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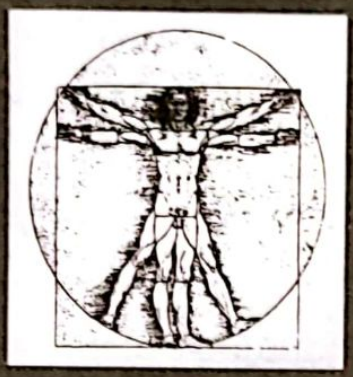

ЗАММ

ACTA MORPHOLOGICA

ПУБЛИКАЦИЈА НА ЗДРУЖЕНИЕТО НА АНАТОМИ И МОРФОЛОЗИ НА МАКЕДОНИЈА

PUBLICATION OF MACEDONIAN ASSOCIATION OF ANATOMISTS AND MORPHOLOGISTS

Vol.5 (2) 2008

UDC:616.153.915:618.173

МЕНОПАУЗА, ЛИПИДЕН ПРОФИЛ И КАРДИОВАСКУЛАРНИ БОЛЕСТИ

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Извадок

Кардиоваскуларните болести (КВБ) се една од главните причини за смрт во западните земји, при што една од две жени умираат токму од КВБ. Пременопаузалните жени се најверојатно заштитени од КВБ во споредба со мажите на иста возраст. Иако жените пред својата 50-годишна возраст ретко заболуваат од КВБ, до 70 години инциденцата за КВБ е иста како кај мажите, што укажува на фактот дека дефицитот од естрогени предизвикува забрзано зголемување на ризикот од КВБ. .

Целта на оваа студија е да се еволуира влијанието на менопаузата врз липидниот профил кај постменопаузални жени.

Беше изведена студија на пресек која вклучи 46 здрави жени во менопауза и 24 здрави жени во пременопауза како контролна група. Проценката на липидниот метаболизам беше направена преку следниве параметри: вкупен холестерол, HDL и LDL холестерол, триглицериди, аполипопротеини А и Б1, како и односот apoB/A1.

Студијата покажа значителна статистичка разлика во нивото на вкупниот холестерол (p= 0,0034; p<0,05), како и LDL-C (p= 0,0021; p<0,05) и ApoB (p=0,027; p<0,05) помеѓу двете групи, додека не се пронајде значителна разлика во нивото на триглицеридите (p= 0,067; p>0.05), HDL-C (p=0,623; p>0,05), apoA1 (p=0,196; p>0,05) и во односот Apo B/A1 (p= 0,069; p>0,05).

Општо земено, липидниот профил кај постменопаузалните жени се покажа полош отколку кај пременопаузалните жени.

Клучни зборови: менопауза, липиден профил , КВБ

MENOPAUSE, LIPID PROFILE AND CARDIOVASCULAR DISEASE

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Abstract

Cardiovascular diseases (CVD) are the primary cause of death in women of westernized countries, with more than one in two women dying from CVD. Premenopausal women appear to be protected from CVD compared to me at the same age. Although women under the age of 5 rarely develop CVD, by age 70 the incidence of CVD is equal in men and women, suggesting that estrogen deficiency causes a rapid acceleration of CVD risk.

The aim of his study was to evaluate the impact of menopause on the lipid profile in postmenopausal women in our population.

We performed cross sectional of 46 postmenopausal women. The control group included 24 healthy premenopausal women. Assessment of lipid metabolism was conducted using the following variables: total serum cholesterol levels, HDL cholesterol, LDL cholesterol, triglyceride level (TG), Apolipoprotein A1 (apoA1), Apolipoprotein B (apoB) and the ratio between Apo B/ Apo A1.

There was a significant difference in total cholesterol levels (0,0034; p<0,05), as well as in LDL-c (p= 0,0021; p<0,05)) and ApoB (p=0,027; p<0,05) among healthy premenopausal and postmenopausal women, and there was no statistically significant difference in TG level (p= 0,067; p>0,0)), HDL-c (p=0,623; p>0,05) and apoA1 (p=0,196; p>0,05). Similar results with no significant difference in the triglyceride level were obtained as far as the Apo B/A1 ratio is concerned (p= 0,069; p>0, 05).

We found a poorer lipid profile among postmenopausal women compared to premenopausal women.

