CORONARY ARTERY DISEASE (CAD) RISK FACTORS AND CARDIO-RESPIRATORY FITNESS IN PRE AND POST-MENOPAUSAL WOMEN

Parimal Dua, Supriya Kumar Misra, Amit Karmakar, Kunal Dutta, Chandradipa Ghosh*
Department of Human Physiology with Community Health,
Vidyasagar University, Medinipore,West Bengal

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ABSTRACT

Coronary artery disease (CAD) is the leading cause of mortality and morbidity worldwide including India. During reproductive life women are at lower risk for CAD than men but this difference tends to disappear after menopause. It is well established that hypertension, blood lipids and physical inactivity are the primary risk factors and obesity, diabetes, stress and age are the secondary risk factors for CAD. In present study 183 sedentary female subjects who were Bengali by race were selected by standard self-reported questionnaire method. The selected subjects were grouped into pre-menopausal and post-menopausal categories according to the stages of reproductive life they were belonging to. Studies of obesity parameters such as BMI and body fat% demonstrated that Grade-I obesity was higher in pre-menopausal women whereas grade-II and grade-III obesity were predominant in post-menopausal women. Significantly higher percentage of post-menopausal women were found with WHR>0.85, considered to be significant risk factor of CAD in terms of central obesity. The post-menopausal women showed significantly higher levels of weight, systolic blood pressure, total cholesterol, LDL-C and triglycerides, and lower level of HDL-C than their pre-menopausal counterpart. BMI, Diastolic blood pressure, PFI scores and VO_2 max of these women were recorded and found not be significantly different in these two categories.

Keywords: Coronary Artery Disease, Risk factors, Women, Obesity, Blood lipids, VO_2 max, Physical activity

No: of Tables: 1 **No:of Figures : 3** **No: of References: 101**

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in women especially in the post menopausal life. In this phase deficiency of estrogen happens to be the major underlying reason for increasing incidence of CAD in women (Colombel1 & Charbonnel, 1997; Gorodeski & Utian, 1994). Younger women usually remain at lower risk for CAD than men but after menopause the development of CAD risk is more rapid in women (Saltiki & Alevizaki, 2007) finally attaining the same rate as for men after age 70 (Heller, 1978; Gorodeski & Utian, 1994). It is well established that smoking, hypertension, hypercholesterolemia, obesity, diabetes mellitus and physical inactivity are the primary risk factors for CAD whereas stress, race, age and sex are the secondary risk factors (Duraiswamy et al., 2012; Sathish et al., 2002; Kalra et al., 2011; Sharma & Ganguly, 2005; Paterno, 2003). Reports from various sources reveal that the risk of coronary artery disease increases with increasing age, body weight, blood pressure and decreasing physical activity (Holm & Penckofer, 1992; Kuller & Meilahn, 1996; Brochier & Arwidson, 1998; Burnette, 1998). Age has an importance on development of CAD because it is associated with other risk factors like blood lipids, hypertension, obesity and diabetes. Accumulation of lipid on the inner linings of coronary arteries is called atherosclerosis. Atherosclerosis is often the underlying development for the consequences of coronary artery disease (CAD). It has been observed in post-menopausal women that reduced level of high density lipoprotein cholesterol (HDL-C) to be stronger CAD risk factor than elevated levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) (Jacobs et al., 1990; Bass et al., 1993; Kuhn & Rackley, 1993). The loss of protection from HDL is considered to be critical for the increased incidence of CAD in postmenopausal women. Several reports reveal that isolated low HDL-C level represents a significant risk of CAD even in the absence of elevated LDL cholesterol, total cholesterol or elevated triglyceride levels (Lip, 1995; Ernst & Resch, 1993; Folsom et al., 1997). Moreover an elevated plasma triglyceride is also found to be independent risk factor of CAD in post-menopausal women (Bass et al., 1993; Leaf, 1990). On the other hand, a strong relationship has been observed between hypertension and CAD in women (Johnson et al., 1986; Sigurdsson et al., 1984; Fiebach et al., 1989; Collins et al., 1990). In post-menopausal women an abrupt increase in the incidence of coronary artery disease is associated with increased prevalence of hypertension. Increased diastolic blood pressure has also been observed in the early menopause (Gustafsson, 1996). Physical activity is another parameter which reduces the incidence of coronary artery disease in women. It has also been found that physical activity has a significant association with VO_2 max and the other risk factors of CAD (Stanley et al., 2005). On the other hand, VO_2 max has significant associations with the risk factors of CAD (Stanley et al., 2005). In case of moderate levels of physical fitness and moderate levels of physical

