devet žena. Iako se čini da nema korelacije između početka menopauze i višeg nivoa glukoze, povećan rizik od metaboličkog sindroma se pojavljuje nakon prelaza u menopauzu [5]. U menopauzi dodatni faktori značajno povećavaju kardiovaskularni rizik. Tako je nedavna meta-analiza pokazala da pušenje cigareta za 25% povećava relativni rizik od velikih kardiovaskularnih događaja kod žena u poređenju sa muškarcima [6].

Faktori rizika specifični za ženski pol i njihova povezanost sa rizikom od KVB postaju sve više istraživani i poznati i naglašavaju važnost temeljne reproduktivne i akušerske anamneze za stratifikaciju kardiovaskularnog rizika. Faktori rizika specifični za pol uključujući hipertenzivni poremećaj u trudnoći, gestacijski dijabetes, prevremeni porođaj i abrupciju placente, preuranjenu menarhu, ranu menopauzu i vazomotorne simptome u menopauzi, i sindrom policističnih jajnika, sterilitet i lečenje steriliteta, autoimmune bolesti i depresiju, povezani su sa povećanim kardiovaskularnim rizikom [7,8].

Hipertenzija je veoma rasprostranjen i moćan kardiovaskularni faktor rizika kod žena koji je povezan sa infarktom srca, srčanom slabošću, moždanim udarom, atrijalnom fibrilacijom, perifernom arterijskom boles-

INTRODUCTION

Cardiometabolic diseases, including type 2 diabetes mellitus and hypertension, are among the leading causes of morbidity and mortality in Serbia. At a younger age, the prevalence of cardiometabolic diseases is higher in men than in women; however, this advantage gradually diminishes with aging, particularly during menopause, when women are at increased cardiovascular risk. Although reproductive aging is characteristic of both sexes, the stages of reproductive aging are better described in women. Estrogens are the prototype female hormones and exhibit full activity in the years preceding menopause. Menopause is a stage of life characterized not only by a decline in estrogen levels and a relative excess of androgens, but also by numerous psychophysiological changes resulting from hormonal imbalance [1].

It is expected that by 2025, there will be more than 1 billion women in menopause worldwide [2]. Women more often face inadequate diagnosis and treatment of cardiovascular diseases compared to men. Even when traditional cardiovascular risk factors are present in women, physicians do not attribute adequate importance to them, which leads to poorer disease outcomes. Hypertension is more common among women and carries a twofold higher risk of mortality compared to men [3]. Women with diabetes have a higher risk of ischemic heart disease, by 3 to 7 times, compared to men, in whom the risk is only 2 to 3 times higher in the presence of type 2 diabetes mellitus [4]. Type 2 diabetes mellitus has been confirmed in one out of nine women. Although there appears to be no correlation between the onset of menopause and higher glucose levels, an increased risk of metabolic syndrome emerges after the transition to menopause [5]. During menopause, additional factors significantly increase cardiovascular risk. A recent meta-analysis showed that smoking increases the relative risk of major cardiovascular events by 25% in women compared to men [6].

Sex-specific risk factors and their association with cardiovascular disease (CVD) risk are increasingly being studied and recognized, emphasizing the importance of a detailed reproductive and obstetric history for cardiovascular risk stratification. Sex-specific risk factors, including hypertensive disorders in pregnancy, gestational diabetes, preterm delivery and placental abruption, early menarche, early menopause and vasomotor symptoms in menopause, polycystic ovary syndrome, infertility and infertility treatment, autoimmune diseases, and depression, are associated with increased cardiovascular risk [7,8].

Hypertension is a highly prevalent and powerful cardiovascular risk factor in women, associated with myocardial infarction, heart failure, stroke, atrial fibrillation, peripheral arterial disease, and chronic kidney

ti i hroničnom bolesti bubrega. Sistolni krvni pritisak počinje da raste oko vremena prelaska u menopauzu i postaje sve češće povišen nakon 65 godina kod žena u poređenju sa muškarcima. Mlade žene sa hipertenzijom su u većem riziku od oštećenja ciljnih organa u poređenju sa muškarcima istih godina. Pad nivoa estrogena dovodi do autonomne disfunkcije, generalizovane endotelne disfunkcije i povećane aktivnosti renin-angiotenzin-aldosteron sistema i tako doprinosi povećanju krvnog pritiska [9,10].

Dislipidemija je dobro poznati faktor rizika za KVB, sa direktnom relacijom između LDL holesterola i aterosklerotske kardiovaskularne bolesti. Kod žene je hiperlipidemija češća u periodu menopauze. Tako žene u menopauzi češće imaju veći nivo ukupnog holesterola, triglicerida i LDL holesterola i smanjeni nivo HDL holesterola, što ih stavlja u veći rizi za KVB [11,12]. Visoki nivoi non-HDL holesterola i triglicerida su važniji faktori rizika za KVB kod žena nego kod muškaraca, posebno kod žena sa dijabetesom. Povećani indeks telesne mase (BMI) je povezan sa povećanim kardiovaskularnim rizikom kod oba pola, ali postoje polne razlike u distribuciji masti, visceralne i potkožne. U menopauzi kod žena se poveća količina visceralnih masti u poređenju sa ženama pre menopauze sličnih godina, što doprinosi insulinskoj rezistenciji i inflamaciji [1,11–13].

Cilj našeg istraživanja bio je da ukažemo na učestalost nepromenljivih i promenljivih faktora rizika i njihovu povezanost sa metaboličkim poremećajima i hipertenzijom kod žena pre menopauze i u menopauzi.