Key words: menopause, CVD, lipid profile

Introduction

Menopause is best defined as the absence of menses for 12 consecutive months. The menstrual history is the most reliable indicator of the postmenopausal state, as well as the certain hormonal measures. For exemple estradiol (E_2) and FSH levels both vary widely in the perimenopause during an individual menstrual cycle (1). The perimenopause has been defined as a period of menstrual irregularity and hormonal variability, beginning

when the menstrual cycle length changes from an established pattern into longer, shorter, or more variable cycles with an average duration of 4 yr, ending 1 yr after the final menstrual period. This means that women can expect to have menstrual irregularities for approximately 4 yr before their final menses. Although it is commonly believed that E_2 levels fall gradually throughout the perimenopause, concentrations are preserved until relatively late in the premenopausal period, as E_2 does not decline significantly until women experience at least 3 months of amenorrhea (1).

However, atherosclerotic disease occurrence is different in men and women, as the onset begins approximately 10 yr later in women than men, and myocardial infarction is uncommon until women reach their sixth decade (2).

Controversy exists about whether menopause increases the risk of CVD independent fromnormal aging. Some studies have demonstrated increased risk of CVD after menopause, and others have not (3). For example, Framingham investigators found a 4-fold increase in CVD in the 10 yr following natural menopause. Premature, surgically induced menopause has shown increase of risk of CVD (3). Yet the question of whether natural menopause is an independent risk factor for CVD has not been answered as it is very difficult to design studies that can separate the effects of the normal aging process from menopause.

Studies assessing the relationship of menopause with measures of atherosclerosis have yielded interesting results. Sutton-Tyrrell *et al.* (4) showed that 45% of postmenopausal women (n = 294) had clinically significant carotid intimae-media thickness (e"0.75 mm) compared to 16% of age-matched premenopausal women. Carotid intimae-media thickness has shown to be a strong predictor of CVD risk (5). Aortic calcification, a measure of atherosclerosis, was higher in postmenopausal women, and the extent of calcification increased with the number of postmenopausal years (6). Similarly, coronary-artery-calcium deposits in women, measured by computed tomography (CT), were twice lower in men until the age of 60, when the difference decreased (7).

The relative importance of factors that influence cardiovascular risk in postmenopausal women are unknown. Alterations in lipid metabolism with estrogen deficiency are thought to be a substantial component of CVD risk in postmenopausal women (8), but there are also direct effects of estrogen deficiency on body fat distribution (central obesity), insulin action, the arterial wall, and fibrinolysis that may influence cardiovascular risk. These factors contribute to an increased prevalence of the metabolic syndrome in postmenopausal women compared to premenopausal women (9), and this postmenopausal worsening of the metabolic profile may contribute to the future risk of CVD.

Although the association between abdominal adiposity and the constellation of lipid abnormalities is well known, the underlying pathophysiology is not clear. High amounts of abdominal fat are associated with increased insulin resistance, free fatty acid (FFA) levels, and decreased adiponectin. These factors contribute to increased secretion of apolipoprotein B (apo B)-containing particles, leading to hypertriglyceridemia and increased hepatic lipase (HL) activity resulting in a predominance of small dense LDL particles and a reduction in large antiatherogenic HDL_2 particles. A similar pattern of lipid abnormalities emerges with menopause

Changes in LDL with menopause

Postmenopausal women have higher total cholesterol, LDL cholesterol, triglycerides (TG), and lipoprotein (a) [Lp(a)] levels and lower HDL cholesterol levels than premenopausal women (10,11,12). Although elevated LDL is not a component of the metabolic syndrome, LDL levels increase by 10–20% (13, 14) with menopause, and the greatest change in LDL concentration appears to occur early in the transition from pre menopause to post menopause (15). LDL particle composition also changes with menopause. The prevalence of small, dense LDL is low in premenopausal women (10–13%), but increases to 30–49% in postmenopausal women (16, 17, and 18). LDL is comprised of a spectrum of particles that vary in size, density, chemical composition, and atherogenic potential. A preponderance of small, dense LDL is associated with the increased risk of myocardial infarction (19) as well as the severity of CVD (20). The risk of CVD is 3-fold higher in women with small, dense LDL than in those with large, buoyant LDL (21). Mackey et al. (19) recently showed by electron beam CT that postmenopausal women with high coronary calcium scores had smaller LDL particle size, higher LDL levels, and fewer large HDL_2 particles than postmenopausal women with low coronary calcium scores.

Changes in TG with menopause

Many longitudinal studies have shown that TG levels increase with the transition through the menopause (16), and the increase in TG also appears early in the postmenopausal period (14). Poehlman et al. (20) found that the prospective transition to post menopause was associated with a 16% increase in TG. Although men generally have higher TG levels than women, TG increases in the middle-age (between the age of 40–69 in women, but not in men (22), and TG appears to be a better predictor of CVD risk in women than in men (22). Lindquist (23) reported a prospective increase in TG levels in women who became postmenopausal during a 6-yr period, whereas there was no change in TG in the similarly aged women who remained either premenopausal or postmenopausal. Increasing TG with menopause may be related to the fact that TG levels are highly correlated with increasing abdominal fat content and insulin resistance.

