Lipid Profile and Menopausal Status

* Fouad Hamad Al-Dahhan FRCOG * Lamia M. Al-Naama Ph.D Med. Bioch. UK
* Ahlam Disher CAB Gyn & Ob

Abstract

Background: Dyslipidemia is a major cause of cardiovascular disease, which, in turn, is the most common cause of female morbidity and mortality. Postmenopausal women (natural and surgical) are at higher risk of developing cardiovascular disease, especially coronary artery atherosclerosis.

Objective: To observe the relationship between blood lipids: total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglycerides (TGs), and very low density lipoprotein-cholesterol (VLDL-C), LDL-C/HDL-C ratio (atherogenic index) and menopausal status, and to determine the co-factors that may explain this relationship.

Methods: A prospective, cross-sectional study, which includes 279 women, age range from 35-55 years agreed to participate in this study. They were divided into 4 groups according to their menopausal status. These were pre-, peri- natural and surgical post-menopausal. Data were collected from participants in a pre-coded questionnaire and an overnight fasting blood sample was collected for biochemical analysis.

Results: Postmenopausal women had higher levels of lipids than pre or peri-menopausal. TC concentration and LDL-cholesterol levels were higher in natural and surgical menopause than in pre and pri-menopausal women (p<0.01 and p<0.05 respectively). While LDL/HDL-C ratio (atherogenic index) were higher in the surgical postmenopausal women than in pre-menopausal group (p<0.05). No significant inter-group differences were found in HDL-C. Triglycerides, and VLDL levels were higher in surgical menopause group than in both pre- and peri-menopause groups (p<0.05). No significant differences were demonstrated in pre-, peri-, and natural menopausal women with regard to triglyceride and VLDL levels in each group and those were discussed.

KeyWords: Menopause, Lipid profile

Introduction

Dyslipidemia is a major cause of cardiovascular disease, which is the most common cause of male and female morbidity and mortality (1). The incidence of cardiovascular disease (CVD) increases after menopause. This may be due to, in part, to changes in the plasma lipid-lipoprotein levels that occur following menopausal transition. Elevated total cholesterol, LDL-cholesterol and triglycerides are more common in post- than premenopausal women (2-4).

There are very few studies on the effects of menopause and related lipoproteins. Despite this, it is commonly believed that surgical menopause are associated with altered lipoprotein changes as well as with increase vascular risk. (5)

In two prospective studies women who became postmenopausal showed a slight but significant reduction in the high-density lipoprotein (HDL) – cholesterol and an increase in triglycerides and low-density (LDL)-cholesterol as compared with premenopausal women (2,6). However, Kuller et al (7) found no significant changes in LDL-cholesterol concentrations in women passing from premenopausal to postmenopausal status, whereas they observed that the HDL2 fraction and apoprotein A-1 were decreased, particularly in those with very low blood–estrogen concentration. Despite the extensive research on the effects of oestrogens and progestagens on lipid and lipoprotein metabolism (8,9) it is not yet clear whether changes in sex steroid concentrations are related to changes in lipid concentrations associated with menopause status. Moreover, there are very few data on the effects of body weight and fat distributions on the lipid concentrations in middle-aged women ranging from premenopause to menopause.

Therefore, in this study we investigated the relationship between the menopausal status and related hormonal variation with plasma lipid concentrations, taking into account the effects of age, body weight, body mass index. All data presented here were obtained from the first cross-sectional examination of a longitudinal survey performed in Basrah (Iraq) in a large cohort of women in pre-, peri-, and menopausal status.

Methods

Two hundred seventy nine Iraqi women between the age 35-55 years were participated in this cross-sectional study. They were attending for routine check up in Well Woman Clinic in Basrah. All
women with a body mass index (BMI) less than 30, cardiovascular, renal, liver, and other endocrine or metabolic disorders that might affect lipid metabolism were excluded. None of them was pregnant or in puerperium or on hormonal contraception, or taking medications known to interfere with lipid metabolism at the time of participation.

