Original Article

The Association between Hypertriglyceridemic Waist Phenotype, Menopause, and Cardiovascular Risk Factors

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Abstract

Background: The incidence of cardiovascular disease (CVD) and its risk factors increase after menopause, thus realizing that the effect of menopause on women's health is becoming ever more vital.

Objective: The aim of this study was to investigate the menopausal effect on cardiovascular risk factors in elevated triglycerides (TG) and waist circumference (WC) phenotype, and to compare this phenotype among pre- and postmenopausal women.

Method: A total of 4146 women were randomly selected for this study from three districts of Isfahan, Arak, and Najafabad in Isfahan Healthy Heart Program (IHHP). Anthropometric, physical, and biochemical factors were assessed using standard methods. All variables were studied based on the menopause status and the levels of TG and WC.

Results: Twenty-five point three percent of the postmenopausal women and 9.5% of the pre-menopausal women were hyper-TG/WC phenotype; however, the highest percent (77.1%) belonged to high-WC women in the postmenopausal group. In comparison with the postmenopausal women, the premenopausal women were more physically active, with higher education level, but lower BMI, WC, waist to hip ratio, and less likely to be smoker. In postmenopausal women, biochemical factors including fasting blood sugar and lipid profiles were significantly higher than the premenopausal women. There was no significant difference for multivariate-adjusted means of cardiovascular risk factors for menopause in different phenotypes of the WC and TG groups after adjustment for age and BMI.

Conclusion: Hyper- TG/WC phenotype was more prevalent in postmenopausal women and menopause is not independently associated with CVD risk factors.

Keywords: Cardiovascular diseases, hyper triglyceride, waist circumference

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Introduction

Cardiovascular diseases (CVD) are one of the leading causes of morbidity and mortality in both sexes worldwide and even in Iran.[1] Although CVD incidence in premenopausal women is low, however after menopause, CVD increase faster.[2] The prevalence of CVD has raised as a result of lifestyle change during recent decades.[3] Several risk factors including obesity, dyslipidemia, high blood pressure, and smoking are associated with higher CVD incidence.[4] There are variables that may enhance the discrimination of persons at high risk for CVD. Previous studies declared that waist circumference (WC) is related with visceral adipose tissue and correlated with metabolic abnormalities.[5] Central obesity is strongly associated with all metabolic disorders, cancers, and cardiovascular risk,[6] but WC alone could not differentiate intra-abdominal from subcutaneous abdominal adiposity.[7] Therefore, in individuals with increased WC, high triglycerides (TG) concentration could be used as an indicator for adipose tissue and metabolic complications.[8] Moreover, fasting TG level could be considered as an excellent predictor for LDL-cholesterol (LDL-C) particle size.[9]

High fasting TG and increased WC levels have been recognized as high-risk metabolic abnormality.[10] Elevated TG elevated WC that mean WC more than 90 cm in males or 85 cm in females together with fasting TG levels higher than 177 mg/dL is defined as hyper triglyceridemic waist phenotype has been revealed as strong predictor for CVD.[11,12] Attempts to simplify the screening for CVDs to promote wider use introduced this phenotype as less-expensive measure for CVD risks such as insulin resistance, high apolipoprotein (Apo) B/A ratio, and high LDL-C level.[13]

A significant increase in CVD risks occurs following the menopause transition.[14] This increase is partially caused by changes in plasma lipoproteins levels which happen subsequent to estrogen deficiency.[15] Moreover, it has been shown that the menopause transition is related with harmful changes in the distribution of body fat, particularly, central obesity is increased;[16] however, the risk of central obesity for CVD remained even after adjusting the parity effect in menopausal women in Iran.[17] For many years, it was controversial that higher CVD risk could be as a result of aging or a consequence of menopause, or both.[18] A recent meta-analysis found no significant association between menopausal transition and CVD after controlling for probable confounders.[19] Another report suggested that in postmenopausal women, older age may be responsible for cardiovascular risk by stimulating

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ischemic damage in the ovaries or endocrine changes,[20] and some have inquired if menopause concerns with cardiovascular risk.[18] Furthermore, the presence of TG/WC phenotype has been suggested as one of the best markers of CVD risk.[21] The aim of this study was to investigate the prevalence of hyper- TG/WC phenotype in pre- and postmenopausal women and the menopause effect on CVD risk factors in women with elevated TG and WC.