activity, the risk of CAD gets significantly lowered (Berlin & Colditz, 1990; Atlanta, 1996; Lakka et al., 1994; Blair et al., 1989).

Obesity is a strong predictor for CAD in women (Willett et al., 1995). An individual is considered obese if body weight exceeds the desirable weight by twenty percent or more. Obesity is also associated with higher risk of hypertension. BMI is considered to be a simple parameter for the detection of the degree of obesity in an individual (Seibert et al., 2014; Espeland et al., 1997). BMI provides a more accurate measure of obesity or being overweight. A higher risk of coronary artery disease has been observed in mild- to moderately overweight women (BMI 25 to 28.9) (Manson et al., 1990; Ducimetiere et al., 1986). Further, women with a modestly increased BMI (>25 and <29 kg/m^2) have been found to have twice the risk of CAD than the leanest women (BMI, 21 kg/m^2) (Willett et al., 1995). Besides it has also been suggested that the distribution of body fat is a stronger predictor of CAD than the total amount of body fat (Ducimetiere et al., 1986; Larsson et al., 1984; Lapidus et al., 1984; Donahue et al., 1987). Excessive intra-abdominal fat is a CAD risk factor associated with obesity. A number of studies have suggested that abdominal adiposity measured by waist-hip ratio (WHR) is associated with increased risk of CAD in women. In a prospective study in Sweden it is conducted that WHR was found to be positively associated with the higher risk of myocardial infarction, stroke and death from all causes in women after adjusting of BMI (Larsson et al., 1984; Lapidus et al., 1984). WHR has been associated with hypertension, elevated triglycerides and reduced HDL-C (Baumgartner et al., 1987; Singh et al., 2011; Marsh, 2003).

The aim of our study is to evaluate the patterns of change in various physiological factors links with CAD in pre-menopausal and post-menopausal women.

MATERIALS AND METHODS

Subjects:

A total number of 183 women from different socio-economic family of Midnapore urban area of West Bengal participated in the present study. Among them 78 pre-menopausal women having the age from 35 to 50 and 105 post-menopausal women having the age from 45 to 60 participated during the period of January' 2013 to September' 2014. The subjects were selected through interviews by specific standard questionnaire method to know the following information such as family healthy history, status of menstrual cycle, marital status, intake of contraceptive pills, sleeping time, physical activity etc for inclusion into the study. Individuals those were suffering from chronic disease or any other disease and additionally those who are habituated with smoking or alcohol were also excluded from the study.

ANTHROPOMETRIC MEASUREMENT:

Measurement of Height

Body height was measured by using the calibrated anthropometric rod. The subject stood barefoot, and erect with heels together and arms hanging naturally by the sides. The subject looked straight ahead and the back of the head was in contact with the vertical wall. The

distance from the floor to the highest position of the head (vertex) was measured. The height was recorded to the nearest centimeter (Sodhi, 1991).

Measurement of Body weight:

Body weight was measured by using calibrated electronic portable weighing machine. The subjects wearing shorts and vest stood at the center of the weighing machine looking straight. The body weight was recorded to the nearest kilogram (Sodhi, 1991).

Calculation of body mass index (BMI):

Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m^2).

