Research Article

Metabolic and Hormonal Changes Associated with Menopause

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Abstract

Background: Menopause is the perpetual cessation of menstruation due to defeat of ovarian follicular activity. Menopause in women leads to various physiological changes in the body.
Objective: To study the metabolic and hormonal changes in postmenopausal women.
Patients and Methods: Forty five postmenopausal women were participated in the study and compared them with 45 premenopausal women who had a regular menstruation. They were attending the Medical City Hospital/ Obstetrics and Gynecology Department during the period from July 2016 until the end of December 2016. Anthropometric and physiological parameters were taken. Biochemical and hormonal parameters were measured for all individuals.
Results: In this study, there was a significant increase in serum apolipoprotein E levels, total cholesterol, triacylglycerol, low density lipoprotein cholesterol, urea, and thyroid stimulating hormone in postmenopausal group as compared to premenopausal group, ($P \leq 0.05$). Serum total tri- and tetra-iodothyronine levels were decrease in postmenopausal group as compared to premenopausal group, but it was not significant. There was a significant increase in apolipoprotein E in postmenopausal women who had family history for dyslipidemia, ($P = 0.001$). There was a significant positive correlation between apolipoprotein E and thyroid stimulating hormone. While there was a significant negative correlations among apolipoprotein E with high density lipoprotein cholesterol and estradiol, ($P \leq 0.01$)
Conclusions: The physiological basis and the complex interaction between thyroid hormones and apolipoprotein E and their relation with estradiol hormone among postmenopausal women trigger the lipids control mechanism.

Key words: *Postmenopause, Apolipoprotein E, Thyroid Hormones.*

INTRODUCTION

The term natural menopause is defined as the perpetual termination of menstruation resulting from the defeat of ovarian follicular activity (WHO).[1] The mean age at natural menopause is 51 years in developed country, while it is 48 years in poor and undeveloped country.[2] The age of natural menopause depends on genetic factors, but modifiable influences which will accelerate or diminish the follicular activity like age at menarche, parity, smoking, socioeconomic status, and occupation.[3] Recent evidence has related mortality risks to the age at onset of menopause. Women who enter menopause earlier have a higher mortality rate, particularly from cardiovascular (CV) causes.[4]

Moreover, it is invented that the apolipoprotein E (apo E) has a risk for the progress of neurodegenerative alterations.[5] Apo E is 299 amino acids long and contains multiple amphipathic α-helices. In peripheral tissues, apo E is mainly created by the liver and macrophages, and mediates cholesterol metabolism in an isoform-dependent method.[6] In the central nervous system, apo E is primarily created by astrocytes, and transports cholesterol to neurons by apo E receptors, which are members of the low density lipoprotein receptor (LDL-R) gene family.[7] Located on

chromosome 19, apo E translates into three common allelic variations E2, E3, and E4.[8] The lipoprotein-binding preference of apo E4 to large, triacylglycerol-rich VLDL (very low density lipoprotein), is associated with increased LDL levels. The enrichment of VLDL with apo E4 increases their clearance from the plasma by receptor-mediated endocytosis in the liver; as a consequence, LDL-R are down-regulated, and plasma LDL concentrations increase.[9]

Thyroid hormone plays a main character in the progress and function of essentially every organ system in humans.[10] This progression is stimulated by thyroid stimulating hormone (TSH).[11]

Furthermore, menopause is one of the mainly important period which favors weight gain and leading to obesity. Obesity can also be considered as a state of exaggerated estrogen production. Through the menopausal transition, estrogen levels decline and concentrations of serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) enhance, whereas the postmenopausal period is marked by amenorrhea. The main consequences of menopause are associated mainly to estrogen insufficiency. It is so composite to differentiate the consequences of estrogen deficiency from those of aging, since aging and menopause are inextricably linked.[12]

The dramatic reduction in circulating estrogens levels results in the improved secretion of insulin by the pancreas, development of obesity, insulin resistance (IR), and metabolic disorders.[13] Estradiol (E2) is the predominant estrogen during the reproductive ages in women and a reduction in E2 levels is seen in women entering menopause. [14]

So, the aim of the present work was to study the metabolic and hormonal changes in postmenopausal women.

PATIENTS AND METHODS

Forty five postmenopausal women were participated in the study and compared them with 45 premenopausal women who had a regular menstruation. They were attending the Medical City Hospital/Obstetrics and Gynecology Department during the period from July 2016 until the end of December 2016. Anthropometric and physiological parameters were taken for all individuals.

Inclusion and Exclusion Criteria:

Menopause was confirmed by the criteria that women are not menstruating for a period of 12 consecutive months with no other abnormality noticed.

Menopausal women with resting blood pressure (BP<139/89) according to WHO hypertension guidelines were included in this study, but women who were smoker, pregnant, treated with steroids or antipsychotics were excluded from the study.

