

# New atherogenic indices: Assessment of cardiovascular risk in post menopausal dyslipidemia

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## ABSTRACT

**Background:** Menopause is the phase of declined ovarian activity and fall in levels of estrogen, usually due to aging and surgical removal of ovaries. Postmenopausal women are at higher risk of developing cardiovascular disease, especially coronary artery atherosclerosis due to elevated levels of plasma lipids. The aim of this study is to observe the relationship between the BMI, anthropometric parameters, lipid profile and determine the role of new atherogenic indices in assessing cardiovascular risk in post menopausal women. **Materials and Methods:** A total number of 75 female subjects were participated in this study. Selection of study subjects based upon their menopausal status and levels of lipid profile. In which 51 subjects were considered as control group with pre menopausal status and normal lipid profile. The rest of the 24 subjects were considered as cases group with post menopausal status and elevated lipid profiles. Anthropometric measurements and various atherogenic indices like, Castelli's Risk Index-I (CRI-I), Castelli's Risk Index-II (CRI-II), TG/HDL-c ratio, atherogenic Index of Plasma (AIP) and Atherogenic Coefficient (AC) were calculated. **Results:** In our study, elevated levels of lipid profile and higher values of anthropometric measurements were ( $P < 0.01$ ;  $p < 0.001$ ) observed in post menopausal than the pre menopausal women. A positive correlation observed comparison between BMI vs. anthropometric measurements but BMI was not correlated with lipid profile & atherogenic indices. All atherogenic indices were found to be significantly ( $p < 0.001$ ) showed higher values in post menopausal women compared to the pre menopausal women. In post menopausal cases, HDL-c was found to be significantly negatively correlated with atherogenic indices and LDL-c was positively correlated with atherogenic indices like CRI-II. These raised atherogenic ratios were can contribute to estimation the risk of cardiovascular disorders (CVD). **Conclusion:** These indices are could be used for identifying individual at higher risk of cardiovascular disease in the clinical practices especially, when the absolute values of lipid profile seem normal or higher and not markedly deranged or in centers with insufficient resources.

**Key words:** Menopausal status, Dyslipidemia, Body mass Index (BMI), Anthropometric parameters, atherogenic index

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## INTRODUCTION

Dyslipidemia is one of the major cause of cardiovascular disorders (CVD), which is the most common cause of male and female morbidity and mortality.<sup>1,2</sup> In female subjects increase in cardiovascular risk could be directly due to estrogen deprivation, or indirectly due to an increase risk factors, such as dyslipidemia, diabetes mellitus, overweight,

or hypertension, and time of menopause.<sup>3</sup> Menopause is a natural event in the ageing process and signifies the end of reproductive years with cessation of cyclic ovarian functions.<sup>4</sup> The average age of menopause is 51 years and less than 1% of women experience it before the age of 40 years. Some women undergoing premature menopause at a very early age, affecting their ability to have children.<sup>5</sup> Apart from being a natural process, menopause could also

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be induced by surgical removal of ovaries or chemotherapy or by high dose radiotherapy related to cancer treatment and premature occurrence due to ovarian failure.<sup>6</sup>

Several studies have shown higher levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c) and triglyceride (TG) are associated with menopausal status.<sup>7-12</sup> Numerous epidemiologic studies have demonstrated a direct correlation between increasing the body mass index (BMI) and elevated lipid profiles and an inverse relationship with high density lipoprotein cholesterol (HDL-c).<sup>13-15</sup> The association between BMI and lipoprotein levels, particularly LDL-c has been suggested to be a contributing factor in the higher rates of cardiovascular events associated with obesity. However, these studies were limited by under representation of obese subjects. Some of the other observational studies of obese patients have confirmed a correlation between BMI and TG or HDL-c, but not with LDL-c levels.<sup>16,17</sup>

The aim of this study is to observe the relationship between the BMI, anthropometric parameters, lipid profile and determine the role of new atherogenic indices in assessing cardiovascular risk in post menopausal women comparison with premenopausal women.

## METHODOLOGY

### Study design

The present study was carried out at Dr.Ramesh Cardiac and Multispecialty Hospital LTD, Vijayawada, Andhra Pradesh, India. The study subjects were selected, who were visit to hospital for their general health check up. The study protocol was approved by the Institutional Ethical Committee and study was conducted during the period from 2012-2014. Selection of postmenopausal women based upon certain inclusion criteria such as the cessation of menstruation for a minimum of one year and elevated lipid profile considered as cases. Likewise, certain exclusion criteria are, who were had a regular menstruation considered as premenopausal subjects. All subjects with hepatic, metabolic, renal disease and those who were on exogenous hormones supplement or on hormone replacement therapy or use of lipid lowering drugs and surgical removal of ovaries were excluded from the study. An informed written consent was obtained from all the study subjects who participated in our study.

