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Association of Dyslipidemia and Obesity After Menopause

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Abstract

Background Aging and hormonal changes in menopause are factors which may play the most important role in the development of all events of this stage of women's life. Of importance in this respect is obesity and related events as insulin resistance, oxidative stress, dyslipidemia and consequent increase in the risk of cardiovascular disease.

Objective To evaluate the association of dyslipidemia with the development of obesity and related events as lipid peroxidation after menopause, and to correlate the different parameters with each other.

Methods Thirty seven premenopausal women aged (33.95±7.9 years) and 41 postmenopausal women aged (59.9±7.2 years) were involved in this study. All were normal and without a previous history of any disease or illness. Blood specimens were collected after 12 hour fast for measurement of serum lipids (total cholesterol TC, Triglycerides TG, and high density lipoprotein cholesterol HDL-C) by enzymatic spectrophotometric methods. Low density lipoprotein cholesterol (LDL-C) was estimated by calculation. The athrogenic index (AI) indicates the ratio of LDL-C to HDL-C, while sex hormones (estradiol, E_2, follicle stimulating hormone, FSH and luteinizing hormone, LH) and oxidized LDL (ox-LDL) were measured by ELISA methods. All participants were subjected to anthropometric measurements including body mass Index (BMI) and waist circumference (WC).

Results Marked significant increase in BMI and WC in the postmenopausal women as compared with the premenopausal women and was associated with a significant low E_2, high serum TG, TC, LDL-C, AI and ox-LDL with low HDL-C.

Conclusion Changes in serum levels of sex hormones at menopause may be the trigger for the development of post-menopausal obesity, dyslipidemia and elevated Ox-LDL, and that at a given age all these factors should be considered for evaluation of body fat distribution and related health risks.

Key Words menopause, obesity, dyslipidemia, sex hormones, ox-LDL

Introduction

The main circulating estrogen during the premenopausal age is 17β- Estradiol. Levels of this hormone are controlled by the developing follicle and resultant corpus luteum. Essentially all estradiol in post-menopausal women is derived from peripheral conversion from estrone [(1)].

This is due to estrone production, resulting largely from peripheral aromatization of androstendione. This aromatase activity increases with aging by two to four folds; this is further amplified by increased adiposity that typically accompanies the aging process [(2)].

Menopause was found to associate changes in body weight or distribution of body fat.

An apple shaped body or male type distribution of adipose tissue, is associated with high risk of coronary heart disease (CHD) than pear-shaped body or female-type distribution of body fat. This factor may be quantified by using the waist circumference (WC) [3].

Insulin resistance, which associates obesity, increases the activity of hormone sensitive lipase in adipose tissue resulting in increased level of circulating fatty acids. These fatty acids are carried to the liver to be converted to TG and cholesterol. The major components of the dyslipidemia that may associate obesity are increased TG and modified small dense LDL particles with decreased HDL and impairment of LDL-receptor (LDL-R) activity which contributes to delayed TG rich lipoprotein clearance [4]. These modified LDL are mostly taken up by macrophage scavenger receptors, rather than the normal LDL-R pathway, thus inducing athero-sclerosis and increasing the risk of cardiovascular disease [4,5].

The present study was designed to study the link between obesity, dyslipidemia and ox-LDL with the changes in sex hormones in the postmenopausal period.

Methods

Subjects

The study was carried out during the period from August 2008 till January 2009. It included 37 pre-menopausal women with age range of 18-43 years and 41 postmenopausal women with age range of 47-73 years. All women were attending AL-Kadhimya Teaching Hospital. They were, all, healthy with no previous illness or taking any drug which may interfere with any of the tests in this study.

All women of the study were subjected to anthropometric measurements including BMI and WC, and both groups of the study were subdivided according to BMI into 3 subgroups: normal (< 25 Kg/m^2), overweight (25-29.9 Kg/m^2) and obese (> 30 Kg/m^2).

Methods

Ten mls of blood were collected into a plain tube in the morning after 12 hour fast. The serum obtained after centrifugation of blood at 3200 rpm for 10 min. was separated and divided into small aliquots for measurement of serum E2, FSH, LH and Ox-LDL by ELISA technique. Serum lipids (TG, TC, and HDL-C) were determined by enzymatic spectrophotometric methods (Kits from BioMereux, France). The LDL-C was calculated according to Friedwald formula [6] and the atherogenic index (AI) is the ratio of LDL-C to HDL-C.

Results

In addition to the higher age in the postmenopausal women and the significant reduction in E2 and elevation in FSH and LH, there was also a significant rise in TG, TC and LDL-C with a significant reduction in HDL-C and a significantly higher atherogenic index, AI (Table 1).

