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The Concentration High-Density Lipoprotein in the Menopausal Transition

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ABSTRACT

Menopausal transition is a period characterised by psychic, somatic changes as well as changes in reproductive capabilities of a woman as a consequence of ovarian's function termination. Menopausal transition includes the stage of premenopause and perimenopause, to reach finally the menopause stage itself. The aim of this study is to determine the differences in HDL concentrations at women in premenopause, perimenopause and postmenopause, and to determine the connection between BMI and WHR with HLD concentrations during the menopausal transition, as well as to determine the relation between menarche and length of reproductive age with HDL concentrations in menopausal transition. The assesses included in this study were aged from 40 to 55, with average age 48.1 ± 3.9 years. The biggest average HDL value was found at the group of postmenopausal assessees(1.65 mmol/L), and in comparison with the values in other two groups, there is a significant difference (F=4.23, p=0.016). Based on the obtained results, we cannot conclude that there is a significant relation between menarche and length of reproductive age and HDL among the premenopausal and postmenopausal assessees. There is also a significant difference between WHR and HDL among the premenopausal and perimenopausal assesses. In this study, we obtained astonishing result in comparison with the studies and researches done so far, primarily referring to increased HDL at perimenopausal and postmenopausal assessees.

Key words: *Menopausal transition, high-density lipoprotein (HDL)*

Introduction

Menopausal transition is a period of dynamic changes in reproductive and non-reproductive tissues so therefore it is considered to play a leading role in biological and health condition of an aging woman. During menopausal transition, the aging is as important as menopause[1]. Menopausal transition, during its period, shall go through premenopause and perimenopause stages, in order to reach finally the menopausal stage. If we neglect the fact that the average age for menopause is 51.4, we can concluded then that women spend one-third of their lives in postmenopausal stage. Hormonal profile of menopausal transition is changing. Higher basal FSH in normal cycles of women is related to unfavourable lipids level and increased cardiovascular risks[2]. In menopause, metabolic changes in various tissues and organs occur as a result of changed hormonal profile[3]. Transition to menopause includes central neuroendocrine changes as well as changes within the ovarii, the most characteristic of which is the absolute decrease of folicles' number. The influence of oestrogen to lipid metabolism is evident in both, physiological status dependant on life age, as well as in psychological conditions. Oestrogens stimulate synthesis of triglycerides in liver and decrease the hepatic triglyceride lipase activity (HTGL), as well as lipoprotein lipase activity (LPL). Due to such impact, oestrogens lead to increased endogenous status of triglycerides and very low density lipoproteins, VLDL, as well as decrease removal of those particles from circulation. Oestrogens increase the HDL cholesterol level and also increase the protein synthesis in liver, as well as the apolipoprotein A (apo A) which makes a part of HDL. Oestrogens have a very favourable impact to the level of atherogenic LDL particles[4]. HDL metabolism is partially connected through Apo lipoproteins with metabolism with triglyceride-rich hilomicrones and VLDL. HDL is biosynthetized in liver and small intestine, from where it is excreted. It is considered that HDL reacts with probable HDL receptor in liver thus being removed from circulation,

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TABLE 1
AVERAGE HDL CONCENTRATIONS

	Group I (n=50)	Group II (n=50)	Group III (n=50)	*P* value
HDL, mmol/L	1.48 (1.38, 1.57)	1.48 (1.39, 1.58)	1.65 (1.55, 1.75)	0.016

Values are estimated arithmetical median values and related 95% reliability interval. Group I – premenopausal assessees; group II – perimenopausal assessees; group III – postmenopausal assessees.

TABLE 2
REGRESSION COEFFICIENT FOR HDL IN RELATIO TO MENARCHE

	Group I			Group II			Group III		
	Regression coefficient	95% IP	*P* value	Regression coefficient	95% IP	*P* value	Regression coefficient	95% IP	*P* value
HDL, mmol/L	0.005	–0.053, 0.063	0.870	–0.010	–0.058, 0.037	0.663	–0.013	–0.074, 0.047	0.666

Group I – premenopausal assesses; group II – perimenopausal assesses; group III – postmenopausal assesses.