METODOLOGIJA

Prospektivnom studijom obuhvatili smo 200 sredovečnih žena koje su se javile lekaru na redovan preventivni pregled tokom decembra 2024.godine.

Istraživanje je dizajnirano kao studija preseka i obuhvatilo je 200 sredovečnih žena koje su se javile na redovan preventivni pregled tokom decembra 2024. godine. Sve ispitanice su dale pisani informisani pristanak za učešće u istraživanju, a studija je sprovedena u skladu sa etičkim standardim. Pacijentkinje smo podelili u dve grupe. Bila je 131 (65,5%) žena u perimenopauzi koje su imale tipične znake perimenopauze duže od 6 meseci i 69 (34,5%) žena u menopauzi sa odsustvom ciklusa duže od 12 meseci, a starosti između 50 i 59 godina. Na osnovu uzete ginekološke anamneze pacijentkinje su bile podeljene u ove dve grupe. Dijagnoza arterijske hipertenzije kod ispitanika je postavljena na osnovu preporuka Evropskog udruženja za hipertenziju.

Od svih pacijentkinja dobijeni su socio-demografski podaci: godine života, mesto stanovanja, porodični status, obrazovanje i zanimanje. Takođe, uzeti su anamnestički podaci (ranije bolesti, porodične bolesti, pušenje,

disease. Systolic blood pressure begins to rise around the time of the menopausal transition and becomes more frequently elevated after the age of 65 in women compared to men. Young women with hypertension are at greater risk of target organ damage compared to men of the same age. The decline in estrogen levels leads to autonomic dysfunction, generalized endothelial dysfunction, and increased activity of the renin–angiotensin–aldosterone system, thereby contributing to elevated blood pressure [9,10].

Dyslipidemia is a well-known risk factor for CVD, with a direct relationship between LDL cholesterol and atherosclerotic cardiovascular disease. In women, hyperlipidemia is more common during menopause. Thus, women in menopause more frequently have higher levels of total cholesterol, triglycerides, and LDL cholesterol, as well as lower levels of HDL cholesterol, placing them at higher risk for CVD [11,12]. High levels of non-HDL cholesterol and triglycerides are more important risk factors for CVD in women than in men, particularly in women with diabetes. Increased body mass index (BMI) is associated with increased cardiovascular risk in both sexes; however, there are sex differences in fat distribution, including visceral and subcutaneous fat. During menopause, women experience an increase in visceral fat compared to premenopausal women of similar age, which contributes to insulin resistance and inflammation [1,11–13].

Our study aimed to assess the prevalence of non-modifiable and modifiable risk factors and their association with metabolic disorders and hypertension in premenopausal and menopausal women.

METHODOLOGY

A prospective study included 200 middle-aged women who attended a routine preventive medical examination during December 2024.

The study was a cross-sectional design and included 200 middle-aged women who presented for a routine preventive examination in December 2024. All participants provided written informed consent to participate in the study, and the study was conducted in accordance with ethical standards.

The patients were divided into two groups. There were 131 (65.5%) women in perimenopause who had typical signs of perimenopause for more than 6 months, and 69 (34.5%) women in menopause with absence of menstruation for more than 12 months, aged between 50 and 59 years. Based on the gynecological history, the patients were classified into these two groups. The diagnosis of arterial hypertension was established according to the European Society of Hypertension recommendations.

konzumacije alkohola, obim fizičke aktivnosti). Od laboratorijskih analiza određivane su krvna slika i biohemija, urađen je klinički pregled sa dodatnim dijagnostičkim procedurama, EKG, ehokardiografija i EHO abdomena.

Istraživanje je sprovedeno u skladu sa važećim etičkim standardima i principima dobre kliničke prakse, uz poštovanje smernica Helsinške deklaracije.

Statistička analiza

Statističke analize podataka su sprovedene korišćenjem softverskog programa SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). Kontinuirane varijable nisu imale normalnu raspodelu pa su prikazane kao medijana (*min _ max*) a razlika između grupa je testirana Mann-Whitney testom. Kategorijalne varijable su prikazane kao broj (procenat) i razika učestalosti je testirana hi-kvadrat testom.

Kriterijum za statističku značajnost je bio $p < 0,05$.

REZULTATI

Istraživanjem je obuhvaćeno 200 ispitanica ženskog pola. Ispitanice su bile podeljene u dve grupe. Prvu grupu su činile žene pre menopauze, mlađe od 49 godina i žene u menopauzi starosti od 50 do 59 godina (Tabela 1).

Sociodemografske karakteristike bile su ujednačene. Zanimanje i obim fizičke aktivnosti bio je sličan kod obe grupe ispitanika kao i navika pušenja cigareta. Postojala je statistički značajna razlika u ste-

Sociodemographic data were obtained from all patients, including age, place of residence, marital status, education, and occupation. Anamnestic data were also collected (previous diseases, family history, smoking, alcohol consumption, and level of physical activity). Laboratory analyses included complete blood count and biochemical parameters. A clinical examination was performed, along with additional diagnostic procedures, including ECG, echocardiography, and abdominal ultrasound.

The study was conducted in accordance with current ethical standards and the principles of Good Clinical Practice, as outlined in the Declaration of Helsinki.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA). Continuous variables did not have a normal distribution and were therefore presented as median (Min–Max), and differences between groups were tested using the Mann–Whitney test. Categorical variables were presented as numbers (percentages), and differences in frequency were tested using the chi-square test.

The criterion for statistical significance was $p < 0.05$.