### Data collection

Systemic examination of each subject was carried out; it included name, age, and address, type of diet, occupation,

physical exercise, present & past medical illness, family history, and menstrual cycle history. Anthropometric assessments such as height in meter (m), weight in kilogram (kg), waist circumference (WC), hip circumference (HC) and waist & Hip ratio (WHR) in centimeters (cm) were calculated.<sup>18</sup> Body mass index (BMI) was calculated by weight in kilograms divided by the square of the height in meter (kg/m<sup>2</sup>). Selection of study subjects based upon their menopausal status and levels of lipid profile. In which 51 subjects were considered as control group with pre menopausal status and normal lipid profile. The rest of the 24 subjects were considered as cases group with post menopausal status and elevated lipid profiles.

### Collection of a blood sample and estimation of lipid profile

Fasting blood samples were collected in the morning between 7 a.m. and 8 a.m. by venepuncture of antecubital vein with all aseptic precautions, using a dry disposable syringe under sterile conditions in a sterile plain vial. Serum was separated by centrifugation at 3000 rpm for 15minutes. Fresh serum was used for estimation of TC, TG and HDL-c. The tests were carried out in an automated clinical auto analyzer. Further, LDL-c, VLDL-c, and Non HDL-c were calculated by using Friedewald's formula.<sup>19</sup> Plasma lipid abnormality was based on the expert panel of the National cholesterol education programme (NCEP) cut of values.<sup>20</sup> Further, atherogenic indices like, Castelli's Risk Index-I (CRI-I)=TC/HDL-c, Castelli's Risk Index-II (CRI-II) = LDL-c/HDL-c, Atherogenic Coefficient(AC) = (TC- HDL-c)/HDL-c, TG/HDL-c ratio, and Atherogenic Index of Plasma (AIP) = log (TG/HDL-c) are calculated from the individuals.

### Statistical analysis

The collected data were analyzed by using graph pad prism, version 6. The differences in groups were determined by performing the one-way analysis of variance (ANOVA), student's t-test, and also performed the Pearson's correlation and linear regression tests for post menopausal group. Data were expressed either as mean  $\pm$  standard error mean (SEM). The statistical significance was set at the *p* value of \**p*<0.05; \*\**p*<0.01; and \*\*\**p*<0.001.

## RESULTS

Table 1 showed the mean  $\pm$  SEM values of age, height, weight, anthropometric indices of pre and post menopausal groups. The mean age of postmenopausal (62.20 $\pm$ 1.46) and pre menopausal (39.71 $\pm$ 1.53) subjects were expressed in years. In our study observed that, mean age of post menopausal women was significantly (*p*<0.001) different with pre menopausal women. The mean age of post menopausal

group was the greater than that of premenopausal control women. BMI was significantly ( $p < 0.046$ ) different in post menopausal women ( $27.98 \pm 1.58$ ) with pre menopausal women ( $25.06 \pm 0.65$ ). The anthropometric measurements like, waist circumference ( $34.68 \pm 0.60$ ;  $42.63 \pm 0.53$ ), hip circumferences ( $52.43 \pm 1.56$ ;  $68.25 \pm 1.50$ ) and waist-hip ratio (WHR) ( $0.68 \pm 0.01$ ;  $0.63 \pm 0.01$ ) were observed in pre and post menopausal women respectively. Among these control to cases groups, significant ( $p < 0.001$ ) values of waist circumference & hip circumference was observed, except WHR ratio. However, there was no significant association values were observed in height (m), weight (kg), when compared to both groups. Table 2 showed Pearson's correlation analysis of interrelationships BMI *vs.* waist circumference, hip circumference, waist-hip ratio, weight and lipid profiles in post menopausal cases. In our study observed, BMI was positively correlated with Weight ( $r = .740$ ;  $p = .000$ ), waist circumference ( $r = .540$ ;  $p = .006$ ) and hip circumference ( $r = .442$ ;  $p = .031$ ) but, it was negatively correlated with lipid profiles and atherogenic indices.