Changes in HDL with menopause

Most studies show that total HDL levels fall slightly during menopause (9, 12, 21, 24), whereas others reveal no changes (25). Menopausal changes in HDL metabolism are more complex than what the measurement of total HDL reveals. This is the case because the more antiatherogenic HDL_2 levels decrease (by 25%); the more HDL3 levels increase (11, 26, 27, and 28). HDL_2 particles

are the large, buoyant, and more cardio protective subspecies of total HDL. The strong inverse relationship between HDL cholesterol and abdominal adiposity appears to be largely depending on variations in HDL_2 levels (29).

Changes in apolipoproteins; their role and significance

In order to explain why apolipoproteins may be risk predictors a brief revision of lipoprotein metabolism is required (30). Apolipoprotein B-100 (apoB) is the chief protein component constituent of the atherogenic very-low-density lipoprotein (VLDL), of intermediate-density lipoprotein (IDL) and of LDL particles, each particle including one apoB molecule. Hence, plasma apoB levels reflect the total numbers of atherogenic particles. In humans, VLDL particles carry endogenously synthesized triglyceride from the liver into the plasma where they undergo lipolysis to IDL with the action of lipoprotein lipase. IDL is lipolysed by hepatic lipase, converting to LDL, or taken up by the liver via the LDL receptor. ApoB is also essential for the binding of LDL particles to the LDL receptor for cellular uptake and degradation of LDL particles.

Both LDL and TG contain apolipoprotein B-100 (apo B) as their major apolipoprotein. According to a growing trend most, if not all of apo B-containing lipoproteins are atherogenic. Although different subspecies of apo B-containing lipoproteins may vary in their atherogenic potential, a simplifying concept is that most of these subspecies carry similar atherogenicity. If so, then measurement of serum total apo B signifies the atherogenic potential of the whole lipoprotein fraction. Total apo B levels are clearly a strong predictor of CHD risk (31). Total apo B levels correlate relatively strongly with non-HDL cholesterol levels. The correlation is particularly strong in the absence of elevated serum triglycerides, but weakens somewhat as triglyceride levels rise. (32,33) Still, non-HDL cholesterol includes all the cholesterol in apo B-containing lipoproteins. Because there is one apo B molecule per lipoprotein particle, total apo B concentrations are a measure for the total particle number in LDL+TG, whereas non-HDL cholesterol provides the cholesterol content of these same lipoproteins. Whether total apo B or non-HDL cholesterol is a better predictor of CHD risk has not been determined through robust prospective studies. In routine clinical practice, non-HDL cholesterol is more readily available, more reliable, and less expensive than total apo B. On the other hand, the methodology for measurement of total apo B is improving and is becoming more widely available. Physicians therefore have an option whether to use non-HDL cholesterol or total apo B levels.

ApoA-I is the major apolipoprotein constituent of the anti-atherogenic high-density lipoproteins (HDL). Levels of apoA-I are strongly associated with those of HDL cholesterol. ApoA-I is critically involved in removing excess cholesterol from tissues and incorporating it into HDL for reverse transport, either directly or indirectly via LDL to the liver. HDL also contains apoA-II, but its function and role in atherogenesis is unclear.

Many epidemiological studies have shown that apolipoproteins are better predictors of cardiovascular risk than conventionally measured lipids, specifically LDL cholesterol and HDL cholesterol. One of them is *Women's Health Study*. It included 15 632 initially healthy US women aged 45 or older over a 10-year period (34). Despite the authors conclusion that non-HDL cholesterol and the ratio of total cholesterol to HDL cholesterol were as good as or better than apolipoprotein fractions in the prediction of future CVD events, apoB was in fact the single most significant lipid-related predictor of the occurrence of CVD events in the study.

Material and methods

We carried out a cross sectional analysis on 24 premenopausal and 46 postmenopausal women who were required to be: not on any hypolipidaemic medication, hormone replacement therapy or any other medication known to interfere with lipoprotein metabolism; not consuming any fatty acid supplements; or following a weight reducing or any other diet. The postmenopausal status was defined as 1 year or more of amenorrhea. Blood samples were taken from our subjects after an overnight fast. Serum levels of total cholesterol, HDL cholesterol and triglycerides were determined enzymatically, LDL cholesterol using Friedwald's formula, apolipoprorotein A1 and B were determined immunoturbidimetrically. Data are presemted as the mean value ± SD. After testing the data for normality, we used the Student unpaired *t* test. The value of $p < 0,05$ was taken to be statistically significant.