Measurement of Waist circumference:

Waist circumference (WC) was measured according to the recommendation of WHO (WHO, 2008b). This was measured at the level of waistline. Waist circumference was measured mid way between the lower rib margin and the iliac crest.

Measurement of Hip circumference:

Hip circumference (HC) was measured according to the recommendation of WHO (WHO, 2008b). It was measured horizontally at the level of gluteus that is maximum bulge of hip.

Measurement of Thigh circumference:

Thigh circumference (TC) was measured according to the standardization of Lohman et al., (1991). Thigh circumference was the horizontal girth at the level of gluteal fold on the right thigh.

Calculation of Body fat%:

Body fat% was calculated from skin fold thickness which was taken by skin fold calipers (Holtain Ltd., Crymych U K). Skinfold at the site of biceps, triceps, suprailiac, suprascapularae and mid thigh were considered to calculate Body fat%. For measurement of Body fat% at first body density is calculated by Jackson and Pullok formulae. Then Body fat% was calculated according to Siri equation (Siri, 1961).

MEASUREMENT OF BLOOD PRESSURE:

Blood pressure was recorded using standard auscultatory method in sitting position after a rest period of the subjects according to the recommendation of WHO (Heller et al., 1978). 'Calf' of the mercury sphygmomanometer was wrapped on the upper arm of the subjects and the mouthpiece of the stethoscope was placed over the brachial artery. Pressure was raised to the maximum and then gradually released. The systolic blood pressure (SBP) was measured at the appearance of first 'Korotkoff' sound and the diastolic blood pressure (DBP) was assured at the disappearance of the 'Korotkoff' sounds.

BIOCHEMICAL ANALYSIS:

Fasting blood samples (12 to 14 hours fasting) were collected from all selected individuals to determine the blood cholesterol level. About 5 ml of blood was collected from vein of all individuals by 5 ml syringe and then allowed to clot, centrifuge and the supernatant serum was kept frozen at -20^{0}c until analysis.

Total Cholesterol (TC) was analyzed using a test kit (DiaSys, USA). The analysis was carried out according to Richmond

(Richmond, 1973). HDL-C level was also estimated by Wybenga and Pilleggi's method (Wybenga et al., 1970). Triglycerides (TG) level was estimated by GPO method (Fossati & Prencipe, 1982). LDL-C level was calculated using the Friedewald formula (LDL-C=TC- HDL-C-TG/5) (Friedewald et al., 1972).

VO2 Measurement:

The equations reported by Léger et al. were used to estimate the maximum oxygen consumption (VO_2 max, ml/kg/min) from the 20m shuttle run test score (Leger et al., 1988).

Physical Fitness Index (PFI) Measurement:

Physical fitness index was measured by using Harvard step test method (Brouha et al., 1943; Neisner & Laurie, 1969).

Statistical analysis

Mean and standard deviations of all selected variables were calculated for subjects in each age group. T- Values were also calculated to identify the existence significant difference of the mean values of different risk factors of CAD among the different age groups. Student two tail t-test was performed to identify the significance of the difference in the mean values of the selected variables in each pair of age groups.

RESULTS

The physical characteristics i.e. anthropometric parameters (like height, body mass, body fat%, WHR, WTR, HTR), biochemical parameters (like TC, HDL-C, LDL-C, TG) and Physiological parameters (like SBP, DBP, PFI, VO_2 max) of pre- and post-menopausal women are presented in Table 1. Table 1 reveals that in our study among total number of 183 subjects, 78 belonged to pre-menopausal group and 105 belonged to post-menopausal group. Significant differences were observed between body mass ($p<0.01$), body fat% ($p<0.01$), WHR ($p<0.01$), WTR ($p<0.05$) and SSB ($p<0.01$) of the pre-menopausal and post-menopausal groups of women (Table 1). Significant differences were also found between the biochemical parameters like TC ($p<0.01$), HDL-C ($p<0.01$), LDL-C ($p<0.01$), TG ($p<0.01$) of those groups of women (Table 1).