**Table 1: Showed the mean±SEM values of age, anthropometric indices of pre and post menopausal women**

Parameter	Pre menopausal	Post menopausal
Age (years)	39.72±1.53	62.21±1.46***
Height (m)	1.58±0.009	1.54±0.02 <sup>ns</sup>
Weight (kg)	62.61±1.36	65.08±2.07 <sup>ns</sup>
BMI	25.06±0.65	27.98±1.58*
WC (cm)	34.68±0.60	42.63±0.53***
HC (cm)	52.43±1.56	68.25±1.50***
WHR	0.68±0.01	0.63±0.01 <sup>ns</sup>

<sup>ns</sup> $p > 0.05$ : Statistically non significant; \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ : Statistically significant

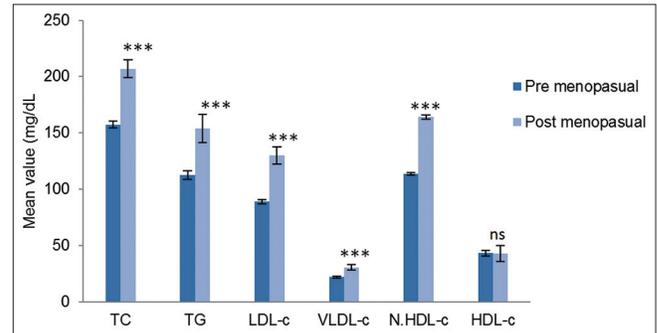
**Table 2: Showed Pearson correlation (r) between BMI with anthropometric indices and lipid profile in post menopausal cases subjects**

Parameters	Post menopausal cases	
	r	p
BMI vs. WC	0.540	0.006**
BMI vs. HC	0.442	0.031*
BMI vs. WHR	-0.206	0.334
BMI vs. Weight	0.740	0.000**
BMI vs. TG	-0.068	0.754
BMI vs. TC	0.097	0.652
BMI vs. LDL-c	0.124	0.563
BMI vs. VLDL-c	-0.063	0.770
BMI vs. HDL-C	0.184	0.390
BMI vs. Non HDL-c	0.063	0.769
BMI vs. CRI-I	-0.147	0.493
BMI vs. CRI-II	-0.036	0.869
BMI vs. TG/HDL-c	-0.147	0.494
BMI vs. AIP	-0.131	0.542
BMI vs. AC	-0.145	0.500

\* $p < 0.05$ : correlation is significant at the 0.05 level (2 tailed), \*\* $p < 0.01$ : correlation is significant at the 0.01 level (2-tailed)

Table 3 and Figure 1 showed the mean ± SEM values of lipid profile of both pre and post menopausal groups. In our study observed, elevated levels of total cholesterol ( $207.00 \pm 7.86$ ), triglyceride ( $153.83 \pm 12.65$ ) LDL-c ( $130.04 \pm 7.65$ ), VLDL-c ( $30.42 \pm 2.52$ ) and Non HDL-c ( $164.13 \pm 7.09$ ) in post menopausal women, which were significantly ( $p < 0.001$ ) different with pre menopausal women.

Table 4 and Figure 2 showed mean ± SEM values of various atherogenic indices of pre & post menopausal subjects. Among these subjects post menopausal women have higher atherogenic indices compared to control subjects and found to be statistically significant ( $p < 0.001$ ,  $p < 0.01$ ). In our study, higher values of Castelli's risk index-I ( $4.90 \pm 0.03$ ;  $p < 0.001$ ) and Castelli's risk index-II ( $3.06 \pm 0.03$ ;  $p < 0.001$ ) were observed in post menopausal women. In case of TG/HDL-c ratio showed, significant ( $p < 0.001$ ) higher value was observed in post menopausal ( $3.77 \pm 0.36$ ) compared to pre menopausal women ( $2.72 \pm 0.87$ ). Both



**Figure 1:** Lipid profile in pre and post menopausal women

**Table 3: Showed the mean±SEM values of lipid profile of pre and post menopausal women**

Parameter	Pre menopausal	Post menopausal
TC	157.45±2.96	207.00±7.86***
TG	112.63±3.65	153.83±12.65***
LDL-c	89.05±1.85	130.04±7.65***
VLDL-c	22.09±0.77	30.42±2.52***
HDL-c	43.15±1.01	43.00±1.79 <sup>ns</sup>
Non- HDL-c	113.84±2.38	164.13±7.09***

$p > 0.05$ : Statistically non significant; \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ : Statistically significant

