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Association of high sensitive C-reactive protein and lipid markers in predicting atherosclerotic cardiovascular risk in dyslipidemic women

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ABSTRACT

This study found a strong association between elevated levels of highly sensitive C-reactive protein (hs-CRP) and vital lipid markers in dyslipidemic pre-, peri-, and postmenopausal women, indicating the need to screen them early for atherosclerotic cardiovascular risk. These subjects were advised to make dietary and lifestyle changes to overcome dyslipidemia and prevent the development and progression of atherosclerotic cardiovascular disease (ASCVD) during menopause. No such studies have examined the relationship between hs-CRP and lipid markers, especially in dyslipidemic women. Surprisingly, significant associations were also observed between hs-CRP and triglycerides (TG), as well as between hs-CRP and LDL-cholesterol (LDL-C) in premenopausal women with dyslipidemia. These correlations suggest that hs-CRP and the studied lipid markers are better indicators of the possible onset of ASCVD in women at later ages.

INTRODUCTION

Cardiovascular disease is the leading cause of death among women, and its prevalence increases after menopause. Asian countries have the greatest cardiovascular disease (CVD) burden. Dyslipidemia is common in women, and the lipid profile worsens as menopause approaches [1]. Menopause is related to altered lipid metabolism due to hormonal changes, such as decreased estrogen levels and increased fibrinogen levels, which lead to the development of CVD [2]. Women's metabolism is impacted by changes in hormone levels throughout their lives, irrespective of their menopausal status [3]. Among the most significant risk factors for CVD, dyslipidemia is the most prominent one and helps predict the condition [4]. In healthy, asymptomatic people, dyslipidemia is a strong predictor of coronary artery disease [5,6] and is characterized by increased serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglyceride (TG) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels [7,8]. Dyslipidemia affects more than half of the adult

population worldwide. In Africa, Southeast Asia, Europe, and the Americas, the prevalence of dyslipidemia with hypercholesterolemia ranges from 22.6% to 54%. According to the World Health Organization (WHO), dyslipidemia is responsible for 2.6 million fatalities per year [9]. In India, high triglyceride levels are associated with low HDL cholesterol levels in rural and urban populations [10].

An increased risk of cardiovascular disease (CVD) is associated with dyslipidemia. Indian women have lower HDL levels than women of other nationalities. Indians have higher triglyceride levels and lower HDL cholesterol levels, yet their total cholesterol levels are lower than those in the United States and the United Kingdom [11]. Increased CVD morbidity and mortality are seen in individuals with high CRP levels [12]. Those with serum hs-CRP levels of ≤ 1 mg/L are at a lower cardiovascular risk, those with levels of 1-3 mg/L are at an intermediate risk, and those with levels > 3 mg/L are at a high risk. No studies have examined the connection between hs-CRP and other lipid markers. Hence, this study investigated the association of hs-CRP with lipid markers in dyslipidemic women at various phases of menopause to enhance cardiovascular health in postmenopausal women.

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Resources and approaches

This cross-sectional study was carried out from July 2021 to February 2022 at NRI Medical College Hospital in Chinakakani, Guntur District, Andhra Pradesh, India. Two hundred and ten women between 18 and 65 years of age who visited the Gynecology Outpatient Department of the hospital during this period were enrolled and stratified into premenopausal, perimenopausal, and postmenopausal groups according to the Stages of Reproductive Aging Workshop (STRAW) [13] classification, with each group consisting of 70 participants. Permission for the research was obtained from the Institutional Ethics Committee (Approval number: IEC-NRIMC:168), and written informed consent was received from each participant.

Inclusion criteria

Women between the ages of 18 and 65.

Exclusion criteria

The study excluded pregnant women and those with cancer, kidney disease, congestive heart failure, chronic illnesses, or those on hormone therapy.

METHODS

Five milliliters of venous blood was collected from overnight fasted volunteers (10 to 12 hours) and analyzed on a Vitros 5600 fully automated analyzer. High-sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetry and estradiol was measured by competitive immunoassay. Total cholesterol was measured using enzyme cholesterol oxidase peroxidase and 4-aminophenazone (CHOD-PAP) [14], and triglycerides were measured using glycerophosphate oxidase-peroxidase-4-aminophenazone (GPO-PAP) [15]. HDL-C was assessed by Polyanion Precipitation using oxidase, while direct LDL-C was measured by the cholesterol esterase and oxidase method.

Statistical analysis

The obtained data was analyzed using one-way analysis of variance. Descriptive statistics, such as mean ± standard deviation (SD) and median and interquartile range, were used to summarize continuous variables. Pearson's correlation was performed between hs-CRP and lipid parameters using the statistical software SPSS 20.0. At the 1% level, *p*-values of 0.05 were considered significant.