Results

Table 1 shows the indicators of lipid metabolism in premenopausal and postmenopausal women. The average of total cholesterol level in premenopausal and postmenopausal women was 5, 76 mmol/l and 6, 97 mmol/l respectively, and 1, 65 mmol/l and 2, 19 mmol/l for triglycerides. HDL-C concentrations were higher in premenopausal (1, 45 mmol/l) than in postmenopausal (1, 34 mmol/l) women, while LDL-C were lower (2, 94 mmol/l and 3, 68 mmol/l for the same two groups. The Apo A levels were 2, 43 mmol/l in premenopausal versus 2, 19 mmol/l in postmenopausal womeh, and the concentrations of atherogenic Apo B were 1, 74 mmol/l and 2, 15 mmol/l

Table 1 Lipid profile on healthy premenopausal and postmenopausal women

	Healthy premenopausal women (n = 24)	*healthy postmenopausal women (n =46)*	*p*
Chol(.mmol/l)	5,76 ± 0,837	6,97 ± 0,814	0,0034
TG (mmol/l)	1,65 ± 0,693	2,19 ± 0,890	0,067
HDL-C (mmol/l)	1,45 ±0,647	1,34 ± 0,468	0,623
LDL-C (mmol/l)	2,94 ±0,553	3,68 ± 0,999	0,0021
ApoA1 (mmol/l)	2,43 ±0,784	2,19 ± 0,635	0,196
Apo B (mmo l/l)	1,74 ± 0,418	2,15 ± 0,475	0,027
Apo B/A1	0,79 ± 0,226	0,98 ± 0,381	0,069

The atherogenic index, ApoB/A1 ratio was 0, 79 in premenopausal and 0, 98 in postmenopausal group, i.e. in both groups it was less than one.

The analytical statistic method revealed that there was a significant difference in the total cholesterol levels (p=0,0034; p<0,05), as well as in LDL-c (p=0,067; pp<0,05) and ApoB (p=0,027; p<0,05) among healthy premenopausal and postmenopausal women, but there was no statistically significant difference in the TG level (p=0,067; p>0,05), HDL-C (p=0,623; p>0,05) and ApoA1 (p=0,196; p>0,05). Similar results were obtained as far as the Apo B/A1 ratio (p=0,069; p>0, 05).

Discussion

CVD is the leading cause of death of women in developed countries, but very little is known about atherosclerotic disease progression in women. There has been a recent emphasis on the metabolic syndrome as an atherosclerotic risk factor and its impact on CVD risk in women (35). Many of the features of the metabolic syndrome (central obesity and dyslipidemia with elevated TG, reduced HDL, and small dense LDL particles) emerge with estrogen deficiency in postmenopausal women, which may explain the acceleration of CVD in women after menopause. Accumulation of excess abdominal fat with transition through the menopause plays a central role in connecting the metabolic syndrome with the metabolic alterations of menopause and may account, in part, for the temporal separation in CVD risk between men and women (36).

It is unclear whether menopause is a cardiovascular risk factor for all women or only for those who carry a predilection toward central adiposity. Endogenous estrogen appears to be cardio protective, and postmenopausal estrogen deficiency unveils a constellation of closely associated adverse changes in metabolic risk factors. The emergence of these risk factors may be a direct result of ovarian failure or, alternatively, an indirect result of the metabolic consequences of central fat redistribution with estrogen deficiency. It is not clear whether the transition to menopause increases cardiovascular risk in all women or only those that develop the features of the metabolic syndrome. Women who develop insulin resistance with small, dense LDL after menopause may be carriers of a genetic predisposition that is masked by the effects of estrogen and unmasked after menopause. This subset of women may require targeted management to prevent future cardiovascular risk. Current evidence implies that multiple risk factors for CVD emerge in the postmenopausal period, but features of the metabolic syndrome may be present even before menopause. More research is clearly needed to further characterize the mechanisms by which women develop these metabolic changes during menopause.

Conclusion

The postmenopausal changes in lipid metabolism reveal an overall shift toward a more atherogenic lipid profile with significantly increased total cholesterol and LDL and Apo B levels, TG and Apo B concentration reduced HDL. This classic dyslipidemia is closely associated with increasing amounts of visceral fat which may explain why these features emerge with the menopause. It is likely that these adverse changes in lipid metabolism during the menopausal transition will contribute to future CVD risk. Nevertheless, it is important to note that a single risk factor does not involve an absolute risk of future cardiovascular events. The inclusion of a combination of demonstrable risk factors as well as the lipid and non-lipid variables (e.g. CRP, smoking or age) within predictive algorithms will provide a more accurate prediction of an individual's overall risk of CVD.

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