**Table 4: Showed the of mean±SEM values of atherogenic indices of pre and post menopausal women**

Parameter	Pre menopausal	Post menopausal
CRI-I	3.72±0.01	4.90±0.03***
CRI-II	2.11±0.16	3.06±0.03***
TG/HDL-c	2.72±0.12	3.77±0.36***
AIP	0.40±0.02	0.52±0.04***
AC	2.71±0.01	3.90±0.03***

<sup>ns</sup> $p > 0.05$ : Statistically non significant; \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ : Statistically significant

atherogenic index of plasma ( $0.52 \pm 0.04$ ) and atherogenic coefficient ( $3.90 \pm 0.03$ ) value are significantly ( $p < 0.001$ ) higher in post menopausal cases. The all atherogenic indices were found to be significantly elevated in post menopausal women compared to pre menopausal women. Table 5 showed Pearson's correlation between lipid profiles with atherogenic indices. Linear regression analysis also showed (Table 6) statistically significance with HDL-c vs. lipid profile (TC, TG, & LDL-c) and atherogenic indices.

## DISCUSSION

Earlier studies suggested that, menopausal status occurred at age 40- 49 years.<sup>21-23</sup> Based upon earlier reports, selection of premenopausal women at less than 40 years of age as control subjects and post menopausal at age of above 40 years as cases subjects. Due to age variation among the subjects, we were observed too much mean difference

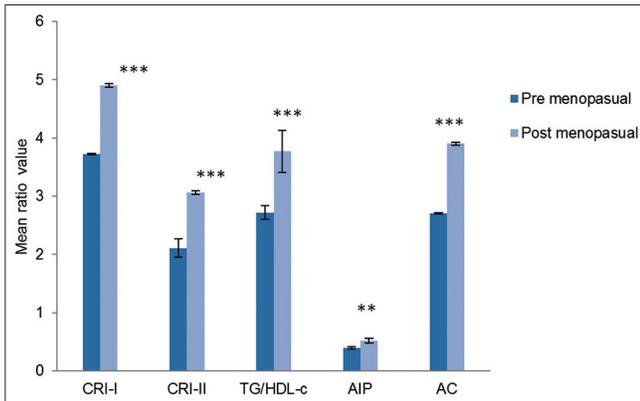


Figure 2: Atherogenic indices in pre and post menopausal women

**Table 5: Showed Pearson's correlation (r) between lipid profile and atherogenic indices in post menopausal cases**

Parameters	Post menopausal	
	r	p
TC vs. LDL-c	0.895	0.000**
TC vs. CRI-II	0.523	0.009**
TG vs. VLDL-c	1.000	0.002**
TG vs. CRI-I	0.477	0.018*
TG vs. TG/HDL-c	0.916	0.000**
TG vs. AIP	0.908	0.000**
TG vs. AC	0.437	0.033**
LDL-C vs. Non-HDL-c	0.886	0.000**
LDL-C vs. CRI-II	0.737	0.000**
HDL-c vs. TC	0.533	0.007**
HDL-c vs. TG	-0.234	0.270 <sup>ns</sup>
HDL-c vs. CRI-I	-0.538	0.007**
HDL-c vs. CRI-II	-0.264	0.213 <sup>ns</sup>
HDL-c vs. TG/HDL-c	-0.566	0.004**
HDL-c vs. AIP	-0.593	0.002**
HDL-c vs. AC	-0.538	0.007**

\*p<correlation is significant at the 0.05 level (2 tailed),\*\*p<correlation is significant at the 0.01 level (2-tailed)

between the pre and postmenopausal subjects. Some metabolic/physiological changes observed may have occurred as results of aging. To avoid such problems, selection of subjects by implementing certain inclusion and exclusion criteria mention above. The mean age group of our study, similar to earlier studies reported.

Previous reports suggested that, anthropometric measures of abdominal obesity appear to be more strongly associated with risk factors incident CVS disorders and death than the BMI.<sup>24-25</sup> Lawrence et al., suggested that 1cm increases in WC is associated with a 2% increases in risk of future CVD and 0.01 increases in WHR is associated with a 5% increases in risk.<sup>26</sup> World health organization (WHO) also states that abdominal obesity is defined as a waist-hip ratio above 0.90 for males and above 0.85 for females, or BMI above 30.0. The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) states that women with waist-hip ratios of more than 0.8, and men with more than 1.0, are at increased health risk because of their fat distribution.<sup>27</sup> Another research revealed that, female representations are most often in the 0.6-0.7 range for WHR, suggesting a preference towards lower WHR.<sup>28</sup> According to the National cholesterol education programme (NCEP) waist circumference cut of values is >88 cm.