Percentage of pre- and post-menopausal women falling into different categories of obesity according to BMR, Body fat% and WHR are presented in Figure 1, 2 and 3 respectively. Figure 1 reveals that out of 78 pre-menopausal women 30 (38.46%) belonged to normal (<25 kg/m^2), 38 (48.72%) in grade-I (25-30 kg/m^2), 6 (7.7%) in grade-II (30-35 kg/m^2), and 4 (5.13%) in grade-III (35-40 kg/m^2) obesity. In case of post-menopausal women out of 105 women 18 (17.14%) belonged to normal, 33 (31.43%) in grade-I, 39 (37.14%) in grade-II and 15 (14.28%) in grade-III obesity.

The percentages of different grades of obesity according to body fat% in pre-menopausal and post-menopausal group are presented in Figure 2. Figure 2 reveals that out of 78 pre-menopausal women, 24 (30.77%) belonged to normal (18 to 24% body fat), 48 (61.54%) belonged to borderline obesity (25 to 30 % body fat) and 6 (7.69%) belonged to obesity (>30% body fat). Beside this, out of 105 post-menopausal women 8 (7.62%) belonged to normal, 24 (22.86%)

belonged to borderline obesity and 73 (69.52%) belonged to obesity.

Progression of two groups of subjects in the risk zone according to central adiposity is shown in Figure 3. Figure 3 reveals that out of 78 pre-menopausal women, 15 (19.23%) have WHR <0.85 and 63 (80.77%) have WHR >0.85 and in case of post-menopausal group, out of 105 women, 11 (10.48%) have WHR <0.85 and 94 (89.52%) have WHR >0.85. In case of WTR and HTR, there is a significant difference also observed between pre-menopausal group and post-menopausal group of women.

Table 1: Comparison of age, anthropometric parameters, blood lipids and blood pressure of pre and post-menopausal women

Variables	Pre-menopausal (n=78)	Post-menopausal (n=105)	Level of significance
Age (year)	43.6±4.09	49.6±3.72	**
Anthropometric obesity parameters			
Height (cm)	152.9±5.47	151.7±6.85	ns
Body Mass (kg)	56.67±7.10	62.50±8.36	**
BMI ($kg.m^{-2}$)	26.30±3.30	29.10±3.42	**
Body fat (%)	27.90±4.07	33.70±3.98	**
WHR	0.91±0.07	0.95±0.06	**
WTR	2.07±0.13	2.11±0.14	*
HTR	2.26±0.15	2.30±0.16	*
Blood lipids			
TC ($mg.dl^{-1}$)	151.92±27.20	171.31±24.26	**
HDL-C ($mg.dl^{-1}$)	40.7±6.78	31.1±4.95	**
LDL-C ($mg.dl^{-1}$)	95.57±24.47	125.6±17.20	**
TG ($mg.dl^{-1}$)	71.74±21.30	113.3±18.23	**
Physiological parameters			
SBP (mmHg)	128.5±20.35	139.3±21.63	**
DBP (mmHg)	77.2±14.74	79.7±8.46	ns
PFI	59.1±8.79	58.9±9.22	ns
VO_2 max ($ml.kg^{-1}.min^{-1}$)	42.8±3.78	42.1±3.54	ns

Values given are mean ± SD.

Significance (*p<0.05, **p<0.01), ns; not significance

Student two tail t-tests were performed between pre- and post-menopausal women including comparisons.

Figure 1: Obesity categories in pre- and post-menopausal women according to BMI.