RESULTS

Based on lipid parameters, dyslipidemic women were selected from the pre-, peri-, and postmenopausal groups, and their numbers are presented in Figure 1. The percentages are nearly identical in the premenopausal (41%) and postmenopausal (40%) groups. Figure 2 shows the median (interquartile range) of high-sensitivity C-reactive protein (hs-CRP) in premenopausal, perimenopausal, and postmenopausal women with dyslipidemia: 2.25 (3.5), 3.1 (4.5), and 3.85 (5.2), respectively. Table 1 shows the correlation

of hs-CRP with lipid markers (TC, TG, HDL-C, and LDL-C) in various stages of menopause in dyslipidemic women. The table shows a significant positive correlation between triglycerides and hs-CRP in premenopausal women with dyslipidemia and a negative association between HDL-C and hs-CRP in peri- and postmenopausal women with dyslipidemia. A positive association was observed between total cholesterol and hs-CRP in postmenopausal women. The American Heart Association classifies hs-CRP levels as low, moderate, or high cardiovascular risk groups, respectively, at 1 mg/L, 1-3 mg/L, and >3 mg/L (Table 2). Peri- and postmenopausal women with hs-CRP levels >3 mg/L had elevated levels of TC, TG, and LDL-C, as well as decreased levels of HDL-C.

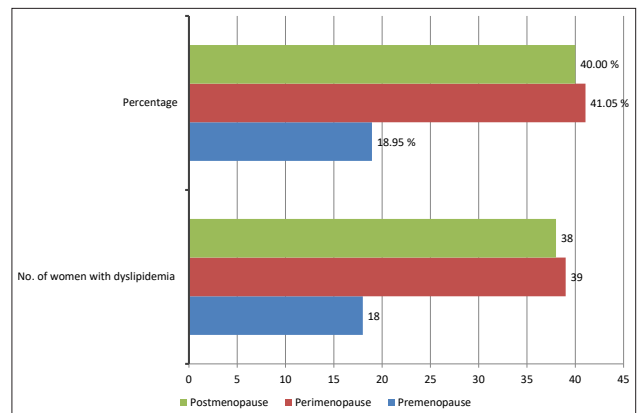


Figure 1. Proportion of dyslipidemia in pre-, peri- and postmenopausal women

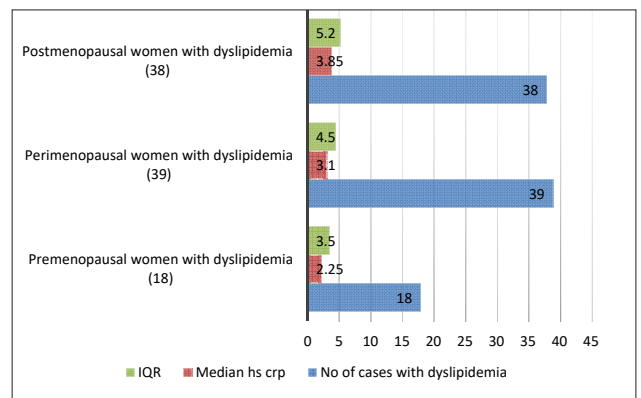


Figure 2. Median and Interquartile range of hs-CRP in pre-, peri- and postmenopausal women with dyslipidemia

Table 1. Correlation of hs-CRP with lipid markers in pre, peri and postmenopausal women with dyslipidemia

Correlation	Premenopause (18)		Perimenopause (39)		Postmenopause (38)	
	r	p	r	p	r	p
TC Vs hs-CRP	-0.194	0.441	0.165	0.315	0.400*	0.013
TG Vs hs-CRP	0.978**	0.000	0.243	0.136	0.261	0.114
HDL Vs hs-CRP	-0.269	0.280	-0.443**	0.005	-0.082	0.624
LDL Vs hs-CRP	-0.562*	0.015	0.089	0.592	0.303	0.065

r - correlation coefficient; *p*<0.05is considered as significant
 * - Correlation is significant at the 0.05 level (2-tailed)
 ** - Correlation is significant at the 0.01 level (2-tailed)

Table 2. Distribution of lipid markers at different levels of hs-CRP in pre-, peri- and postmenopausal women with dyslipidemia

