

Lack of Association Between Lipid and Lipoprotein Profile and Menopause Status in Women with Cardiac Syndrome X

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Cardiac syndrome X (CSX) or angina pectoris is characterized by positive findings on exercise electrocardiography and normal results on coronary angiography). It frequently occurs in menopausal women. On the other hand, studies indicated that menopause is associated with alteration in lipid profile and increased risk of cardiovascular diseases. Therefore, this study aimed to determine the possible influence of menopause on lipid and lipoprotein profile in women with CSX. Fifty women with CSX (mean age: 52.4±7.65 years) and 50 healthy women as control (50.0±5.62 years) were studied. CSX and control groups were divided as pre- and post-menopause subgroups. The plasma lipid and lipoprotein profile of subjects was estimated colorimetrically. The total cholesterol (TC), triglyceride (TG), lipoprotein A(LP[a]), low density lipoprotein (LDL), high density lipoprotein (HDL), apoprotein A1(APOA1), apoprotein B (APOB) were significantly higher among those in the CSX group than those of the control group. (TC: 158.2±5.7 vs. 114.5±5.1mg/dl; P=0.001, (TG: 152.1±11.4 vs. 105.9±8.9mg/dl; P=0.002, LP[a]: 44.2±7.9 vs. 22.2±4.3mg/dl; P=0.017, LDL: 88.9±3.7 vs. 66.1±23.4mg/dl; P=0.001, HDL: 36±1.4 vs. 29.3±0.8mg/dl; P=0.001, APOA1: 120.9±1.6 vs. 107.7±1.5mg/dl; P=0.001, and APOB: 95.2±3.4 vs. 74.4±2.6mg/dl; P=0.001). The differences of lipid and lipoprotein profile between pre- and post-menopause CSX was not significant. In conclusion, plasma lipid disorders play important roles in the development of CSX. Changes that occur in the lipid profile after menopause are not associated with increased CSX.

Key words: apoprotein, cardiac syndrome x, lipid, lipoprotein profile, menopause, microvascular

INTRODUCTION

The occurrence of typical chest pain and ST-segment changes suggestive of myocardial ischemia in patients who otherwise have completely normal coronary arteriograms is called as “syndrome X”(Kemp 1973),

“cardiac syndrome X” [CSX], or microvascular angina. The pathophysiology of the chest pain in CSX is poorly understood. But there are many suggested mechanisms.

It is well-known that majority of CSX patients are women, of whom most are post-menopausal and have symptoms of ovarian failure (Banks et al. 2010). Menopause is

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a natural event in the ageing process. It signifies the end of reproductive years with the cessation of cyclic ovarian functions as manifested by cyclic menstruation. It is heralded by menopausal transition, a period when the biological, endocrine, and clinical characteristics of approaching menopause begins (Burger et al. 2002). In addition, the hormonal changes related with menopause such as low plasma levels of estrogen and specific increase in leutenizing and follicle-stimulating hormone levels exerts a significant effect on the metabolism of plasma lipids and lipoproteins (Sacks et al. 1992). The behavior of lipoproteins during the menopausal transition and their relationship with the sex hormones and body fat distribution is still unknown (Berg et al. 2004). Furthermore, atherogenic changes in lipid and lipoprotein profiles have been found in studies on surgically induced menopause (Lip et al. 1997; Griffin et al. 1993; Wakatsuki et al. 1995) and epidemiological studies comparing premenopausal women with post-menopausal women (Bouthon et al. 1990; Stevenson et al.1993; Stamfer et al. 1999; Dallongeville et al. 1995; De-Aloysio et al. 1999; Tremollieres et al. 1999). On the other hand, the risk of coronary artery disease increases in women during post-menopause. This increased risk may be related with changes in the lipid profile characterized by alterations in low density lipoprotein particle size and buoyancy (Carr et al. 2000). Moreover, low-density lipoprotein (LDL) has been indicated in the development of coronary heart diseases (Berg et al. 2004). This has been attributed in part to adverse changes in plasma lipids and lipoprotein levels due to reduced estrogen levels (Poehlam et al. 1995). The effect of the hormonal changes associated with menopause on the plasma lipid levels play important role in most cardiac related disorders associated with menopause (Do et al. 2000). Therefore, this study aimed to estimate the plasma lipid and lipoprotein profile of pre-and post-menopausal women in CSX patients.