In our study observed; higher BMI values are observed in post menopausal cases. BMI has been widely used as an indicator of total adiposity; its limitations are clearly recognized by its dependence on race.<sup>29</sup> These results may be depends upon the irrespective of body weight, physical exercise and dietary habits of the individuals. The Body Mass Index (BMI) is commonly utilised to represent the degree of body fat, it however does not capture body fat distribution, which the waist circumference does. Earlier studies indicate that even with a "normal" BMI, those with an elevated waist circumference can have a two fold increase in cardiovascular disease risk.<sup>30</sup>

**Table 6: Showed Linear regression analysis of HDL-c vs. lipid profile and atherogenic in post menopausal cases**

Dependent variable	Predictor variables	p value
HDL-c	Total cholesterol	0.007**
	Triglyceride	0.270 <sup>ns</sup>
	LDL-c	0.033*
	VLDL-c	0.269 <sup>ns</sup>
	CRI-I	0.006**
	CRI-II	0.212 <sup>ns</sup>
	TG/HDL-c	0.004**
	AIP	0.002**
	AC	0.006**

p>0.05: Statistically non significant; \*p< is significant at the 0.05 level (2 tailed),\*\*p< is significant at the 0.01 level (2-tailed)

In our study, anthropometric parameters like waist circumference and hip circumference are significantly different in postmenopausal than the pre menopausal women but not observed with WHR. Very less differentiation was observed between the pre and post menopausal women. In general, Asian Indians have significantly greater total abdominal fat and visceral fat area.<sup>31</sup> Factors implicated include estrogen deficiency in menopause which was found to be associated with a change in fat distribution. More fat is deposited around the abdomen than at the thighs or hips as seen in women in the reproductive age which presents as greater increases in fat mass and waist hip ratios.<sup>32</sup> The increase in abdominal fat was determined to be distributed as increase in trunk fat, subcutaneous fat and visceral fat.<sup>33</sup> Several studies indicate that even with a 'normal' BMI, those with an elevated WC can have a two- to threefold increase in cardiovascular disease risk and premature death.<sup>30, 34-38</sup> Our results showed, values of BMI and anthropometric parameters are not significant when correlated with lipid profiles in post menopausal women. These results indicate BMI and an anthropometric parameters value may be depends upon individual's physical activity or their lifestyle.

As plasma lipids can be divided into the proatherogenic lipoproteins and antiatherogenic HDL-c. Assessment of the relative proportions of cholesterol in these two fractions can be valuable than the individual lipid measurements. One method is to compare levels of HDL-c and non-HDL cholesterol.<sup>20</sup> However, in both subjects observed no difference in value of plasma HDL-c levels, but significant higher levels of non- HDL-c observed in post menopausal women. Atherogenic indices are powerful indicator of the risk assessment of coronary artery diseases. The higher values, higher the risk of developing cardiovascular diseases and *vice versa*.<sup>39</sup> Atherogenic ratios like, Castelli's Risk Index-I (CRI-I), Castelli's Risk Index-II (CRI-II), Atherogenic Coefficient(AC)<sup>40-42</sup> TG/HDL-c ratio,<sup>43</sup> and Atherogenic Index of Plasma (AIP)<sup>44</sup> are calculated. Grady et al., suggested that, a lower atherogenic index in premenopausal women indicates a greater proportion of reduced risk of coronary heart disease.<sup>45</sup>

The average ratio of total cholesterol to HDL-c (CRI-I) of healthy individuals is about 3.5 or lower<sup>40,46</sup> (i.e., at least 30% of the plasma cholesterol is in the HDL-c fraction) and in case of LDL-c/HDL-c ratio (CRI-II) is 3 or lower.<sup>47,48</sup> The Canadian working group had chosen the TC/HDL-c ratio (CRI-I) secondary goal therapy considering it to be a more sensitive and specific index of cardiovascular than total cholesterol, particularly in individual with TG > 300mg/dl.<sup>49</sup> Another research study has shown the association of CRI-I with coronary plaques formation.<sup>50</sup> In PROCAM study it was observed, subjects

with LDL-c/HDL-c (CRI-II) >5 had six times higher rate of coronary events.<sup>51</sup> The above results and previous study results explained that, both CRI-I and CRI-II used to assessing the CVS risk.