Parameters	Group	hs-CRP <1 mg/L		hs-CRP 1-3 mg/L		hs-CRP >3 mg/L		F	p
		No. of dyslipidemia cases	Mean±SD	No. of dyslipidemia cases	Mean±SD	No. of dyslipidemia cases	Mean±SD		
TC	PRE	33	175.66 ±31.98	23	178.5 ±35.26	13	188.84 ±43.57	0.650	0.525
	PERI	18	189.33 ±29.78	23	195 ±31.54	29	204.75 ±25.87	1.726	0.186
	POST	16	188.56 ±35.74	24	199.04 ±39.52	30	212.83 ±32.40	2.584	0.083
TG	PRE	33	123.42 ±50.69	23	134.70 ±51.34	13	161.61 ±62.93	2.394	0.099
	PERI	18	154.55 ±72.96	23	140.04 ±55.53	29	192.44 ±78.3	3.866	0.026*
	POST	16	145.37 ±65.15	24	168.87 ±58.28	30	202.66 ±98.95	2.933	0.60
HDL	PRE	33	44.78 ±10.25	23	42.25 ±9.68	13	40.15 ±9.17	1.149	0.323
	PERI	18	40.0 ±7.9	23	39.78 ±5.79	29	36.0 ±6.53	2.862	0.064
	POST	16	40.62 ±8.1	24	37.20 ±5.99	30	35.53 ±7.0	2.792	0.068
LDL	PRE	33	109 ±35.86	23	115.36 ±36.9	13	107.36 ±33.87	0.656	0.522
	PERI	18	118.04 ±25.65	23	122.35 ±28.35	29	129.67 ±24.97	1.177	0.314
	POST	16	116.61 ±37.13	24	125.76 ±34.95	30	135.35 ±30.69	1.68	0.194
VLDL	PRE	33	24.68 ±10.13	23	26.94 ±10.26	13	32.32 ±12.58	2.394	0.099
	PERI	18	30.91 ±14.59	23	28.0 ±11.10	29	38.48 ±15.67	3.866	0.026*
	POST	16	29.07 ±13.03	24	33.77 ±11.65	30	40.53 ±19.79	2.933	0.60

* - p < 0.05 is considered as significant. F calculated by one way ANOVA

DISCUSSION

Dyslipidemia is considered a modifiable risk factor for the development of atherosclerotic cardiovascular disease (ASCVD) and stroke [17]. The current study found that 18.9%, 41.1%, and 40% of premenopausal, perimenopausal, and postmenopausal women, respectively, have dyslipidemia, indicating an increased risk of cardiovascular disease (CVD). During the perimenopausal stage, when extensive hormonal fluctuations occur in peri- and postmenopausal women, the prevalence of dyslipidemia is similar to that in premenopausal subjects. This is consistent with earlier findings [18], which reported a significant prevalence of dyslipidemia in postmenopausal women.

A significant positive association was observed between total cholesterol (TC) and high-sensitivity C-reactive protein (hs-CRP) in dyslipidemic postmenopausal women. However, a substantial negative correlation was seen between high-density lipoprotein cholesterol (HDL-C) and hs-CRP in the dyslipidemic perimenopausal group. Additionally, TG and hs-CRP are correlated in premenopausal women with dyslipidemia (Table 1). Previous research by Baranwal [19] on 168 diabetic subjects found a positive relationship between TC, TG, and hs-CRP and a negative correlation between hs-CRP and HDL. A similar correlation was found in a study by Koley *et al.* involving both men and women [20]. hs-CRP is a powerful predictor of cardiovascular events and an inflammatory marker [21].

Low estrogen levels that accompany menopause result in an altered lipid profile due to increased lipase activity in the liver [22]. Age at the time of the last menstrual cycle influences the change in follicle-stimulating hormone and estradiol levels during menopause. This results in a drop in HDL cholesterol levels and a minor increase in solid LDL particles, which elevates the risk of cardiovascular

disease [23]. Additionally, epidemiology, pathophysiology, and therapeutic aspects play significant roles in producing tiny, dense LDL particles that lead to coronary heart disease risk. In a diabetic condition, lipid metabolism results in thrombotic blockage of the coronary artery and endothelial wall damage due to lipid-rich plaques, which increases the chances of atherosclerosis [24].

Peri- and postmenopausal women at high risk (hs-CRP levels >3 mg/L) had higher levels of TC, TG, and LDL-C, as well as lower levels of HDL-C (Table 2). This type of association between hs-CRP and lipid markers in subjects with dyslipidemia is the root cause of inflammation of the blood vessels that leads to atherosclerosis. This study demonstrated that peri- and postmenopausal women with dyslipidemia had higher median hs-CRP levels than premenopausal women with the same condition. These results are consistent with those of Klisic *et al.*,

who found elevated hs-CRP levels in obese postmenopausal women [25].





CONCLUSIONS

This study examined peri- and postmenopausal women with dyslipidemia and found that they had elevated levels of hs-CRP. This marker was strongly associated with vital lipid parameters, indicating the possibility of ASCVD in these subjects later in life. Therefore, it is crucial to screen perimenopausal women with dyslipidemia for elevated hs-CRP levels to identify them and encourage dietary and lifestyle changes to prevent ASCVD development during the postmenopausal period.

LIMITATIONS

The present study is single-centered, has a small sample size, and includes only subjects of one race. These factors may introduce selection bias and limit the generalizability of the findings. Therefore, multicentered studies with a large sample size are needed to understand the severity of the problem and validate the findings.

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