Subjects and Methods

Participants

Derived from multistage cluster random sampling method, above 12000 participants, from three districts of Isfahan, Arak, and Najafabad in three phases were selected form Isfahan Healthy Heart Program (IHHP). IHHP was a community-based interventional program that was conducted by Isfahan Cardiovascular Research Institute and Isfahan Provincial Health Office with the aim of CVD prevention and healthy lifestyle promotion.

Additional information concerning IHHP design and sampling process was presented in previous publications.[1,22] For this cross-sectional study, we used information from the initial phase of IHHP. Based on our inclusion criteria that was consisted of having glucose and lipid profiles, dietary, socio-demographic, and anthropometric information, a total of 4146 women were selected for this study. A written informed consent was taken from each participant. Isfahan University of Medical Sciences Ethics Committee has approved this study.

Anthropometric Assessment

Measurement of weight and height was completed by expert technicians while individuals had light clothes and no shoes. Weight of the participants was measured using a calibrated scale and height was measured by a measuring tape. Calculation of body mass index (BMI) was based on the formula (weight in kilogram divided by squared height in meters [kg/m^2]). WC was measured horizontally between lowest rib and the iliac crest and the greatest point of hip was measured for hip circumference.

Biochemical Assessment

Fasting blood samples were collected while participants were overnight fasting. After taking plasma, blood samples were frozen and sent to Isfahan Cardiovascular Research Institute central laboratory for further assessment. Fasting plasma glucose (FPG), serum total cholesterol, and triglyceride levels were measured using enzymatic colorimetric method. Serum HDL-C was determined after removing non-HDL-C using dextran sulfate-magnesium chloride. Friedewald equation[23] was used to calculate LDL-C level.

Other Variables Assessment

Data regarding socio-demographic, smoking habit, family history, and menopause situation were gathered by a pretested questionnaire. Physical activity was assessed using Baecke questionnaire.[24]

Statistical Methods

We used SPSS software for our statistical analysis and $P \leq 0.005$ was used for statistical differences. Two independent sample t-test was applied to compare means of continuous variables and to compare categoric variables, chi-square test was used. To test the differences between pre- and post- menopause in hyper- TG/WC and other groups we used ANCOVA test in adjusted models. The first adjustment was made for age and further adjustment was made for BMI.

Results

Analyses were done on 4146 women, 2947 premenopausal and 1199 postmenopausal. The prevalence of hyper- TG/WC and its components in pre- and postmenopausal women are showed in Figure1. Twenty-five point three percent of the postmenopausal women and 9.5% of the premenopausal women were hyper- TG/WC; however, elevated WC group allocated the highest percentage and the percentages of the postmenopausal women were higher than the premenopausal women in all groups. Characteristics of the study participants based on menopausal status are shown in Table 1. In comparison with postmenopausal women, premenopausal women are more physically active, with higher education level, and less likely to be smoker. Postmenopausal women tended to have elevated BMI, WC, and waist to hip ratio. No significant differences were found in the weight of the two groups. Cardiovascular risk factors of the study participants are provided in Table 2. In post-menopausal women, biochemical factors including FBS, cholesterol, HDL, LDL, CRP (C-reactive protein), Apo A, Apo B, and TG levels are significantly higher than premenopausal women.

The cardiovascular risk factors of the study participants based on the presence of hyper- TG/WC in pre- and postmenopausal

Table 1. Characteristics of the study participants based on menopausal status*

	Pre- menopause (n=2944, 71%)	Post- menopause (n = 1199, 29%)	P- value
Age (years)	32.15 ± 0.17	59.80 ± 0.30	0.000
Physical activity (mets/sec)	709.45 ± 7.33	570.45 ± 11.15	0.000
Smoking (%)	0.6	1.3	0.035
Education (%)			0.000
0–5 years	43.4	88.6	
6-12 years	44.6	9.6	
>12 years	12.0	1.8	
Weight (kg)	66.32 ± 0.23	66.27 ± 0.37	0.91
BMI(kg/m^2)	26.20 ± 0.09	27.57 ± 0.13	0.000
Waist circumference (cm)	88.73 ± 0.25	97.10 ± 0.37	0.000
Waist to hip ratio	0.87 ± 0.001	0.96 ± 0.002	0.000

*Data are means ± standard error unless indicated.