MATERIAL AND METHODS

Study population

Fifty CSX patients were studied. The CSX group was divided into pre-menopausal (n= 19) and post-menopause (n= 31) subgroups. The patients were recruited from the Department of Cardiology in Urmia University of Medical Sciences (UMSU), Urmia, Iran. All had a previously established diagnosis of classic syndrome X, with a typical history of exertional angina, an abnormal exercise electrocardiogram, and completely normal results on coronary angiography, with no inducible spasm on ergonovine-provocation testing. Non-cardiac causes of chest pain, such as gastrointestinal and musculoskeletal

disorders, and absence of any specific cardiac disease were also investigated and ruled out as appropriate. The control group which consisted 50 healthy women was also divided into pre-menopausal (n= 11) and post-menopause (n= 39) subgroups. None of the controls had a previous history of chest pain or acute/ chronic diseases. The study was approved by UMSU Research Ethics Committee and all subjects gave written informed consent.

Laboratory assays

A 5-ml tri-sodium-citratd blood sample was obtained from each subject and centrifuged at 2000×g for 15 minutes. Plasma was aliquoted and stored at -80°C until analysis. Then The total cholesterol (TC), triglyceride (TG), lipoprotein A (LP[A]),LDL, high density lipoprotein (HDL), apoprotein A1(APOA1), and apoprotein B (APOB)of subjects analyzed colorimetrically using the enzymatic method (Pars Azmun, Iran).

Statistical analysis

The data were analyzed using SPSS 16.0 software. Age and BMI were shown as mean standard deviation (SD). The levels of lipid profile were shown as mean ± standard error of mean (SEM).

The differences between the groups and subgroups were interpreted on the basis of independent- samples *t*-Test and for qualitative data on the basis of chi-square test. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the main demographic characteristics and the mean plasma lipid and lipoprotein profile of CSX and control groups. All lipid and lipoproteins levels of CSX patients were significantly higher than those of

Table 1: Demographic characteristics and plasma lipid and lipoprotein profile of CSX and controls.

	CSX (N=50)	Control (N=50)	P _{value}
Age (years)	52.4±7.65	50±5.62	0.077
BMI (Kg/m ²)	27.98±4.51	25.58±2.92	0.002
TC (mg/dl)	158.2±5.7	114.5±5.1	0.001
TG (mg/dl)	152.1±11.4	105.9 ±8.9	0.002
LDL (mg/dl)	88.9±3.7	66.1 ±2.4	0.001
HDL (mg/dl)	36±1.4	29.3 ±0.8	0.001
APOB (mg/dl)	95.2±3.4	74.4±2.6	0.001
APOA1 (mg/dl)	120.9±1.6	107.7 ±1.5	0.001
LP[A] (mg/dl)	44.2±7.9	22.2±4.3	0.017

Table 2: Demographic characteristics and plasma lipid profile of pre- and post-menopause CSX and controls.

	CSX			Control		
	Pre-menopause (N=19)	Post-menopause (N= 31)	P _{value}	Pre-menopause(N=11)	Post-menopause (N=39)	P _{value}
Age (years)	44±0.96	57.5±0.64	<0.001	48±0.69	57.1±1.03	<0.001
BMI (Kg/m ²)	26.9±0.95	28.7±0.83	0.18	25.5±0.43	25.9±1.01	0.62
TC(mg/dl)	155.5±9.7	159.9±7.1	0.70	111.67±5.41	124.55±12.42	0.30
TG (mg/dl)	136±13.1	161.5±16.6	0.30	105.13±9.69	109.00±22.64	0.86
LDL-C (mg/dl)	84.1±5.7	91.9±4.8	0.30	63.8±2.6	73.9±5.7	0.08
HDL-C(mg/dl)	38.5±1.8	35.5±1.5	0.30	28.8±0.9	30.9±1.9	0.33
APOA ₁ (mg/dl)	124±3.2	119.1±1.7	0.14	107.21±1.71	109.27±3.61	0.58
APOB (mg/dl)	89.7±4.9	98.5±4.5	0.21	71.4±2.6	85.2±6.3	0.02
LP[A] (mg/dl)	45.8±12.5	43.2±10.4	0.87	22.0±5.2	19.2±4.4	0.96

the controls. On the other hand, [table 2](#) reveals the main demographic characteristics and the mean plasma lipid and lipoprotein profile of pre- and post-menopause CSX and controls. The differences of lipid and lipoprotein profile between pre- and post-menopause CSX and controls (except for APOB) were not significant.