RESULTS

The study included 200 female participants. The participants were divided into two groups. The first group consisted of premenopausal women younger than 49 years

Tabela 1. Kardiovaskularni faktori rizika kod žena pre menopauze i kod žena u menopauzi

Table 1. Cardiovascular risk factors in premenopausal and menopausal women

	Ispitivane grupe / *Study groups*		*P*
	Pre menopauze / *Premenopause*	Menopauza / *Menopauze*	
Ukupan broj, n (%) / *Total number, n (%)*	**131 (65.5%)**	**69 (34.5%)**	
Zanimanje / *Occupation*			
Sedentarno / *Sedentary*	71 (54.2%)	41 (59.4%)	0.497
Fizički aktivne / *Physically active*	60 (45.8%)	28 (40.6%)	
Porodična anamneza / *Family history*			
Pozitivna / *Positive*	77 (58.8%)	40 (58.0%)	0.912
Negativna / *Negative*	54 (41.2%)	29 (42.0%)	
Pušenje / *Smoking*			
Ne / *No*	85 (64.9%)	41 (59.4%)	0.477
Da / *Yes*	46 (35.1%)	28 (40.6%)	
Gojaznost (BMI) / *Obesity (BMI)*			
Do 25 / *Up to 25*	66 (50.4%)	23 (33.3%)	**0.021**
Više od 25 / *More than 25*	65 (49.6%)	65 (55.7%)	
Obim struka / *Waist circumference*			
Do 84 cm / *Up to 84 cm*	76 (58.0%)	25 (36.2%)	**0.003**
Iznad 84 cm / *More than 84 cm*	55 (42%)	44 (63.8%)	

Podaci su prikazani kao broj (%), boldirana p vrednost – statistički značajna razlika

Data are presented as numbers (%); bold p-values indicate a statistically significant difference.

penu uhranjenosti i veličini obima struka. Kod žena u menopauzi značajno su češće bili prisutni parametri gojaznosti, BMI viši od 25 ($p = 0,021$) i obim struka veći od 84 cm ($p = 0,003$) (Tabela 1).

Žene u menopauzi su češće imale hipertenziju ($p < 0,001$) i diabetes mellitus tip 2 ($p = 0,002$). Poremećaj ritma je bio podjednako čest kod obe grupe ispitanika kao deficit vitamina D. Hipotireoza je bila značajno češća ($p = 0,027$) kod mlađe grupe žena u perimenopauzi, i sve one su bile na supstitucionoj terapiji (Tabela 2).

Dislipidemiju smo procenili kroz vrednost ukupnog holesterola, LDL holesterola, HDL holesterola i triglicerida. Žene u menopazi imale su povišenu vrednost ukupnog holesterola i LDL holesterola dok se vrednost HDL holesterola nije statistički značajno razlikovala. Ukupni holesterol kod žena pre menopauze je iznosio 5,4 mmol/l (opseg 2,9–11,4), a kod žena u menopauzi 6,0 mmol/l (opseg 3,4–8,3), ($p < 0,001$). Vrednost LDL holesterol kod žena pre meneopaze bila je 3,0 mmol/l (opseg 1,4–6,0), kod žena u menopauzi 3.6 mmol/l (opseg 1,4–5,6), ($p = 0,001$). Vrednosti triglicerida su bile statistički značajno veće kod žena u menopauzi i iznosile su 1,7 mmol/l (opseg 0,6–5,2) u poređenju sa nivoom kod žena pre meneopaze 1,4 mmol/l (opseg 0,1–14,0), ($p = 0,002$) (Tabela 3).

Visoke vrednosti homocisteina (iznad 16 µmol/l) su značajno bile učestalije kod žena pre meneopaze 9

and menopausal women aged 50 to 59 years (Table 1).

Sociodemographic characteristics were comparable between the groups. Occupation and level of physical activity were similar in both groups, as was cigarette smoking. There was a statistically significant difference in nutritional status and waist circumference. In menopausal women, obesity-related parameters were significantly more frequent, including BMI > 25 ($p = 0.021$) and waist circumference > 84 cm ($p = 0.003$) (Table 1).

Women in menopause more frequently had hypertension ($p < 0.001$) and type 2 diabetes mellitus ($p = 0.002$). Arrhythmia was equally common in both groups, as was vitamin D deficiency. Hypothyroidism was significantly more frequent ($p = 0.027$) in the younger group of women in perimenopause, and all of them were receiving substitution therapy (Table 2).

Dyslipidemia was assessed by measuring total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Women in menopause had elevated total and LDL cholesterol levels, while HDL cholesterol levels did not differ significantly. Total cholesterol in premenopausal women was 5.4 mmol/L (range 2.9–11.4), and in menopausal women, 6.0 mmol/L (range 3.4–8.3) ($p < 0.001$). LDL cholesterol levels in premenopausal women were 3.0 mmol/L (range 1.4–6.0), and in menopausal women, 3.6 mmol/L (range 1.4–5.6) ($p = 0.001$). Triglyceride levels were significantly higher in meno-

Tabela 2. Zastupljenost pridruženih bolesti kod pacijentkinja pre menopauze i u menopauzi

Table 2. Prevalence of comorbidities in patients before menopause and in menopause