Table 1: Biochemical parameter values in the pre- and post menopausal women

Parameters	Pre-menopausal	Post-menopausal
Age (years)	33.95±7.9	59.9±7.2
BMI (Kg/m²)	26.66±4.86	28.58±4.78
WC (cm)	80.6±10.0	89.53±12.00*
TC (mg/dl)	178.3±21.3	207.5±34.4*
TG (mg/dl)	126.3±39.3	140.9±55.8
HDL-c (mg/dl)	53.3±6.0	47.02±6.9*
LDL-c (mg/dl)	99.0±24.7	132.12±34.65*
AI	1.9±0.7	3.00±1.14*
LH (ρg/ml)	6.6±2.3	41.58±11.64*
FSH (ρg/ml)	7.2±2.2	55.39±12.54*
E_2 (ρg/ml)	190.7±48.1	56.46±15.48*
OX-LDL (U/l)	57.8±22.3	79.85±35.29*

* p 0.05

In table 2 the comparison between different BMI subgroups of the pre-menopausal group showed a significant increase in BMI , WC , TG and ox-LDL (P < 0.01) with significant decrease in HDL-C in the obese subgroup as compared to the normal or overweight women, but no significant changes in the other parameters (TC, LDL-C and sex hormones) could be seen.

Table 2: The biochemical parameter values in the BMI subgroups of the pre-menopausal women

Parameters	Premenopausal > 25 (kg/m²)	Premenopausal 25-29.9 (kg/m²)	Premenopausal > 30 (kg/m²)
Number	13	13	11
Age (years)	30.23±8.39	35.23±6.7	36.82±7.6
BMI (kg/m²)	21.67±1.7	26.72±1.53	32.5±2.96*
WC (cm)	70.62±4.65	81.38±5.41	91.27±6.81*
TC (mg/dl)	170.92±21.35	180.15±19.26	184.73±22.67
TG (mg/dl)	103.46±23.81	117.69±29.47	163.45±39.24*
HDL-c (mg/dl)	56.23±4.4	53.54±5.16	49.45±6.73*
LDL-c (mg/dl)	93.92±25.0	100.77±23.42	102.82±26.95
AI	1.7±0.59	1.93±0.6	2.16±.084
OX-LDL(U/l)	44.61±17.55	57.82±14.29	73.91±25.71*
LH (ρg/ml)	7.02±2.44	6.33±2.26	5.12±2.22
FSH (ρg/ml)	8.33±1.99	6.78±2.22	6.44±2.1
E_2 (ρg/ml)	209±30.56	192.31±51.2	166.54±54.15

p < 0.01 by ANOVA test

The comparison (by ANOVA test) between different BMI subgroups of the postmenopausal group showed a gradual significant increase in age, BMI and WC. In addition, the obese women of this group had a significant elevation in serum TC, LDL-C, AI and ox-LDL-C (p < 0.01) with a significant reduction in HDL-C (p < 0.01).

There was no significant difference in TG, and serum sex hormones (Table 3).

Table 3: The biochemical parameters in the BMI subgroups of the post-menopausal women

Parameters	Premenopausal > 25 (kg/m²)	Premenopausal 25-29.9 (kg/m²)	Premenopausal > 30 (kg/m²)
Number	12	14	15
Age (years)	55.0±3.84	62.07±7.53	61.8±7.42*
BMI (kg/m²)	23.18±1.37	27.74±1.67	33.55±3.05*
WC (cm)	75.5±3.53	90.29±7.18	100.07±8.17*
TC (mg/dl)	186.5±20.95	206.71±37.87	225.0±31.45*
TG (mg/dl)	111.17±55.91	151.64±44.28	154.53±59.46
HDL-c (mg/dl)	51.75±5.91	46.36±5.96	43.87±6.67*
LDL-c (mg/dl)	113.17±21.52	126.5±36.14	152.53±32.7*
AI	2.24±0.61	2.98±1.13	3.63±1.15*
OX-LDL(U/l)	61.38±16.4	71.09±24.71	102.81±42.96*
LH (ρg/ml)	37.98±11.21	40.11±12.21	45.85±10.83
FSH (ρg/ml)	48.34±12.44	56.66±12.63	59.83±10.69
E_2 (ρg/ml)	61.63±12.99	57.61±16.6	51.25±15.59

* $p < 0.01$ by ANOVA test.

In table (4) the comparison between the obese pre- and post-menopausal women shows, in addition to higher age, FSH and LH, a significantly higher WC, TC, LDLC, AI and Ox-LDL (P <) with a significant reduction in HDL-C and E2 ($p < 0.01$)

The estradiol E2 was significantly negatively correlated with obesity (BMI) in the pre-menopausal women only (figure 1). While WC was positively correlated with each of serum TG and Ox- LDL (Figures 2 and 3).

Table 4: comparison between the obese subgroups in the pre- and post-menopausal women.