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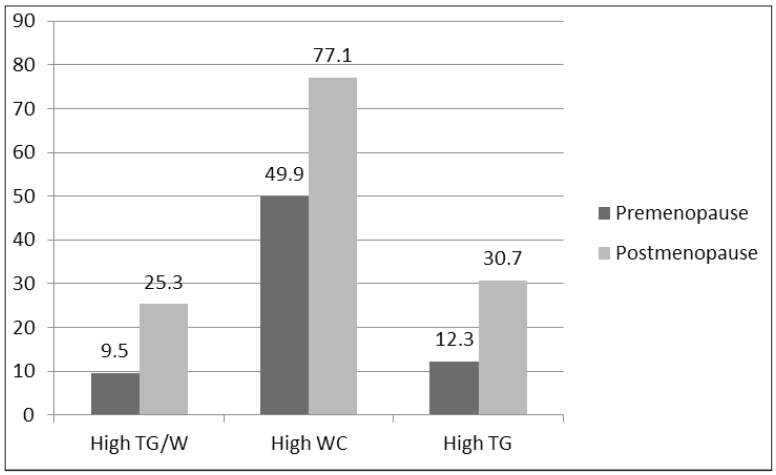

Figure 1. The prevalence of hyper triglyceridemic high WC in pre- and post menopausal women.

Table 2. Metabolic risk factors of the study participants based on menopausal status*

	Pre- menopause (n = 2944, 71%)	Post- menopause (n = 1199, 29%)	P- value
FBS (mg/dL)	87.32 ± 17.46	103.14 ± 36.43	0.000
Triglycerides(mg/dL)	127.82 ± 81.24	185.02 ± 123.14	0.000
Cholesterol (mg/dL)	186.74 ± 38.10	225.60 ± 43.10	0.000
HDL (mg/dL)	46.42 ± 10.68	47.77 ± 11.63	0.001
LDL (mg/dL)	114.93 ± 31.64	140.51 ± 35.33	0.000
CPR (mg/dL)	3.46 ± 3.18	3.75 ± 3.33	0.01
Apo A (mg/dL)	125.45 ± 24.19	137.03 ± 25.39	0.000
Apo B (mg/dL)	94.50 ± 23.02	113.04 ± 25.32	0.000

*Data are means± standard deviation.

groups are presented in Table 3. In premenopausal group, individuals with hyper- TG/WC phenotype have significantly higher level of FBS, total cholesterol, LDL-C, CRP, Apo A, Apo B, and TG levels but lower level of HDL-C. The percentages of metabolic syndrome and diabetes are also higher in this phenotype. In postmenopausal group, except for CRP and Apo A, similar trend have been shown for other metabolic risk factors. All of the risk factors are significantly higher in postmenopausal women. Table 4 demonstrates multivariate-adjusted means and standard error of cardiovascular risk factors for menopause in different phenotypes of WC and TG groups after adjustment for age. In hyper- TG/WC group, FBS is higher in postmenopausal women but not after further adjustment for BMI. In normal-TG/WC group, total cholesterol and LDL-C increase after menopause but they did not remain significant after additional adjustment for BMI. There is no difference for other groups and other risk factors.

Discussion

The objective of the current study was to compare the prevalence of hyper- TG/WC between pre- and postmenopausal women and to test whether menopause, independent of other variables, can be associated with CVD risk factors in women with hyper- TG/WC phenotype. During recent decades life expectancy for women has increased to 74.6 years; it means they live about one-third of their lives in the postmenopausal state,[25] thus realizing the effect of menopause on women's health is becoming ever more important.

In this cross-sectional analysis on women from IHHP study, the postmenopausal women had higher BMI, WC, and waist to hip ratio compared with the premenopausal women. Our observed trend is consistent with others that found an increase in BMI after menopause[26] and revealed that in the menopausal transition, BMI is a significant mediator of sexual hormone level.[27] It has been assumed that the relation between menopause and obesity is linked with adipose-derived markers such as leptin, adiponectin, or insulin resistance[28] independent of age and race;[29] however, others specified that increasing in body fat after menopause is associated with both menopause transition and aging.[30]

Greater android fat distribution in postmenopausal women is associated with diabetes and CVD risk.[31] and adverse lipid profiles such as lower HDL-C and higher LDL-C, total cholesterol, and TG levels.[32] The current study showed that in the postmenopausal women, lipid profiles were higher than the pre-menopausal women. Some of the previous published studies have also reported higher level of TG,[33] total cholesterol, and LDL-C in postmenopausal women.[34] Conversely, evidence about the association between HDL-C and menopause is inconsistent.[35] We observed that HDL-C and Apo A increased in postmenopausal women. On the contrary to previous investigations indicating a gradual decrease in HDL-C in postmenopausal women,[35] our results is in line with others showing a gradual increase in HDL-C after menopause transition.[35] It has been hypothesized that total cholesterol increase could also affect other lipids like HDL-C. In addition, since lipids and menopause are highly associated with age, it is