	Ispitivane grupe / *Study groups*		***P***
	Pre menopauze / *Premenopause*	**Menopauza / *Menopauze***	
Ukupan broj. n (%) / *Total number. n (%)*	**131 (65.5%)**	**69 (34.5%)**	
Diabetes mellitus / *Diabetes mellitus*			
Ne n (%) / *No n (%)*	66 (94.3%)	27 (73.0%)	**0.002**
Da n (%) / *Yes n (%)*	4 (5.7%)	10 (27.0%)	
Hipertenzija / *Hipertension*			
Ne n (%) / *No n (%)*	64 (41.2%)	11(15.9%)	**< 0.001**
Da n (%) / *Yes n (%)*	77 (58.8%)	68 (84.1%)	
Aritmije / *Arrhythmias*			
Ne n (%) / *No n (%)*	59 (88.1%)	31 (97.0%)	0.143
Da n (%) / *Yes n (%)*	8 (11.9%)	1 (3.0%)	
Hipotireoza / *Hypothyroidism*			
Ne n (%) / *No n (%)*	110 (85.3%)	66 (95.7%)	**0.027**
Da n (%) / *Yes n (%)*	19 (14.7%)	3 (4.3%)	
Nivo vitamina D / *Vitamin D level*			
Normalna vrednost n (%) / *Normal value. n (%)*	23 (33.8%)	10 (19.6%)	
Insuficijencija n (%) / *Insufficiency. n (%)*	35 (51.5%)	35 (68.6%)	0.152
Deficit n (/%) / *Deficiency. n (/%)*	10 (14.7%)	6 (11.8%)	

Podaci su prikazani kao broj (%). boldirana p vrednost – statistički značajna razlika

Data are presented as numbers (%); bold p-values indicate a statistically significant difference.

Tabela 3. Biohemijske varijable kod žena pre menopauze i u menopauzi

Table 3. Biochemical variables in premenopausal and menopausal women

Varijable / *Variables*	**Ispitivane grupe / *Study groups***		***P***
	Pre menopauze / *Premenopause*	**Menopauza / *Menopauze***	
Ukupan broj, n (%) / *Total number, n (%)*	**131 (65.5%)**	**69 (34.5%)**	
Ukupan holesterol (mmol/l) / *Total cholesterol (mmol/l)*	5.4 (2.9–11.4)	6.0 (3.4–8.3)	**< 0.001**
HDL holesterol (mmol/l) / *HDL cholesterol (mmol/l)*	1.5 (0.7–3.8)	1.4 (0.8–2.9)	0.257
LDL holesterol (mmol/l) / *LDL cholesterol (mmol/l)*	3.0 (1.4–6.0)	3.6 (1.4–5.6)	**0.001**
Trigliceridi (mmol/l) / *Triglycerides (mmol/l)*	1.4 (0.1–14.0)	1.7 (0.6–5.2)	**0.002**
Homocistein / *Homocysteine*			
Ispod 16 (µmol/l) / *Less than 16 (µmol/l)*	27 (75.0%)	39 (95.1%)	**0.012**
Iznad 16 (µmol/l) / *More than 16 (µmol/l)*	9 (25.0%)	2 (4.9%)	
Mokraćna kiselina / *Uric acid*			
Ispod 400 / *Less than 400*	63 (70.8%)	41 (78.8%)	0.294
Iznad 400 / *More than 400*	26 (29.2%)	11 (21.2%)	

Numeričke varijable su prikazane kao medijana i opseg (min-max) a kategorijalne kao broj (%), boldirana p vrednost – statistički značajna razlika

Numerical variables are presented as median and range (min–max), and categorical variables as numbers (%); bold p-values indicate statistically significant differences

(25,0%) u odnosu na učestalosti kod žena u menopauzi 2 (4,9%), (p = 0,012).

DISKUSIJA

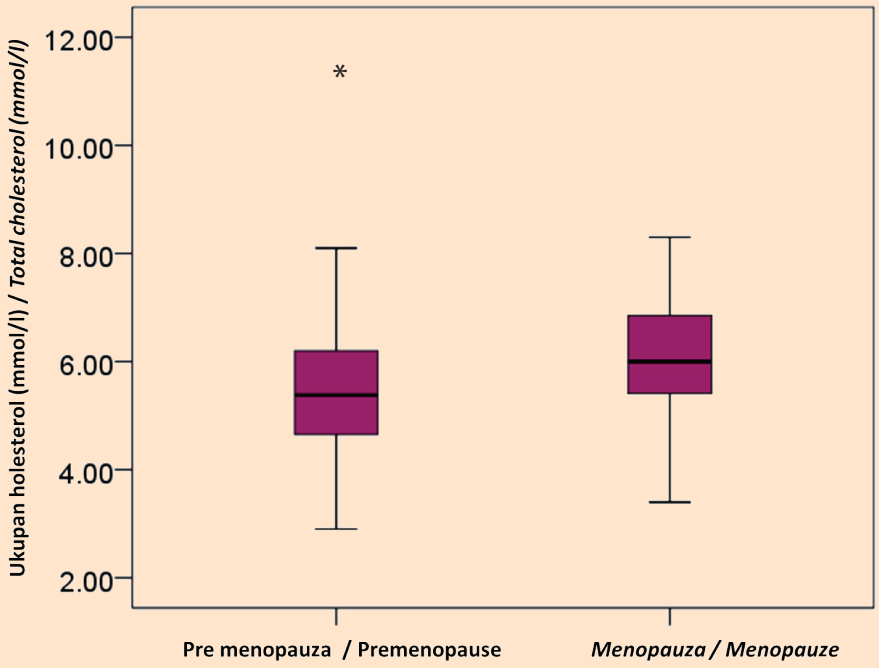
Učestalost veće telesne mase i gojaznosti nastavlja trend rasta, pri čemu su žene zastupljenije u odnosu na muškarce u populaciji gojaznih. Na to ukazuju skorije studije o prevalenci gojaznosti među starijim od 60 godina kod muškaraca od 37,5% i 39,4% kod žena [1]. Promena u reproduktivnim hormonima tokom menopauze i tranzicija u menopauzu doprinose ubrzanom rastu težine i ova pojava je posebno izražena tokom

pausal women, amounting to 1.7 mmol/L (range 0.6–5.2), compared to 1.4 mmol/L (range 0.1–14.0) in premenopausal women (p = 0.002) (Table 3).