The following anthropometric and physiological parameters were assessed for the patients: age, body mass index (BMI), waist circumference (WC), waist to hip (W/H) ratio, systolic- and diastolic- blood pressure (SBP and DBP). Body mass index was deliberated by the formula:-

$$BMI = Weight\ (kg)/\ (Height\ (m^2))^2$$

Fasting blood sample were taken after fasting for at least 12 hours. After the collection of blood sample, serum was separated and stored at (−20°C) until the sample analysis. Apolipoprotein E was measured by the ELISA (Enzyme Linked Immuno Sorbent Assay) kit.

Fasting serum glucose, serum total cholesterol (TC), triacylglycerol (TAG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), serum urea, and creatinine were estimated by chemical analyzer. Serum thyroid profile (total triiodothyronine-TT3, total tetraiodothyronine-TT4, and TSH) in addition to E2 were analyzed by the ELISA kit.

Statistical Analysis:

Data analysis was performed using SPSS Statistics version 17.0 software. Critical statistics included determination of means and standard deviations. Data was examined using t-test and invented significant at $P \leq 0.05$.

RESULTS

Characteristics parameters of postmenopausal women illustrate in table 1.

Table 2 shows the anthropometric and physiological parameters of the study groups. There was a significant increase in age, weight, BMI, WC, and SBP in postmenopausal women as compared to premenopausal women, ($P \leq 0.05$). There was no significant difference in height, W/H ratio, DBP, and number of children born between the two groups.

Table 1: Characteristics parameters of postmenopausal women

Characteristics	Postmenopausal women
Number	45
Marital status - Single - Married	 10 (22.22%) 35 (77.78%)
Menopausal symptoms - Muscle pain - Hot flushes - other	 40 (88.89%) 30 (66.67%) 15 (33.33%)
Family history of dyslipidemia	32 (71.11%)

Table 2: Anthropometric and physiological parameters of the study groups

Parameters	Postmenopausal women (n=45)	Premenopausal women (n=45)	P Value
Age (years)	52.50±6.12	42.30±2.25	0.01
Height (m)	1.53±4.25	1.50±3.85	0.50
Weight (kg)	78.0±10.50	56.50±4.48	0.001
BMI (kg/m^2)	33.32±2.58	25.11±0.30	0.05
WC (cm)	102.85±2.50	80.0±0.50	0.001
W/H ratio	1.50±0.16	0.75±0.12	0.50
SBP (mmHg)	140.0±1.80	111.0±1.30	0.001
DBP (mmHg)	79.33±2.85	75.20±3.71	0.06
Number of children born	1.0±0.50	3.0±0.16	0.70

Table 3 demonstrates the biochemical and hormonal parameters between the study groups. There was a significant increase in serum apo E levels, TC, TAG, LDL-C, urea, and TSH in postmenopausal group as compared to premenopausal group, ($P \leq 0.05$). Serum TT3 and TT4 levels were decrease in postmenopausal group as compared to premenopausal group, but it was not significant. There was a significant decrease in E2 levels in postmenopausal group as compared to premenopausal group, (P= 0.05).

Characteristic of apo E according to family history of dyslipidemia in postmenopausal women represents in table 4. There was a significant increase in apo E in postmenopausal women who had family history for dyslipidemia as compared to none, (P =0.001).

According to data obtained from table 5, there was a significant positive correlation among apo E with BMI, TC, TAG, LDL-C, urea, and TSH, ($P \leq 0.05$); while there was a significant negative correlation among apo E with HDL-C and E2, ($P \leq 0.01$).

Table 3: Biochemical and hormonal parameters of the study groups

Parameters	Postmenopausal women (n=45)	Premenopausal women (n=45)	P Value
FSG (mg/dl)	90.20±3.14	87.0±2.70	0.70
Apo E (nmol/l)	43.50±6.50	15.85±3.20	0.001
TC (mg/dl)	260.0±5.30	150.50±4.85	0.001
TAG (mg/dl)	185.50±4.50	110.32±6.41	0.001
HDL-C (mg/dl)	47.53±2.11	53.23±1.18	0.01
LDL-C (mg/dl)	175.37±14.29	75.21±12.39	0.001
Urea (mg/dl)	48.0±2.30	28.0±0.50	0.01
Creatinine (mg/dl)	1.50±0.14	0.60±0.10	0.50
TT3 (nmol/l)	1.73±0.25	1.93±0.78	0.90
TT4 (nmol/l)	95.80±12.30	98.45±18.70	0.60
TSH (µmol/l)	9.58±2.50	1.80±1.02	0.05
E2 (pg/ml)	22.60±10.50	29.78±12.30	0.05

Table 4: Characteristic of apo E according to family history of dyslipidemia in postmenopausal women

Parameters	Apo E (nmol/l)
Family history (n=32)	56.80±6.12
None (n=13)	30.20±5.88
P value = 0.001	

Table 5: Correlations between apo E and other variables in postmenopausal women

Apo E (nmol/l)	Correlation coefficient (r)
BMI (kg/m^2)	0.59*
TC (mg/dl)	0.98**
TAG (mg/dl)	0.92**
HDL-C (mg/dl)	-0.80**
LDL-C (mg/dl)	0.90**
Urea (mg/dl)	0.70**
TSH (µmol/l)	0.68**
E2 (pg/ml)	-0.63**