Parameters	Pre BMI>30 Mean ±SD	Post BMI>30 Mean ±SD
Number	11	15
Age (years)	36.82±7.6	61.8±7.42*
BMI (kg/m²)	32.5±2.96	33.55±3.05
WC (cm)	91.27±6.81	100.07±8.17*
TC (mg/dl)	184.73±22.67	225.0±31.45*
TG (mg/dl)	163.45±39.24	154.53±59.46
HDL-c (mg/dl)	49.45±6.73	43.87±6.67*
LDL-c (mg/dl)	102.82±26.95	152.53±32.7*
AI	2.16±.084	3.63±1.15*
OX-LDL(U/l)	73.91±25.71	102.81±42.96*
LH (ρg/ml)	5.12±2.22	45.85±10.83*
FSH (ρg/ml)	6.44±2.21	59.83±10.69*
E_2 (ρg/ml)	166.54±54.15	51.25±15.59*

* $p < 0.01$

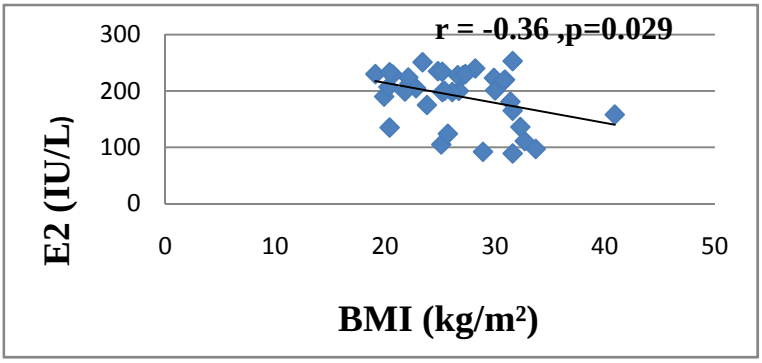
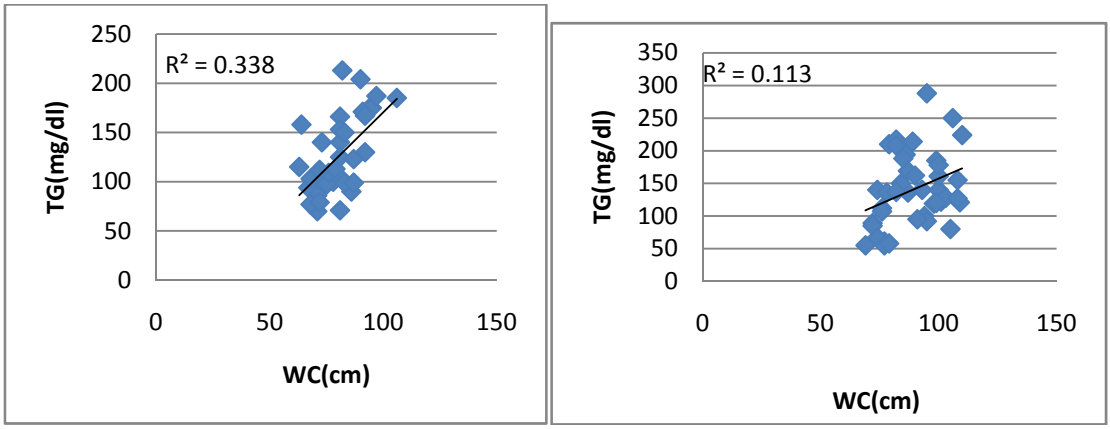


Figure 1: Correlation between body mass index (BMI) and serum estradiol ($E2_)$ in the pre-menopausal group.



A- n: 37 , r = 0.58 , P < 0.01 B- n : 41 , r = 0.33 , P < 0.01

Figure 2: Correlation between the waist circumference (WC) and serum triglycerides (TG) in the pre-menopausal (A) and the post-menopausal (B) groups