Elevated homocysteine levels (above 16 µmol/L) were significantly more frequent in premenopausal women 9 (25.0%) compared to menopausal women 2 (4.9%) (p = 0.012).

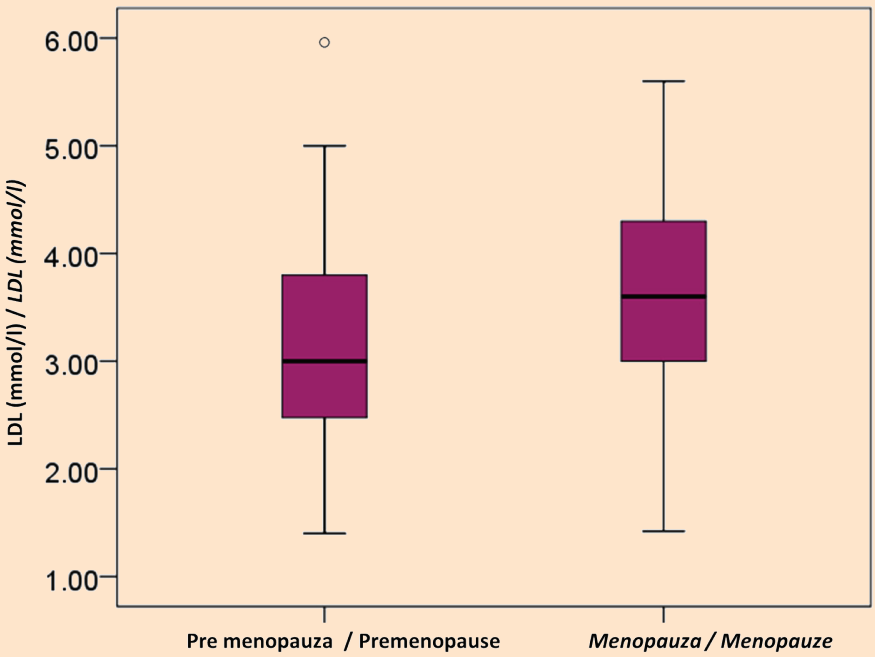
DISCUSSION

The prevalence of increased body weight and obesity continues to rise, with women being more represented than men in the obese population. This is supported



Grafikon 1. Vrednosti ukupnog holesterola kod žena pre menopauze i u menopauzi

Graph 1. Total cholesterol levels in premenopausal and menopausal women



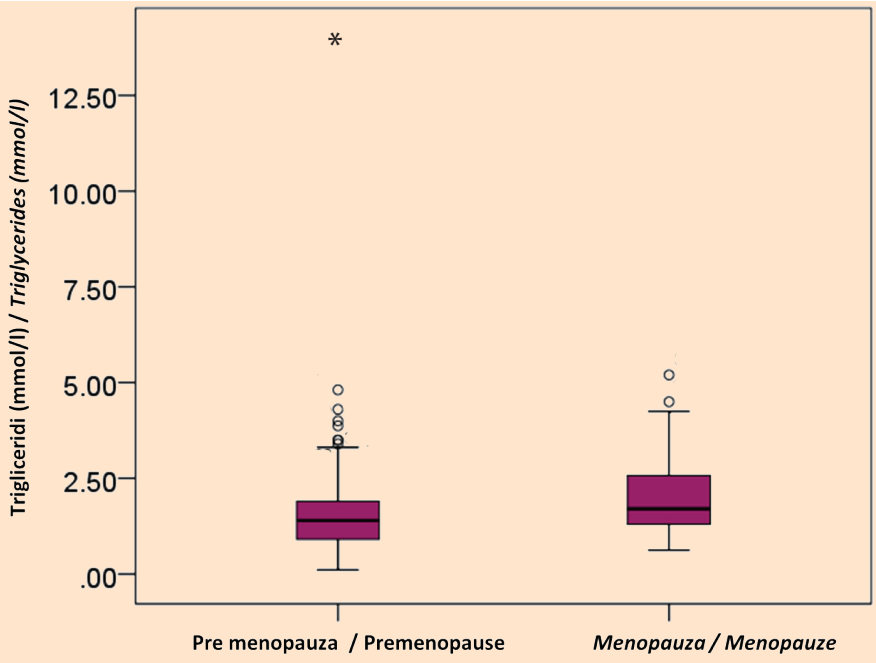
Grafikon 2. Vrednosti LDL-holesterola kod žena pre menopauze i u menopauzi

Graph 2. LDL cholesterol levels in premenopausal and menopausal women

tranzicije menopauze i u prvih nekoliko godina nakon poslednje menstruacije. Tako veća učestalost diabetes mellitusa tip 2 kod žena može biti posledica gojaznosti. Inflamacija u aterogenezi povezana sa gojaznošću i dijabetesom dovodi do povećanog kardiovaskularnog rizika. Kod žena je verovatnije da će se predijabetes razviti u diabetes mellitus tip 2 [9,14].