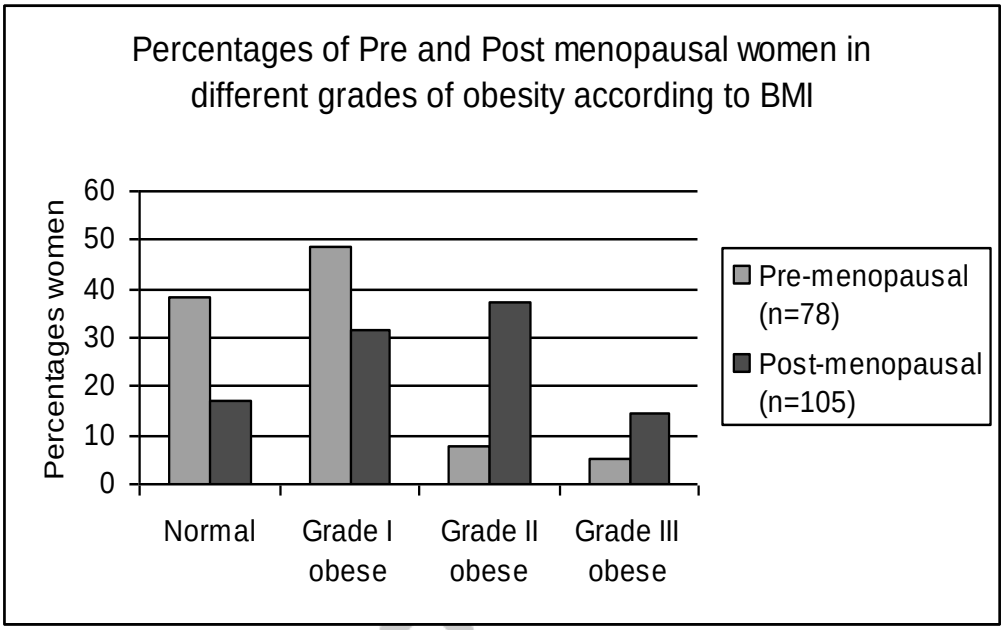


Figure 2: Percentage of pre- and post-menopausal women in different grades of obesity according to Body fat%.

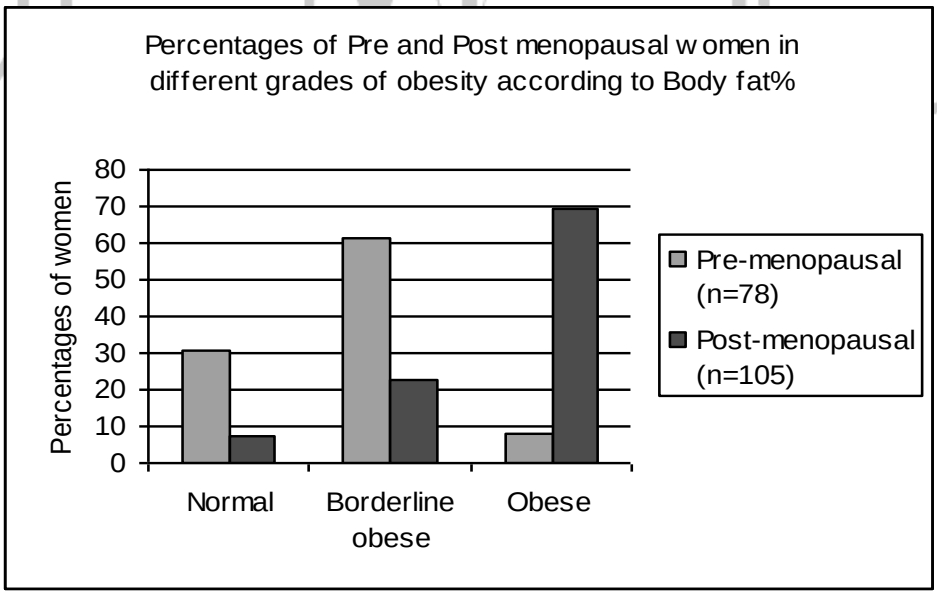
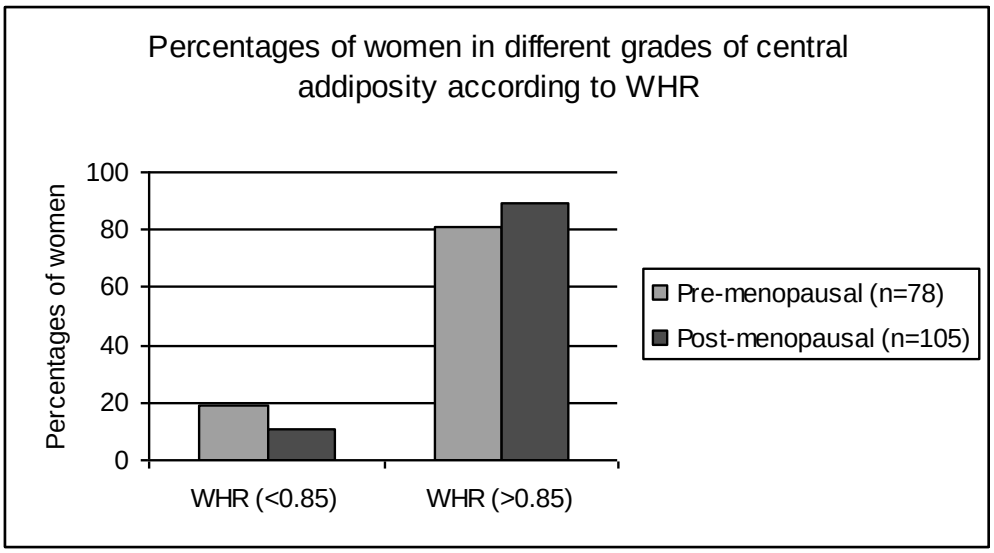