All women gave their informed consent to the study and all procedures followed in this study. They were divided into two main groups according to their age:

**Group I:** 117 participants (Age range 35-44 years old) which represent the premenopausal group (PM) of women.

**Group II:** 162 participants (Age range 44-55 years old) which subdivided into three subgroups according to their menopausal status:

- **Perimenopausal:** (M0) 58 participants, who were presented with feature of climacteric period, but still menstruating.
- **Natural postmenopausal:** (M1) 81 participants, who ad spontaneous menopause.
- **Surgical postmenopausal:** (M2) 23 participants, who had subjected to bilateral oopherectomy with or without hysterectomy for benign cause.

Women were evaluated in the morning after 12-14 hours fast. The same well-trained investigator for the duration of the study performed all evaluations. Blood samples were obtained randomly throughout the menstrual cycle (for menstruating women). After blood samples had been drawn, serum were obtained and immediately frozen at -20°C until analysed within 1 or 2 days. In the evaluation the investigator used a precoded questionnaire including a full clinical history, socio-economic and personal information, habitual or current drug use, smoking habits, careful recording of principal gynecological events, a complete history of weight variations during the subject life.

Anthropometric measurements were obtained whilst women wore underwear. Height (in cm.) and weight (in kg.) were recorded and body mass index was calculated.

**Methods**

The blood samples were measured for metabolic lipid parameters. The serum concentrations of TC, TG, HDL-C (after precipitation with sodium phosphotungstate-MgCl2) were determined enzymatically using kits from Bio Merieux, France. All procedures were followed according to the instructions of the manufacturer and according to Lipid Research Clinics protocol (10). Low-density lipoprotein cholesterol (LDL-C) was calculated by use of the formula of Friedewald et al. (11) \[
\text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{5}.
\] This formula is applicable when serum TG level is less than 400mg/dl. Blood glucose concentration was measured by glucose oxidase method (12). Six women with fasting blood glucose level of >140 mg/dl were excluded from the study.

**Statistics:**

Results were expressed as mean ±SD or as percentage, as suitable. The significance of comparisons between pairs of groups was tested using student t-test or chi-square test as appropriate.

The correlation between lipids, menopause, and its duration and W/H ratio were tested, as well as to identify the degree and type of association between them (positive or negative association). Stepwise regression analysis was done to identify factors explaining the variation between the dependent variables in each group of women understudy. The difference was considered statistically significant for value p<0.05.

**Results**

The clinical characteristics of all participants are shown in Table-I. The biochemical parameters of the participants expressed as mean ± SD are presented in Table II. The serum level of TC was significantly (p≤0.01) higher in M1 and M2 than in M0 and PM. There was no inter-group difference in serum level of HDL-C/LDL/HDL-C ratio (atherogenic index) was significantly higher (p≤0.05, p≤0.01), when compared to PM, in each M1 and M2 respectively, and in M1 than M0 (p≤0.05), while the difference was not significant between M0 and M1, M2 or between the later and M1. There was significant difference (P ≤ 0.05) in TG level in M2 than PM and M0, while there were no inter-group difference. There was no significant difference with regard to serum level of VLDL in between the inter-groups.

The frequency of participants with dyslipidemia shown in tables III. The percentage of these high levels of all lipid parameters were progressively rising from pre-menopausal (PM) to perimenopausal (M0) and menopausal women (M1and M2), being more in M1 than M2 (regarding TC, LDL-C and LDL/HDL-C) and more in M2 than M1 regarding HDL-C, TG and VLDL.

The correlation among the lipid parameters, menopause and its duration is shown in table IV. Duration of menopause is directly associated with
Lipid Profile and... Fouad Hamad Al - Dahhan et al

TC and LDL (p≤0.01) and with LDL/HDL-C (p≤0.05) but not with other lipid parameters. In order to determine the relative effect of each of the clinical criterion in predicting the level of lipid understudy, a stepwise linear regression analysis was carried out and presented in table (V).