*P =0.05, **P ≤ 0.01

DISCUSSION

Women are continuously under the influence of hormonal alterations from menarche to menopause, and pregnancy also causes hormonal fluctuations. The median age at menopause in this study was 52.50 years which is in agreement with the previous studies.[15, 16] Menopause is one of the most important events in a woman's life and brings in a numeral physiological changes,[17] in addition to weight gain is alter in body fat distribution, which some authors illustrate as a changeover from a gynecoid to an android pattern of fat depots.[18]

Obesity is one of the commonest causes of postmenopausal.[19] Excess insulin causes polyphagia, so persons eat more to try to maintain a balance. Women tend to increase weight and suffer changes to their fat circulation in mid-life.[20] Obesity acts as a diabetogenic feature and leads to reduction in insulin receptors on the insulin responsive cells. Also, there is a dominant redistribution of fat as well as a rise of intra-abdominal fat.[21] Furthermore, weight increase and changes in body composition are related to aging. Numerous parameters such as diet, physical activity, growth hormone secretion, and family history might be complicated.[22]

In this study, significant changes have been observed in postmenopausal women. A significant increase in weight, BMI, and WC was found in postmenopausal women. This may be because of relationship between BMI and hypothalamus-pituitary gland axis functions are complex. It is frequently convention that the volume of fat mass increases with age results into the higher BMI noted during aging. Similar observation was reported by Kalashilpa et al.[23]

Issa et al., recommended that metabolic syndrome or obesity risk should be successfully achieved in APOE3 isoform groups to diminish serum LDL-C in postmenopausal Korean women. It has been established that menopause is connected with variations in lipid levels, resultant in an improved risk of atherosclerosis and CV events.[24]

In genetics, numerous gene polymorphisms and mutations have been connected with atherosclerosis and coronary artery disease (CAD), this is the case of the apo E.[25] Population studies have shown higher serum levels of LDL-C in carriers of the E4 allele, leading to an association of this allele with the incidence of cardiovascular diseases (CVD).[26]

Mutations in the LDL-R have also been associated with dyslipidemias, particularly in primary forms of homozygous or heterozygous hypercholesterolemia such as familial hypercholesterolemia (FH), a condition related with early severe atherosclerosis and CAD.[27]

The present study showed an elevation in FSG with a significant rise in serum TC, TAG, and LDL-C in postmenopausal women as compared to premenopausal women which is in agreement with the study of Netjasov et al.[28]

Also, there was a significant variance in serum urea between the two groups, which is due to decrease renal function; decreased renal function is associated with increased CV risk.[29]

However, there were no significant differences in thyroid hormones (T3 and T4) of postmenopausal group as compared to premenopausal group in this study. The T3 levels were approximately similar in both groups. The T4 levels not significantly decreased in postmenopausal group whereas TSH levels increased in

postmenopausal group compared to premenopausal group. High levels of TSH may indicate hypothyroidism in postmenopausal women.[30]

At the onset of menopause, there is a manifest lessening in estrogen concentration which is accompanied with a low level inflammatory condition responsible for many diseases related with menopause. Many studies recommended that estrogen deprivation accompanied with menopause is one of the leading causes for the immune alterations related with this stage.[31, 32]

Dynamic changes in circulating E2 level, including increase at menarche and decrease at menopause, occur in a woman's lifetime. Circulating E2 levels decrease considerably during the menopausal transition, though the levels variant along with races.[33]

An exhaustion of primordial follicles, ovarian E2 secretion ends at menopause and is followed by very low levels of circulating E2 causing the typical symptoms of menopausal. Following menopause, sex steroids maintain to be synthesized in peripheral tissues dependent on steroid forming enzymes specific for every tissue.[34]

Changes of body fat distribution at menopause may be owed to decreased production of estrogen. Changes in body fat distribution with diminishing estrogen are probably due to alterations in adipose tissue metabolism as estrogen is known to impact adipose tissue lipoprotein lipase activity and lipolysis.[35]

Estradiol diminished anti-thrombin and disturbed the function of thrombocytes. Thus, estrogen deficit is related to coagulation disorders, which increases the risk for CVD.[36]

Overall, data analyses reveal that the significant positive correlations among apo E with BMI, TC, TAG, LDL-C, urea, and TSH induce lipid metabolism that can accelerate the progress of pathological events.

The results of the present research indicate that postmenopausal women had higher anthropometric characteristics, FSG, and apo E, but lower E2 concentrations than premenopausal women. These variables, as well as other lipids and hormones analyzed in this study are most likely influenced by gaining weight, especially in postmenopausal. Conclusions: The interactions between thyroid hormones and apo E among postmenopausal women is a typical phenomenon. The physiological basis and the complex interaction between thyroid hormones, apo E regulatory hormones, and their relation with E2 hormone among postmenopausal women trigger the lipids control mechanism. So routine annual thyroid screening should be mandatory to proceed for diagnosis and management of thyroid dysfunction in postmenopausal women.

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