and also transferring surplus cholesterol from peripheral cells to the liver. There is a significant relation between the age and changes in triglyceride levels, total cholesterol and LDL, while BMI is closely related to the changes in the level of triglycerides, LDL, HDL[5]. Total cholesterol, LDL and apolipoprotein B (apo B) show partial increase a year before and a year after the last menstruation, while HDL level reaches its peak around menopausal phase, after which it decreases[6]. Only total cholesterol, LDL and apo B show essential increase in a year before and after the last menstruation, and that fact is similar in all ethnical groups[7]. Elevated values of cholesterol, triglyceride, LDL, apo B and decreased values of HDL and apo A are the features of lipid profile in postmenopause. HDL concentration is much lower at the group of menopausal women[8]. Some studies[9,10] showed significant differences in concentration of lipids and lipoproteins at menopausal women, while the latest researches[11-13] are based on the assessment of changes in LDL and HDL structure and their possible impact to cardiovascular risk at menopausal women. With menopause, HDL concentration decreases and HDL structure changes. HDL_2 concentration decreases, while HDL_3 concentration increases. HDL concentration is reversely proportional to the level of abdominal obesity[14]. Early menarche is related to increased body mass and higher resistance to insulin. According to the latest studies, it affects the increase of HDL cholesterol and decreased level of triglycerides, while longer reproductive period is also related to increased body mass, and opposite from the age of menarche occurrence, it is characterised by decreased level of HDL and all other cholesterols[15].

Goal of research

1. Determine difference in HDL concentrations at women in premenopause, perimenopause and postmenopause.
2. Determine the connection between BMI and WHR and HDL concentrations during menopausal transition.
3. Determine relation between menarche and duration of reproductive age and HDL concentration in menopausal transition.

Assessees and Methods

This prospective, comparative study was conducted in period November 2012 – December 2013, and it included 150 assessees in total, divided in three age groups from 40 to 55.

Selection criteria for this study were: they do not take hormonal supplement therapy, they do not take medicines that could affect the lipid profile, they do not smoke more than twenty cigarettes a day, BMI does not exceed 35 kg/m².

The assessees were processed in three phases: interview, blood sampling, measuring BMI and WHR. The assessee group comprised women volunteers who agreed in writing to be included in the study. Each assessee was introduced with the character of the research.

Blood sampling was conducted in the Department for medical diagnostic of the public institution Health Centre in Tuzla by the trained employees. The vein blood sample was taken from cubital vein for the purpose of the analysis, after which the blood was centrifuged, and HDL was determined from the obtained serum at the machine SIEMENS »Dimension RxL« using direct, »homogenous« method, where through reaction with special detergent we stabilize only HDL fraction from the others (LDL, VLDL). Quantitative determining of HDL is a combination of ultracentrifugation and chemical precipitation where HDL is separated from other lipoproteins.

Body mass and height of assessees was measured at the scale with height meter »SECA«, after which the nutrition status was estimated based on Qeuetelet index (Devenport-Kaup modification) or BMI: body mass in kg/ height in m^2. Based on the waste size measured at the narrowest part and hips size measured at the widest part, WHR was calculated: waist size (cm) / thighs size (cm). Evaluation of the nutrition status was done based on the Qeuetelet index (Devenport-Kaup modification) or BMI where: BMI= body mass in kg/ height in m^2.

Based on the waist size measured at the narrowest part and thighs size measured at the widest part, WHR was calculated using the following formula: WH ratio= waist size (cm)/ thighs size (cm).

To compare numeric variables among the assessees, we used the analysis of variance (ANOVA) or Kruskal-Wallis non-parametric alternative. Multiple pair comparisons were conducted using Tukey or Bonferroni test. Variable values were presented as estimated arithmetic median values with relevant 95% reliability interval. Equality between noticed and expected frequency of category variables were tested with hi-square test. The results are presented as regression coefficients with related 95% reliability interval (IP). At log-transformed variables, regression coefficients are reversely transformed. Statistical importance was confirmed at $p<0.05$. For data processing, we used statistical programme PASW 18 (SPSS Inc., Chicago, Illinois, SAD).

Results

The assessees included in the study aged from 40 to 55, with average age 48.1 ± 3.9. The age statistically differed among the groups: the perimenopausal assessees were two years older in average than the premenopausal ones (95% IP: 0.6-3.5 years), and the postmenopausal assessees were four years older in average than the perimenopausal ones (95% IP: 2.6-5.4 years). There was significant variability between medium HDL concentrations in three study groups (Table 1). The biggest average HDL value was in the postmenopausal group of assessees (1.65 mmol/L), and in comparison with the values in other two groups, there is a significant difference (F=4.23, p=0.016). Multiple pair comparisons showed higher medium concentration at the postmenopausal assessees in relation to the premenopausal assessees (medium difference = 0.17 mmol/L, p=0.029). Higher medium HDL concentrations were also noticed at postmenopausal assessees in relation to perimenopausal assessees (medium difference = 0.16mmol/L, p=0.041). The results of the analysis of relation between menarche and HDL cholesterol concentration at the assessees, conducted utilizing bivarian linear regression model, are presented in the table 2. Based on the obtained regression coefficients and related *P* values, it may be concluded that there is a significant relation between menarche and HDL at the premenopausal, perimenopausal and postmenopausal assessees (Table 2). There is a significant negative relation between BMI and HDL at the premenopausal assessees (Table 3). If the regression coefficient was standardized to interquartile value of change in BMI (IQR=5), the difference of 0.18 mmol/L would be suggested in medium HDL concentration between low and high BMI. Multivariate regression analysis would show that BMI affects HDL concentration. There is a significant negative relation between WHR and HDL at the premenopausal and perimenopausal assesses (Table 4). At WHR change for 0.05, regression coefficient shows the difference of 0.11 mmol/L in medium HDL concentration at premenopausal assessees, and the difference of 0.09 mmol/L in medium HDL concentration at perimenopausal assessees.