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Table 3. Metabolic risk factors of the study participants based on menopausal status and the presence of hypertriglyceridemic waist phenotype*

	Pre- menopause			Post- menopause			P- value
	Hyper- TG / WC	Normal- TG / WC	P-value	Hyper- TG / WC	Normal- TG / WC	P- value	
Metabolic syndrome (%)	93.2	13.9	0.000	95.7	43.0	0.000	0.000
Diabetes (%)	11.1	2.2	0.000	28.9	16.8	0.000	0.000
FBS (mg/dL)	94.91 ± 31.25	84.05 ± 13.67	0.000	112.82 ± 50.24	96.16 ± 29.66	0.000	0.000
Triglycerides (mg/dL)	297.52 ± 117.55	108.79 ± 48.46	0.000	312.10 ± 140.50	138.62 ± 62.60	0.000	0.000
Cholesterol (mg/dL)	226.23 ± 41.29	182.73 ± 35.27	0.000	245.77 ± 44.34	217.20 ± 38.37	0.000	0.000
HDL (mg/dL)	38.78 ± 10.01	47.29 ± 10.42	0.000	41.39 ± 10.30	49.47 ± 11.35	0.000	0.001
LDL (mg/dL)	129.54 ± 37.32	113.70 ± 30.39	0.000	143.03 ± 39.64	139.38 ± 33.48	0.190	0.000
CPR (mg/dL)	3.88 ± 3.50	3.28 ± 2.99	0.009	3.94 ± 3.01	3.59 ± 3.29	0.152	0.011
Apo A (mg/dL)	131.44 ± 25.98	124.03 ± 23.73	0.000	138.00 ± 25.21	135.94 ± 24.67	0.258	0.000
Apo B (mg/dL)	113.93 ± 26.54	92.16 ± 29.66	0.000	123.65 ± 26.80	108.39 ± 23.03	0.000	0.000

*Data are means± standard deviation unless indicated.

Table 4. Multivariate-adjusted means (± SE) of cardiovascular risk factors for menopause in different waist circumference and triglycerides phenotype groups

	Hyper- TG / WC		Normal- TG hyper- WC		Hyper- TG normal- WC		Normal- TG / WC	
	Menopause	Pre-menopause	Menopause	Pre-menopause	Menopause	Pre- menopause	Menopause	Pre- menopause
FBS								
Model 1	105.19 ± 2.69*	95.41 ± 2.54	90.18 ± 2.52	86.68 ± 2.26	101.920 ± 4.06	94.68 ± 3.29	83.48 ± 2.82	86.11 ± 2.30
Model 2	105.07 ± 2.70	95.14 ± 2.57	89.99 ± 2.52	86.45 ± 2.28	102.90 ± 4.10	94.72 ± 3.29	83.74 ± 2.85	86.30 ± 2.33
Total cholesterol								
Model 1	229.01 ± 4.14	226.34 ± 3.89	199.46 ± 3.86	193.88 ± 3.47	231.91 ± 6.23	228.39 ± 5.04	197.61 ± 4.33*	182.71 ± 3.53
Model 2	227.32 ± 4.2	222.72 ± 3.92	198.10 ± 3.85	191.39 ± 3.48	233.99 ± 6.26	229.40 ± 5.02	200.98 ± 4.35	185.88 ± 3.55
LDL- cholesterol								
Model 1	131.81 ± 3.66	128.31 ± 3.42	130.93 ± 3.45	124.86 ± 3.08	133.99 ± 5.52	138.61 ± 4.47	126.97 ± 3.84*	114.83 ± 3.13
Model 2	130.29 ± 3.65	127.69 ± 3.47	127.12 ± 3.42	122.62 ± 3.08	135.66 ± 5.55	139.53 ± 4.45	128.03 ± 3.85	117.69 ± 3.15
HDL- cholesterol								
Model 1	39.47 ± 1.22	38.06 ± 1.15	47.85 ± 1.14	45.66 ± 1.02	37.05 ± 1.84	38.19 ± 1.49	49.66 ± 1.28	48.49 ± 1.04
Model 2	39.69 ± 1.22	38.57 ± 1.16	48.05 ± 1.14	46.06 ± 1.03	36.67 ± 1.85	38.05 ± 1.49	49.09 ± 1.29	48.02 ± 1.05
Apo A								
Model 1	131.45 ± 2.84	130.76 ± 2.67	129.62 ± 2.65	125.16 ± 2.38	128.79 ± 4.30	134.45 ± 3.47	129.89 ± 2.97	125.03 ± 2.42
Model 2	131.52 ± 2.84	131.01 ± 2.70	129.53 ± 2.66	125.36 ± 2.39	128.83 ± 4.35	134.38 ± 3.47	129.59 ± 3.00	124.82 ± 2.45
Apo B								
Model 1	114.59 ± 2.52	115.72 ± 2.38	100.02 ± 2.36	101.07 ± 2.12	107.19 ± 3.83	118.44 ± 3.09	97.19 ± 2.65	95.29 ± 2.15
Model 2	113.95 ± 2.52	114.41 ± 2.39	99.62 ± 2.36	100.18 ± 2.13	107.56 ± 3.86	118.81 ± 3.09	98.35 ± 2.67	96.46 ± 2.17
CRP								
Model 1	3.45 ± 0.38	3.81 ± 0.36	3.15 ± 0.36	3.57 ± 0.32	3.11 ± 0.56	4.21 ± 0.46	2.90 ± 039	3.28 ± 0.32
Model 2	3.44 ± 0.38	3.78 ± 0.36	3.13 ± 0.36	3.56 ± 0.32	3.10 ± 0.57	4.22 ± 0.46	2.93 ± 0.40	3.30 ± 0.30