The level of TC among premenopausal participants was first to be affected directly by the diastolic blood pressure ($R^2=0.957$, p≤0.01), followed by W/H ratio ($R^2=0.004$, p≤0.01) and income ($R^2=0.002$, p≤0.05) respectively and inversely by the duration of periods ($R^2=0.002$, p≤0.05). In M1 group, the TC level was affected directly by the increase in W/H ratio ($R^2=0.959$, p≤0.01), and income ($R^2=0.003$, p≤0.05). The W/H ratio was the only model that entered the analysis in determining the variation in TC level among participants in M1 and M2 ($R^2=0.948$, p≤0.01), ($R^2=0.970$, p≤0.01) respectively. In PM group, the increase level of LDL-C was directly affected by the increase in the diastolic blood pressure ($R^2=0.888$, p≤0.01) and income ($R^2=0.007$, p≤0.05) and inversely affected by lactation ($R^2=0.005$, p≤0.05). In M1 and M2, LDL-C level was directly affected by W/H ratio ($R^2=0.892$, p≤0.01, $R^2=0.876$, p≤0.01) respectively. The level of HDL-C in PM group was directly affected by the family size, age of menarche and inversely by parity. The LDL/HDL-C ratio in PM group was directly affected by diastolic blood pressure ($R^2=0.752$, p≤0.01) and BMI ($R^2=0.036$, p≤0.01). While it had an inverse association with the duration of the cycle ($R^2=0.025$, p≤0.01) and lactation ($R^2=0.002$, p≤0.05). In M0 group, it was directly affected by W/H ratio ($R^2=0.767$, p≤0.01) and inversely by the duration of the cycle ($R^2=0.012$, p≤0.05). In M1 group, W/H ratio was the only model that enter the analysis ($R^2=0.834$, p≤0.01). In M2 group it was directly affected by duration of menopause and the family size ($R^2=0.063$, p≤0.01) and ($R^2=0.921$, p≤0.05) respectively. In PM group, both TG and VLDL were directly affected by the diastolic blood pressure. While the W/H ratio was the one, which directly affected.

In table (VI), a stepwise regression analysis was carried out, it is obvious from this table that the W/H ratio behaved as determinant explaining the variation in the levels of different lipid parameter in different groups of women understudy. The result of analysis shows significant direct associations between the W/H ratio and different variant in this table (p≤0.01). Pearson correlation was carried out between the W/H ratio and other menopause and its duration (data not tabulated), the results show insignificant association between them.

Discussion

It is commonly accepted that altered lipid profile may help to explain why postmenopausal women appear to be more susceptible to atherosclerotic cardiovascular events regardless of the effect of age (13). Few studies, worldwide, examined changes in serum lipid in more than two groups of women of different menopausal status (14,15). In this aspect, this research paper indicates that menopausal status per se may have adverse effects on lipid profile in middle aged women. We found that postmenopausal women had significantly higher concentrations of total cholesterol with respect to pre- and perimenopausal women. This menopausal association was found in both natural and surgical menopause and was compatible with many earlier studies (16–18) and incompatible with others (19).

The deterioration of lipid metabolism especially hypercholesterolemia, seems to be closely related to the onset of atherosclerosis, which has considered to cause CVD as angina, myocardial infarction, cerebral infarction, etc. (20). Although both types of menopause had significantly higher levels of LDL-C than premenopause, it was significantly higher in the natural postmenopausal than perimenopausal women (14, 15, 21, 22) but insignificantly higher in the surgical postmenopausal than the perimenopausal women. This finding was compatible with MacLennan study (23) and incompatible with others (15,21).

Menopausal status was unlikely to alter HDL-C level, since no significant inter-group differences were found regarding its levels. This finding was compatible with findings in certain previous studies (22, 24) and incompatible with findings in others (25,26).

Both natural and surgical postmenopausal women had significantly higher LDL/ HDL-C ratio (atherogenic index) than premenopause women did. In natural menopause this ratio was also significantly higher than perimenopausal women were but this was not the case between surgical postmenopausal and perimenopausal women. This ratio is the most sensitive index for reflecting mild coronary artery disease with a predictive value of 83.3 % at 76.6 % specificity and 77.7 % sensitivity (22).