TABLE 3

REGRESSION COEFFICIENT FOR HDL IN RELATION TO BMI

	Group I			Group II			Group III		
	Regression coefficient	95% IP	*P* value	Regression coefficient	95% IP	*P* value	Regression coefficient	95% IP	*P* value
HDL, mmol/L	**–0.035**	**–0.057, –0.012**	**0.004**	–0.018	–0.042, 0.006	0.143	0.020	–0.009, 0.050	0.177

Group I – premenopausal assesses; group II – perimenopausal assesses; group III – postmenopausal assesses.

TABLE 4

REGRESSION COEFFICIENT FOR HDL IN RELATIO TO WHR, CALCULATED TO WHR CHANGES FOR 0.05

	Group I			Group II			Group III		
	Regression coefficient	95% IP	*P* value	Regression coefficient	95% IP	*P* value	Regression coefficient	95% IP	*P* value
HDL, mmol/L	**–0.105**	**–0.186, –0.023**	**0.013**	**–0.089**	**–0.144, –0.034**	**0.002**	0.017	–0.069, 0.102	0.692

Group I- premenopausal assesses; group II- perimenopausal assesses; group III- postmenopausal assesses.

Discussion

Numerous studies have been addressing the trend of HDL cholesterol value during menopausal transition. The average age in time of the last menstruation at the assesses from this study was 48 years of age, and the literature so far[15] has suggested that menopause usually occurs at the age 51, and that it has not changed for a long period of time. Although the lipid profiles are inclined to deterioration with age, it is not completely clear whether such changes are related to age and life style, or are influenced by other aspects of aging. The age is important independent predictor for LDL and total cholesterol at women, but it does not have such an influence as body structure and life style affecting the HDL, LDL and triglyceride level at women[16]. One of the objectives of this study was to determine the relation between BMI and WHR and HDL concentration at the assessees in menopausal transition, and the results of this study show that there is a negative relation between BMI and HDL in premenopause. We have determined only a significant negative relation between WHR and HDL cholesterol at the premenopausal and perimenopausal assesses. At premenopausal women, WHR has a significant negative correlation with HDL concentration[8]. The results of the researches done within the comprehensive study implemented by the National Health and Nutrition Examination Survey among the assessees aged 35-60 in period 1999-2002[1] showed that there are no significant differences at total level of cholesterol, triglycerides, HDL, LDL cholesterol adjusted to the age, among menopausal periods at women with normal BMI. A difference in HDL cholesterol values was noticed at groups with normal and higher BMI. Therefore, it is important to note that regardless the known and characteristic hormonal profile in menopausal transition, we obtained in this study a surprising result in comparison with the researches and studies conducted so far, primarily related to increased HDL at perimenopausal and postmenopausal assessees. So, the total cholesterol level increases with menopause, LDL share changes and increases, while HDL does not change[17]. The women who gave birth to children usually have lower HDL level than women who did not give a birth[18]. Menopause has unfavourable impact to lipids metabolism, particularly to total cholesterol values, which mainly increases through menopausal transition, although the biggest problem mentioned is decrease of HDL cholesterol[5]. The results of a big study conducted at 9309 women show that menopause influences the level of lipids and lipoproteins. From premenopause to postmenopause there is a significant increase of total cholesterol, LDL, triglycerides, but there are no significant changes in HDL[19]. At postmenopausal women, HDL is lower than at premenopausal women[20], which does not comply with our results.