Model 1: Adjusted for age, Model 2: Further adjusted for BMI.

not clear that increasing in lipid profiles is independent of age effects[35] and some suggested that menopause effect is similar to the consequence of older age.[34] Although there is evidence that after adjusting for age and BMI, menopause was still a predictor for metabolic syndrome,[36] another large study didn't find any significant differences in lipid profiles after adjustment for age.[30]

Although previous studies showed the rising trend in overweight and hyper- TG/WC in Iranian population,[37] the present investigation found that the prevalence of hyper- TG/WC and also high TG or high WC were higher in the postmenopausal women. Moreover in pre- and postmenopausal groups, most of the cardiovascular risk factors were worse in hyper-TG/WC subgroups.

Hyper- TG/WC phenotype is an important predictor for CVD risk[8] and as our result shows women in the hyper- TG/WC group in both menopausal subgroups had worse situation. A previous study showed that larger WC, independent of BMI, was positively associated with cardiovascular risk.[38] Consequently, it was suggested to measure the WC besides BMI to estimate the amount of adiposity.[8] In addition, the presence of small, dense LDL has been associated with higher fasting TG levels.[39] In this regards, it

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has been proposed that the presence of adiposity combined with hyper- TG could be used as first screening tool to identify the future risk of metabolic syndrome and CVD risk.[8] Because of some difficulties accessing new markers of CVD risk, a simple, inexpensive, and practical screening method to identify this metabolic risks is critical.[40]

The effect of independent role of menopause than that of age remains controversial[41] and estrogen replacement in postmenopausal women didn't improve coronary mortality or morbidity.[42] It has been suggested that it is not menopause that has negative effect on cardiovascular risk but the age at menopause is a determinant factor.[20]

Although in postmenopausal women compared with premenopausal women, the incidence and prevalence of CVD are higher,[41] it is not clear which factor is responsible for this situation and this could not predict CVD risk, while hyper- TG/WC phenotype can be a better predictor.

There were several limitations that should be considered in the explanation of our findings. The design of our study was cross-sectional that disallows inferring causal relationship between menopause and cardiovascular risk factors. Further longitudinal studies could conclude the effect of menopause transition on cardiovascular risk factors. Moreover, some lifestyle parameters, might confounding the association between hyper- TG/WC phenotype, menopause, and CVD risk factors, may not fully controlled and obtained in our analysis.

Based on the results of the current study, menopause is not independently associated with CVD risk and hyper- TG/WC phenotype is a better predictor for CVD risk. Although further prospective studies are mandatory to confirm this association, postmenopausal women should be aware of their increasing cardiovascular risk and pay more attention to monitor their CVD risk factors particularly WC and TG levels.

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