The atherogenic link between high triglycerides and HDL-c is due to the higher plasma concentration of triglyceride-rich, very low-density lipoprotein that generates small, dense LDL-c during lipid exchange and lipolysis. These LDL-c particles accumulate in the circulation and form small, dense HDL-c particles, which undergo accelerated catabolism, thus closing the atherogenic circle.<sup>52,53</sup> Protasio et al., explained that ratio of triglycerides to HDL-c was found to be a powerful independent indicator of extensive coronary disease.<sup>43</sup> The ratio TG/HDL-c, initially proposed by Gaziano et al, is an atherogenic index that has proven to be a highly significant independent predictor of myocardial infarction, even stronger than TC/HDL-c and LDL-c/HDL-c.<sup>54</sup> Angela Bacelar et al., reported that TG/HDL-c ratio is possible to approximately determine the presence and extent of coronary artery disease (CAD) by non-invasive methods.<sup>55</sup>

Atherogenic Index of Plasma (AIP) shown an inverse relationship that exist between TG and HDL-c and that the ratio of TG to HDL-c is a strong predictor of infarction and it was used by some practitioners as significant predictor of atherosclerosis.<sup>54</sup> Some of the researchers suggested that, AIP is a highly sensitive marker of difference of lipoprotein in patients. AIP values of -0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high cardiovascular risk.<sup>56</sup> A significant (P<0.01) AIP of values were observed when compared to pre (0.40±0.02) and post (0.52±0.21) menopausal subjects.

Atherogenic Coefficient (AC) calculated as measure of cholesterol in LDL-c, VLDL-c lipoprotein fractions with respect to good cholesterol or HDL-c. It reflects atherogenic potential of the entire spectrum of lipoprotein fractions. Non HDL-c is the second target of therapy after LDL-c as per ATP III guidelines especially in individuals with hyper-triglyceridemia.<sup>20</sup>

In our study observed, there was no difference (Table 3) in levels of HDL-c in both pre and post menopausal subjects but higher levels of lipid profile observed in post menopausal cases.

Previous reports explained HDL-c levels are associated with age in women's, it levels increase progressively to the sixth decade and then decreases.<sup>57,58</sup> Therefore, age may influences HDL-c levels in women. In ARIC study<sup>57</sup>, and Framingham study,<sup>59</sup> observed no significant differences of HDL-c levels in both pre and post menopausal women.

In another study<sup>60</sup> HDL-c levels were higher in older post menopausal than the younger post menopausal women. The above reports suggest that, HDL-c level not only depends upon the menopausal status. Chee jeong et al., also explained menopausal itself is not associated with reduction of HDL-c, lower levels of HDL-c in post menopausal women may depend upon the weight gain and other associated metabolic disorders.<sup>62</sup> In our study, HDL-c levels are significantly negatively correlated with atherogenic indices. These results may be due to higher levels of lipid profiles in post menopausal cases and on the other hand our results were in corroboration with previous studies indicating risk of CVS disorders.<sup>61</sup> So, these results support the earlier studies, HDL-c is an important anti-atherogenic marker for CVS disorders.

## CONCLUSION

The comparison between pre and post menopausal women showed significant higher values of BMI, waist circumference & hip circumferences. In case of lipid profiles, elevated levels of TC, TG, LDL-c, VLDL-c and Non HDL-c were observed in post menopausal women. In our study observed, BMI was not correlated with lipid profiles and atherogenic indices in post menopausal women. We suggested that BMI used as an indicator of total adiposity or fat distribution and it was strengthened by correlation with anthropometric measures. Significant higher atherogenic indices were observed in case subjects, however; these atherogenic indices are negatively correlated with HDL-c. LDL-c was positively correlated with atherogenic indices like CRI-II in post menopausal women. Elevated levels of lipid profiles along with raised atherogenic indices could indicate the cardiovascular risk in post menopausal women. The above observations suggest that, lipid ratios could be used for identifying individuals at higher risk of cardiovascular disease in clinical practices especially, when the absolute values of lipid profile seem normal or higher. Further investigation is needed to know the influence of genetic polymorphism of enzymes which influences lipid metabolism & regulation and role in development of CVS disorders.

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**Authors Contribution:**

**PMR**- Designed the study, performed the laboratory tests, analysed the data and drafted the manuscript. **GSG** - Reviewed the manuscript. **RBP**- Designed the study & selection of subjects and reviewed the manuscript.

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