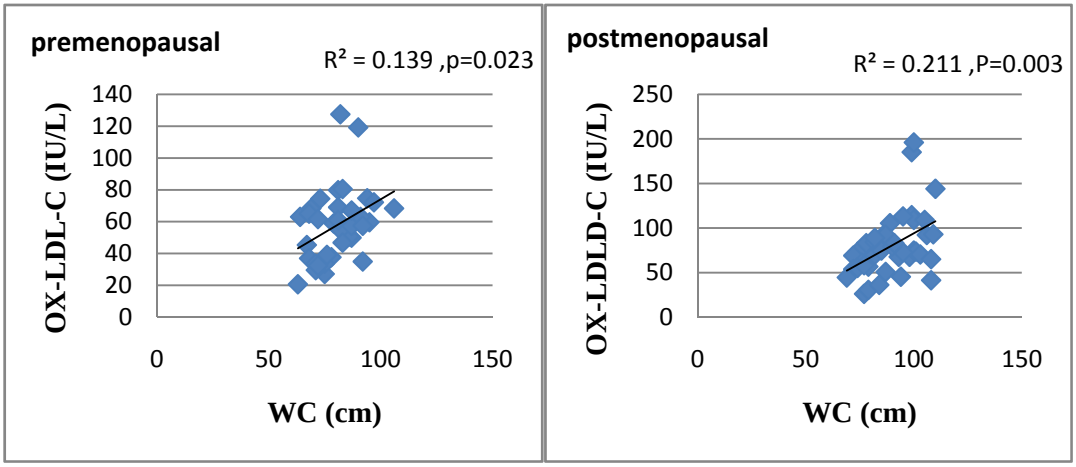


Figure3: Correlation between the waist cirumference (WC) and the Oxidized LDL (Ox- LDL) in the premenopausal and postmenopausal groups

Discussion

The results of the present study that compare between the pre-menopausal and the post-menopausal women (Table 1) reveals clearly that changes in sex hormones is the most important factor which differentiates between these two stages. However studying the relation of these hormones to other measured parameters showed that only E2 was significantly negatively associated changes in BMI in the pre-menopausal women only (Table 1 and Figure 1). This could be explained by the fact that E2 is scarce in the post-menopausal stage and may have no, or, negligible physiological effect; Moreover changes in serum lipids, and oxidative stress status observed in this study may be due to the increase in body weight (high BMI or WC) which may be triggered by the drastic reduction in E2.

Aging, on the other hand, appeared to have an effect on serum lipid concentrations presented by significant increase in TC, LDLC and TG with a significant reduction in HDLC and consequent increase in AI. This is evident in the different BMI sub- groups of the postmenopausal women who showed significant age difference (Table 3), while no such difference could be noticed in the BMI subgroups of the pre-menopausal women of the present study who showed no significant age difference (Table 2). However it should be kept in mind that age difference was associated with changes in sex hormones and accordingly it is probable that changes in serum lipids were due to the combined effects of age and sex hormones.

A recent study showed that fat mass and WC were higher in postmenopausal women compared with the premenopausal women and that weight gain during aging would occur predominantly in the abdominal region [7]. Furthermore, it is known that after menopause WC and visceral adipose tissue accumulation increases beyond the effect of aging. This predisposition processes are more likely to be associated with the time since the menopause than with biological age [8].

So it could be proposed that reduced E2 effect in the post-menopausal women of the present study had resulted in a significant increase in the body weight, presented by high BMI, or high WC, which was positively associated with dyslipidemia and increased Ox-LDL (Table 1 and Figure 2).

In the post-menopausal women aging has been associated with increased concentration of TC, TG, VLDL-C, and LDL-C, and decreased concentration of HDL-C, all of which contributed to a more atherogenic lipid profile (Tables 1 and 4). The cardio-protective effect of estrogen has long been related to its beneficial effect on cholesterol metabolism and deposition, contributing to inhibition of athero-sclerotic plague formation in the arterial walls [9]. Estrogen was reported to lower LDL-C by up regulating LDL receptors in the liver and enhancing LDL catabolism [10]. This could be attributed to the reducing action of estrogen on the activity of adipose tissue lipoprotein lipase which results in less rapid hydrolysis of the circulating triglyceride rich (chylomicrons and VLDL particles), and has been reported to decrease hepatic TG lipase activity [11]. In addition, estrogen is believed to enhance hepatic B/E receptors mediated lipoprotein uptake, and it appears to promote the hepatic synthesis and secretion of apo-A-I. Also Estrogen is thought to enhance the production of larger, less dense and presumably less atherogenic LDL particles [12]. This may explain the presence of higher Ox-LDL concentration in the obese post-menopausal women than their counterpart of the pre-menopausal group (Table 4) with the presence of a positive correlation between OX-LDL levels and obesity measures such as BMI and WC (Figure 3).

The present finding agrees with a previous report, considering BMI as one of the strongest predictors for circulating levels of Ox-LDL and demonstrating the effect of leptin on the generation of reactive species in the endothelial cells with a consequent LDL oxidation [13]

The mechanisms by which abdominal adiposity per se could induce increased oxidative stress are not clear. The oxidative stress could be induced by low grade of inflammation mainly characterized by high concentration of leptin, interlukin-6 (IL-6) and C-reactive protein [14]. Also several authors suggested that low degree of inflammation in obese person is caused by a high secretion of pro-inflammatory cytokines such as TNF-α [15]. This induces the production of IL6 which leads to low grade inflammatory state that leads to excessive production of free radicals and increased lipid peroxidation [16]. Estrogen, on the other hand, was considered a powerful antioxidant, which prevents lipid peroxidation and changes in lipid profile, as observed in the pre-menopausal women [9].

In conclusion these findings suggest that, for a given age, WC, BMI and menopausal status need to be considered when predicting abdominal adipose tissue distribution and related health.

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