U originalnoj kohorti Framinghamske studije, postojala je povezanost između nivoa glikoziliranog hemoglobina (HgA1c) i kardiovaskularnih bolesti kod žena, ali ne i kod muškaraca. Za svako povećanje HgA1c za

by recent studies on the prevalence of obesity among individuals older than 60 years, showing rates of 37.5% in men and 39.4% in women [1]. Changes in reproductive hormones during menopause and the menopausal transition contribute to accelerated weight gain, a phenomenon that is particularly pronounced during the menopausal transition and in the first few years after the last menstruation. Thus, the higher prevalence of type 2 diabetes mellitus in women may be a consequence of obesity. Inflammation in atherogenesis, associated with obesity and diabetes, increases cardio-



Grafikon 3. Vrednosti triglicerida kod žena pre menopauze i u menopauzi

Graph 3. Triglyceride levels in premenopausal and menopausal women

1%, relativne šanse za kardiovaskularne bolesti su porasle za 1,39 puta kod žena. U meta-analizi, stopa fatalne koronarne bolesti bila je veća među pacijentima sa dijabetesom u poređenju sa onima bez dijabetesa (5,4% naspram 1,6%) [14]. Rana dijagnoza dijabetesa je neophodna posebno radi sprečavanja mikrovaskularnih komplikacija.

Hipertenzija može biti posledica disfunkcije vaskularnog endotela i disbalansa endotelnih medijatora (endotelina, azot oksida, prostaciklina) koji kontrolišu vaskularnu funkciju. Estrogeni indukuju sintezu azot oksida (NO), povećavaju formiranje inozitol 1,4,5-trisfosfata (IP3), koji stimuliše oslobađanje Ca^{2+} iz endoplazmatskog retikuluma. Ca^{2+} formira kompleks sa kalmodulinom, koji se zatim vezuje i izaziva početnu aktivaciju eNOS-a. Aktivirana eNOS podstiče transformaciju L-arginina u L-citrulin i proizvodnju NO, koji izaziva relaksaciju glatkih misica vaskulature (VMS). Jasan je potencijalni efekti estrogena na vaskularni endotel. Povećan vaskularni tonus uzrokuje hipertenziju, što dovodi do oštećenja krvnih sudova [10]. Estrogeni podstiču vazodilataciju i mogu ublažiti hipertenziju. Takođe mogu smanjiti vaskularnu propustljivost, reaktivne vrste kiseonika (ROS) i infiltraciju inflamatornim ćelijama. Estrogeni takođe mogu usporiti napredovanje ateroskleroze poboljšanjem lipidnog profila i smanjiti tromboemboliju smanjenjem agregacije trombocita. Verovatno je da oksidativni stres i povećano stvaranje reaktivnih vrsta kiseonika predstavljaju zajedničku molekularnu osnovu koja povezuje imunoinflamaciju sa hipertenzijom što je kod žena u menopauzi sa padom estrogena češće.

Dislipidemija je dobro poznati faktor rizika sa direktnom relacijom između LDL-holesterola i aterosklerotske kardiovaskularne bolesti. Studije koje su uključivale žene su pokazale da je smanjenje LDL-holesterola povezano sa smanjenim rizikom od KVB i u primarnoj i u sekundarnoj prevenciji. INTERHEART je bila velika studija kontrole slučaja koja je nastojala da kvantifikuje rizik od različitih faktora rizika koji se mogu primeniti za kardiovaskularne bolesti. Pušenje i abnormalni lipidni profil (definisano kao povišen odnos ApoB/ApoA1) bili su dva najjača faktora rizika za infarkt miokarda [7,15]. Terapija statinima ima prednosti u smanjenju rizika od KVB, iako starije žene za 20% manje od muškaraca koriste statine, što može biti zbog ređeg propisivanja leka ili veće prevalencija mialgija povezanih sa statinima [16]. Nivo holesterola može da varira tokom životnog veka, od mlade odrasle osobe do trudnoće i do prelaska u menopauzu, a lečenje treba da bude određeno prema tome. Žene su pod povećanim rizikom od dislipidemije u periodu menopauze što se karakteriše višim ukupnim holesterolom, trigliceridima

vascular risk. Women are more likely to progress from prediabetes to type 2 diabetes mellitus [9,14].

In the original Framingham cohort, an association between glycated hemoglobin (HbA1c) levels and cardiovascular disease was observed in women but not in men. For each 1% increase in HbA1c, the relative odds of cardiovascular disease increased by 1.39 times in women. In a meta-analysis, the rate of fatal coronary disease was higher among patients with diabetes compared to those without diabetes (5.4% vs. 1.6%) [14]. Early diagnosis of diabetes is essential, particularly for preventing microvascular complications.

Hypertension may result from vascular endothelial dysfunction and an imbalance of endothelial mediators (endothelin, nitric oxide, prostacyclin) that regulate vascular function. Estrogens induce nitric oxide (NO) synthesis and increase the formation of inositol 1,4,5-trisphosphate (IP3), which stimulates the release of $Ca^{2+}$from the endoplasmic reticulum. Ca^{2+} forms a complex with calmodulin, which then binds and initiates activation of endothelial nitric oxide synthase (eNOS). Activated eNOS promotes the conversion of L-arginine to L-citrulline and the production of NO, which induces relaxation of vascular smooth muscle. The potential effects of estrogen on the vascular endothelium are evident. Increased vascular tone leads to hypertension, which in turn causes vascular damage [10]. Estrogens promote vasodilation and may attenuate hypertension. They may also reduce vascular permeability, reactive oxygen species (ROS), and inflammatory cell infiltration. Estrogens may also slow the progression of atherosclerosis by improving lipid profile and reducing thromboembolism by decreasing platelet aggregation. Oxidative stress and increased production of reactive oxygen species likely represent a common molecular basis linking immunoinflammation with hypertension, which is more frequent in menopausal women due to decreased estrogen levels.