DISCUSSION

CSX mainly characterized by a reduction in coronary artery dilatation reserve; however, intra- coronary ultrasound and Doppler showed early alterations of coronary atherosclerosis in some patients displaying focal or eccentric lesions with pathologically- confirmed fatty deposits, infiltration of macrophage origin foam cells, and endothelial degeneration. The result of the present study revealed that lipid and lipoprotein profiles of patients with CSX are significantly higher than controls, in accordance with study of Liu et al. (2008). They concluded that plasma lipid disturbances and endothelial dysfunction may play important roles in the development of microvascular angina. The dysfunction of endothelium- dependent vasodilatation was mainly related with anomalies in LP[a] and LDL-C, and myocardial endothelial dysfunction was aggravated by lipid abnormalities in these patients (Liu et al. 2008). In addition, in our study APOB levels, which exerts a strong effect to stimulate the esterification of cholesterol in macrophage and promote foam cell formation, is significantly higher than controls like Liu et al., study (Liu et al. 2008). On the other hand, menopause, resulting in a decrease in circulating estrogen levels, may be associated with changes in bone metabolism (Nelson 2008), obesity, hypertension, glucose intolerance, diabetes mellitus and alterations in the lipid profile may become relevant as risk factors of cardiovascular disease (Gast et al. 2008). The risks associated to the post-menopausal

period are mainly due to the reduced availability of estrogen, which has indirect protective effects on lipid, and glucose metabolism as well as direct effects on vessel function. They have vasodilator action due to nitric oxide (NO) release, calcium antagonist like action and an antiproliferative effect on smooth muscle cells (Hulley et al. 1998; Wenger et al. 1993). For example, Abdealla et al. (2011), evaluated the plasma lipids in menopausal Sudanese women. Their results showed a significant difference between the mean of plasma lipids including TC, TG, LDL and HDL of the control group compared to that of the case group. So they concluded that natural menopause transition is associated with a worsening of the plasma lipid profile and increase in the atherogenic index. Additionally, Berg et al. (2004), also demonstrated higher TC, LDL-C and TG in post-menopausal women in comparison with pre-menopausal women.

In addition, estrogen deficiency has been associated with CSX. Rosano et al. (1995), showed that in women with CSX, chest pain symptoms began during menopausal period. These findings are similar to our study. Moreover, in our study the TC is increased in post-menopausal women maybe due to estrogen deficiency, but in spite of other studies, this increase was not significant. The elevated TC, LDL-C, HDL-C and TG in post-menopausal women has been attributed to hormonal changes and failure of follicular development (Sarrel 1990) .

Furthermore, circulating estrogen is regulates lipoprotein lipase (LPL). LPL catalyzes the hydrolysis of VLDL to form intermediate density lipoprotein (IDL) and later LDL. Due to estrogen deficiency after menopause, there will be increased plasma LPL and hepatic TG lipase activity causing plasma LDL accumulation (Rosano et al. 1995). On the other hand, estrogens induce an early increase of LDL receptors, which are responsible for the uptake of plasma lipoprotein and decrease 3-hydroxy-3-

methylglutaryl coenzyme A reductase activity, which is the key enzyme of the biosynthetic pathway (Messa et al., 2005). The lack of estrogen will allowed for uncontrolled levels of LDL. One of the limitations of our study is that the age of pre- and post-menopausal women in CSX and control groups is not matched. Also, the small number of pre-menopausal women in controls and the differences BMI between CSX and controls are other limitations of study.

CONCLUSION

In conclusion, in this study we could not find any significant relationship between lipid and lipoprotein profile with CSX in pre- and post-menopausal women. Only APOB levels increased in post-menopausal women of both groups and it was significant in the controls.

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