In period 1995-2004, the SWAN study was implemented at 2659 women who were followed-up during 7 year period and at whom the lipid changes mainly occurred in later menopausal stages[21]. HDL cholesterol also reached the maximum in late perimenopause and early postmenopause, which is also confirmed by the results of this study. Although this does not comply with the previous studies which show a gradual post-menopausal decrease of HDL[22,23], the noticed trend complies with other studies, showing a gradual increase between pre-perimenopause and late perimenopause[24]. A small prospective study came to a conclusion that HDL reached maximum values, and then decreased between pre and post menopause[24]. Since not so long ago, it was generally accepted that HDL cholesterol values decrease with menopause. However, latest studies show different results. Postmenopausal women have higher HDL values than premenopausal women and according to the results of the latest studies, there was no difference between perimenopausal and postmenopausal women. Menopause is related with HDL elevation, so that higher postmenopausal risk for cardiovascular diseases is not related to HDL values. HDL values are higher in perimenopause than in premenopause and late menopause. Perimenopausal profile is closely related with elevated HDL cholesterol levels. The study in Islamabad[25], which analysed the HDL cholesterol level at premenopausal and postmenopausal assessees in relation to estradiol level, showed a decrease of HDL at postmenopausal assessees in comparison with the premenopausal assessees. The conclusion of that study is that HDL is an independent risk factor for coronary diseases, which is contrary to the results of this study and similar consequent studies. MWMH Project[23] noticed that there is a slight HDL cholesterol increase in a year before menopause, followed by similar decrease in a year after the last menstruation. Epidemiologic studies indicate that there is no relation between the total cholesterol and brain stroke risk, but little attention is paid to HDL. Severity of literature proofs supports inverse relation between HDL values and brain stroke or carotid atherosclerosis, but more data are needed to strongly determine that protective effect[26]. This study demonstrated a permanent increase of HDL cholesterol from premenopause to postmenopause, with particularly emphasised differences between the premenopausal and postmenopausal assessees. Additional follow-up is needed to determine whether HDL noticed in late postmenopause would return to premenopausal levels. In similar study[27], the results showed much higher HDL cholesterol level at postmenopausal assessees than at premenopausal assessees. The obtained results in this study, as well as the results of the Study of Women's Health Across the Nation Heart women[28], indicate that protective effect of HDL may be decreased at women in menopausal transition. The future studies should assess could it be due to the changes in HDL particles size, functionality or relation of changes with other lipids and lipoproteins. Considering the well-known fact that non-atrogenous HDL related to apo A has the cholesterol clearance function from artery walls, that it breaks the disposal of aterogenous lipoproteins, based on the obtained results we cannot conclude that HDL is responsible for increased risk of cardiovascular diseases during menopausal transition. Significant result of this study, when it comes to HDL, confirms only some of the studies conducted so far.

Conclusions

1. HDL increases during menopausal transition and has the highest concentrations at postmenopausal assesses.
2. BMI with HDL concentration has a negative correlation in premenopause.
3. WHR has a negative correlation with HDL concentration in premenopause and perimenopause.

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KONCENTRACIJA LIPOPROTEINA VISOKE GUSTOĆE U MENOPAUZALNOJ TRANZICIJI

SAŽETAK

Menopauzalna tranzicija je period koji karakterišu psihičke, somatske i promjene u reproduktivnoj sposobnosti žene a nastaje kao posljedica gašenja ovarijalne funkcije. Menopauzalna tranzicija će u svom trajanju preći preko premenopauze i perimenopauze, da bi došla do same menopauze. Cilj istraživanja je bio utvrditi razlike u koncentracijama HDL kod žena u premenopauzi, perimenopauzi i postmenopauzi, utvrditi povezanost BMI i WHR sa koncentracijama HDL tokom menopauzalne tranzicije, te utvrditi povezanost menarhe i dužine reproduktivne dobi sa koncentracijama HDL u menopauzalnoj tranziciji. Ispitanice, uključene u studiju, su bile stare od 40 do 55 godina, s prosječnom starošću od 48.1 ± 3.9 godine. Najveća prosječna vrijednost HDL-a nađena je u grupi ispitanica koje su u postmenopauzi (1.65 mmol/L), i u odnosu na vrijednosti u druge dvije grupe postoji značajna signifikantna razlika (F=4.23, p=0.016). Na osnovu dobijenih rezultata ne možemo zaključiti da postoji značajan odnos između menarhe i dužine reproduktivne dobi sa HDL kod ispitanica u premenopauzi, perimenopauzi i postmenopauzi. Postoji značajan negativan odnos između BMI i HDL kod ispitanica u premenopauzi, a multivariatnom regresijskom analizom se pokazalo da BMI utiče na koncentraciju HDL. Značajan je i negativan odnos između WHR i HDL kod ispitanica u premenopauzi i perimenopauzi. U ovom istraživanju smo dobili iznenađujući rezultat u odnosu na dosadašnja istraživanja, koji se prije svega odnosi na povećan HDL u perimenopauzalnih i postmenopauzalnih ispitanica.