Dyslipidemia is a well-known risk factor with a direct relationship between LDL cholesterol and atherosclerotic cardiovascular disease. Studies including women have shown that reduction of LDL cholesterol is associated with reduced cardiovascular risk in both primary and secondary prevention. INTERHEART was a large case-control study that aimed to quantify the risks associated with various cardiovascular disease risk factors. Smoking and abnormal lipid profile (defined as an elevated ApoB/ApoA1 ratio) were the two strongest risk factors for myocardial infarction [7,15]. Statin therapy has benefits in reducing cardiovascular risk; however, older women use statins 20% less frequently than men, which may be due to less frequent prescribing or a higher prevalence of statin-associated myalgia [16].

i LDL-holesterolom a nižim HDL-holesterolom. Visoki nivo non-HDL-holesterola i triglicerida su važniji faktori rizika za KVB kod žena nego kod muškaraca, posebno žene sa dijabetesom [17]. Povišen nivo lipoproteina(a) se smatra faktorom rizika koji ispoljava protrombotički, proinflamatorni i proaterogeni efekat kod oba pola.

Hipertenzija, dijabetes, fizička neaktivnost i upotreba alkohola bili su snažnije povezani sa infarktom miokarda kod žena nego kod muškaraca što je pokazala Interhart studija [7]. Prospektivna multicentrična studija imidžinga za procenu bola u grudima (PROMISE) pokazala je da su žene sa stabilnim simptomi koronarne bolesti imale veće opterećenje faktorima rizika od muškaraca [8].

Povećani indeks telesne mase (BMI) je povezan sa povećanim rizikom od KVB kod oba pola ali postoje polne razlike u distribuciji masti, visceralne i potkožne [18]. Žene pretežno akumuliraju potkožno masno tkivo, dok muškarci akumuliraju više visceralnih masti. U menopauzi kod žena se povećava količina visceralnih masti i infiltracije mišića mastima u poređenju sa ženama pre menopauze sličnih godina, što doprinosi insulinskoj rezistenciji i inflamaciji [1,19]. Pojedini faktori rizika za KVB su povezani sa većom količinom masti i gojaznošću. Tako je hipertenzija povezana sa prekomernom težinom i gojaznošću kod žena, a dijabetes je povezan sa abdominalnom gojaznošću kod žena [18]. Smanjenje težine je povezano sa padom nivoa holesterola, nižim krvnim pritiskom i smanjenjem rizika za razvoja diabetes mellitus tipa 2.

Rezultati našeg istraživanja su u skladu sa nalazima evropskih studija koje pokazuju da se učestalost metaboličkih poremećaja i hipertenzije značajno povećava nakon menopauze. Takođe, rezultati biohemijskih analiza lipidnog profila ukazuju na značajno više vrednosti ukupnog i LDL holesterola kod žena u postmenopauzi u poređenju sa ženama pre menopauze, što dodatno potvrđuje nepovoljne metaboličke promene u ovom periodu života [20].

Kod grupe žena u perimenopauzi značajno češće se potvrđuje hipotireoza gde je najčešći uzrok Hashimoto tireoiditis. Razlog za veći broj potvrđenih slučajeva hipotireoze osim boljih dijagnostičkih mogućnosti je hronični stres i poremećaj imunog sistema zbog modernog načina života. Hormonski disruptori iz okoline (u plastici, kozmetici, pesticidima) i nedostaci mikronutrijenata mogu biti razlog sve češćeg oboljevanja od hipotireoze [21]. Žene su posebno osetljive zbog uticaja estrogena na imuni odgovor i hormonske oscilacije mogu izazvati autoimunu bolest kod genetski predisponiranih žena [22].

Prisustvo estrogenskih receptora (ERa i ERb) u velikom broju u visceralnom masnom tkivu [18] podrža-

Cholesterol levels may vary throughout the life course, from young adulthood to pregnancy and the menopausal transition, and treatment should be determined accordingly. Women are at increased risk of dyslipidemia during menopause, characterized by higher total cholesterol, triglycerides, and LDL cholesterol, and lower HDL cholesterol. High levels of non-HDL cholesterol and triglycerides are more important risk factors for cardiovascular disease in women than in men, especially in women with diabetes [17]. Elevated lipoprotein(a) levels are considered a risk factor with prothrombotic, proinflammatory, and proatherogenic effects in both sexes.

Hypertension, diabetes, physical inactivity, and alcohol use were more strongly associated with myocardial infarction in women than in men, as demonstrated by the INTERHEART study [7]. The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) showed that women with stable symptoms of coronary disease had a higher burden of risk factors compared to men [8].

Increased body mass index (BMI) is associated with increased cardiovascular risk in both sexes; however, there are sex differences in fat distribution, including visceral and subcutaneous fat [18]. Women predominantly accumulate subcutaneous fat, whereas men accumulate more visceral fat. During menopause, women experience increased visceral and intramuscular fat infiltration compared with premenopausal women of similar age, contributing to insulin resistance and inflammation [1,19]. Certain cardiovascular risk factors are associated with increased fat mass and obesity. Hypertension is associated with overweight and obesity in women, while diabetes is associated with abdominal obesity in women [18]. Weight reduction is associated with lower cholesterol levels, lower blood pressure, and a reduced risk of developing type 2 diabetes mellitus.