It was hypothesized that estrogen lack after menopause increased the level of lipoprotein lipase enzyme that hydrolysis chylomicrones and TG.
In this study, we found that TG and VLDL levels were not significantly higher in surgical than natural postmenopausal women or in the later than in the pre-or perimenopausal women. This result is compatible with previous studies (15, 24, 28) and not with others (29, 30) whereas, both levels were higher in surgical postmenopausal women than in pre-and perimenopausal women. This result is compatible with MacLennan et al study (23) and incompatible with Pasquali et al study (15). This increased level of TG and VLDL is associated significantly and directly with central obesity (raised W/H ratio) in the surgical postmenopausal women. These differences in the inter-group comparisons between the natural postmenopausal and the perimenopausal women, in one hand, and between the surgical postmenopausal and perimenopausal women (regarding the level of lipids), in another hand, may be explained by our suggestion that both types of postmenopausal status act through different mechanisms in altering lipid profile and so have different nature of dyslipidemia. This finding was compatible with Everson et al study (26).

In our population understudy, the natural postmenopausal women had the highest percentage of participants with dyslipidemia as represented by undesirable levels of cholesterol (≥ 200 mg/dl), LDL-C (≥ 130 mg/dl) and LDL/ HDL-C ratio (≥ 3). Whereas the surgical postmenopausal women had dyslipidemia represented as highest percentage of undesirable level of HDL-C (≤ 40 mg/dl), TG (≥ 200 mg/dl) and VLDL (≥ 40 mg/dl). This different nature of dyslipidemia was also shown in Everson et al study (26).

It is a matter of controversy whether menopause per se affects fat distribution (31,32). No association between W/H ratio (central body obesity) and menopause and its duration were observed. On the other hand, central obesity were associated significantly with increase in serum LDL-C level in peri- and natural postmenopausal women, increased serum HDL-C level in surgical postmenopausal women, increased atherogenic index (LDL/ HDL-C ratio) in natural postmenopausal women, and increased serum level of both triglyceride and VLDL in perimenopausal women. From that we suggest that central obesity (elevation of W/ H ratio) was associated significantly with altered lipid profile during menopausal transition. Other factors that were found to have significant associations with dyslipidemia include the following: blood pressure (systolic and diastolic), income, duration of periods, lactation, family size, age at menarche, parity, BMI, duration of cycle, duration of irregular cycles and the level of education.

It is not fully clear why those were associated with dyslipidemia in certain group(s) and not in others, and whether these factors were causes or effects of altered lipid profile in the inter-group comparisons. Some of these risk factors were found to be associated directly and significantly with W/H ratio like (systolic blood pressure, lactation, BMI, duration of cycles, and family size) and others were not.

Unfortunately, we have no data from previous studies for comparison with these findings. Whether these factors were effects or causes of changes in lipid profile is not clearly known. The direct association between lipids and blood pressure may be due to their atherogenicity, as expressed above. BMI and the duration of menopause were associated with LDL/HDL-C; this indicates their relative importance in predicting CVD which is more common among obese and postmenopausal women (33).

The association between lipids and pattern of menstruation may be due to hormonal effects. The association between the family size and both LDL-C and LDL/HDL-C in the surgical postmenopausal women may be explained by the lack of social support, among them which intern, make them at risk of developing CVD in the future. This finding was supported by a previous research (26).

As lactation was associated inversely with both LDL-C and LDL/HDL-C ratio, this indicates its protective role against CVD. We suggest that these factors could act through more than one mechanism. In the future, larger studies carried out for longer period of time may be able to explain these questions.

Predicting these factors may help in adopting a strategy to control these mechanisms through modifying these relative risk factors to prevent or at least improve the adverse lipid profile during menopausal transition, mainly during postmenopausal period in an attempt to improve the cardiovascular risk profile in this stage of life. It is thought that estrogen replacement therapy with or without progesterone plays a significant role in this aspect (16-18). Therefore, HRT may improve lipid profile in women in an attempt to decrease the risk of cardiovascular disease. This will require a further study.
Lipid Profile and … … …

References