The results of our study are consistent with findings from European studies showing that the prevalence of metabolic disorders and hypertension significantly increases after menopause. In addition, lipid profile analyses indicate significantly higher levels of total and LDL cholesterol in postmenopausal women than in premenopausal women, further confirming unfavorable metabolic changes during this period of life [20].

In the group of perimenopausal women, hypothyroidism was significantly more frequently observed, with Hashimoto's thyroiditis being the most common cause. In addition to improved diagnostic capabilities, the higher number of confirmed cases of hypothyroidism may be related to chronic stress and immune system disturbances associated with modern lifestyles. Environmental endocrine disruptors (found in plastics, cosmetics, and pesticides) and micronutrient deficien-

va direktnu ulogu estrogena u modulaciji funkcije visceralnog masnog tkiva. Estrogen inhibira taloženje lipida u adipocitima, koristeći dva načina, direktnim smanjenjem lipogeneze kroz slabljenje aktivnosti enzima lipoprotein lipaza (LPL), a indirektno utičući na lipolizu kroz poboljšanje funkcija lipolitičkog enzima hormon-senzitivne lipaze (HSL) [23]. Estrogen takođe indirektno reguliše lučenje leptina od strane masnog tkiva i utiče na unos hrane, potrošnju energije i samim tim na povećanje telesne mase [1,18].

Ograničenja ovog istraživanja jeste relativno mala veličina uzorka, koja može uticati na statističku snagu studije i generalizaciju dobijenih rezultata. Iz tog razloga u ovom istraživanju nisu sprovedene multivarijantne analize. Buduća istraživanja na većem uzorku ispitanika mogla bi omogućiti primenu kompleksnijih statističkih metoda i dodatnu potvrdu dobijenih nalaza.

ZAKLJUČAK

Žene kao i muškarci imaju tradicionalne promenljive kardiovaskularne faktore rizika, ali osim njih žene imaju i polno specifične koji značajno povećavaju kardiovaskularni rizik. Postoji polni dimorfizam u distribuciji telesne masti i potkrepljujući dokazi o regulatornoj ulozi estrogena, posebno 17b-estradiola u metabolizmu i regionalnoj distribuciji masnog tkiva. Sklonost ka androidnoj distribuciji masti je prepoznata kod starijih žena i verovatno je odgovorna za kaskadu hroničnih zdravstvenih poremećaja, uključujući hipertenziju, diabetes mellitus tipa 2 i velike kardiovaskularne događaje. Ovi podaci su značajni zdravstvenom sistemu jer kontrola telesne mase kod svih uzrasta, a posebno kod žena u menopauzi treba da predstavlja prioritetni cilj. Eksperimentalni podaci i kliničke studije ukazuju na složene razlike u regulaciji vazomotorne funkcije mikrovaskularnih krvnih sudova kod žena i muškaraca što doprinose razumevanju polnih razlika i specifičnosti rizika za ishemijsku bolest kod žena. Bolje razumevanje patofizioloških mehanizma može pomoći u planiranju novih strategija za prevenciju, otkrivanje i lečenje kardiometaboličkih bolesti koje su u potpunosti prilagođeni ženama.

Sukob interesa: Nije prijavljen.

Notifikacija: Rad je prethodno prezentovan na 34. Evropskom sastanku o hipertenziji i kardiovaskularnoj zaštiti, održanom od 23. do 26. maja 2025. godine u Minanu, Italija. Sažetak je objavljen u *Journal of Hypertension* (2025), Vol. 43, Br. suppl. 1.

cies may contribute to the rising incidence of hypothyroidism [21]. Women are particularly susceptible due to the influence of estrogen on immune response, and hormonal fluctuations may trigger autoimmune disease in genetically predisposed individuals [22].

The presence of estrogen receptors (ERα and ERβ) in large numbers in visceral adipose tissue [18] supports the direct role of estrogen in modulating visceral fat function. Estrogen inhibits lipid accumulation in adipocytes through two mechanisms: directly, by reducing lipogenesis via decreased activity of lipoprotein lipase (LPL), and indirectly, by influencing lipolysis through enhancement of hormone-sensitive lipase (HSL) activity [23]. Estrogen also indirectly regulates leptin secretion from adipose tissue and affects food intake and energy expenditure, thereby influencing body weight [1,18].

A limitation of this study is its relatively small sample size, which may affect statistical power and the generalizability of the results. For this reason, multivariate analyses were not performed. Future studies with larger sample sizes may allow the application of more complex statistical methods and further validation of these findings.

CONCLUSION

Women, like men, have traditional modifiable cardiovascular risk factors; however, in addition, they have sex-specific factors that significantly increase cardiovascular risk. There is sexual dimorphism in body fat distribution, supported by evidence of the regulatory role of estrogen, particularly 17β-estradiol, in metabolism and regional fat distribution. A tendency toward android fat distribution is observed in older women and is likely responsible for a cascade of chronic health disorders, including hypertension, type 2 diabetes mellitus, and major cardiovascular events. These findings are important for the healthcare system, as body weight control at all ages, particularly in menopausal women, should be a priority. Experimental data and clinical studies indicate complex differences in the regulation of vasomotor function of microvascular blood vessels between women and men, contributing to the understanding of sex differences and the specific risk of ischemic heart disease in women. A better understanding of pathophysiological mechanisms may help plan new strategies tailored to women for the prevention, detection, and treatment of cardiometabolic diseases.

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