Figure 3: Percentage of pre- and post-menopausal women in different grades of central adiposity according to WHR



DISCUSSION

Menopause is generally defined as the cessation of menstruation in women and it is a transitional phase of life in which women enter into non-reproductive phase from reproductive phase (Staessen et al., 1998). Obesity seems to be an independent risk factor for CAD in women that correlated with BMI, body fat% and WHR (Manson et al., 1990; Rimm et al., 1995). Some studies have shown that body mass index (BMI) was the most widely used measure of obesity, whereas others (Fatima et al., 2014) have been proposed that percentage of body fat (BF%) is also the physiologic measure of obesity (Ranasinghe et al., 2013). In this study it was found that obesity was increased in women after menopause because BMI and percentage of body fat both were found significantly higher in post-menopausal women (Figure 1, 2). An excessive BMI through the associated excessive body fat contributes to the increased risk of CAD in post-menopausal women (Heitmann et al., 2000; Zhu et al., 2003). Waist circumference and waist-to-hip ratio (WHR) have been widely used as indicators for determining central fat obesity (Gillum et al., 1998; Warne et al., 1995; Rexrode et al., 1998). A study has suggested that Waist circumference is an independent risk factor of CAD (Rimm et al., 1995). On the other hand, a larger hip circumference relative to BMI and waist circumference seems a strong inverse predictor of CAD and mortality (Lissner et al., 2001; Heitmann et al., 2004; Bigaard et al., 2004; Snijder et al., 2004). It has been observed that abdominal adiposity, as measured by waist-hip ratio (WHR), is associated with increased risk of CAD in women (Lapidus et al., 1984; Prineas et al., 1993). WHR has been associated with hypertension, elevated triglycerides and reduced HDL-C ((Baumgartner et al., 1987; Singh et al., 2011; Marsh, 2003). It was shown that WHR (>0.85) linked with obesity were increased after menopause. Therefore, WHR and BMI both are strong

predictors of obesity as well as CAD in post-menopausal women. In our study it was observed that overweight pre-menopausal women showed a similar response. Another study has also reported similar trend in post-menopausal women (Folsom et al., 1993). In another prospective study, it has been found that the WHR measured in women to be a stronger predictor of CAD than BMI (Lapidus et al., 1984). It has been showed that women with higher waist-hip ratio or waist circumference had a markedly increased the risk of CAD even after adjustment of hypertension and elevated cholesterol levels (Rexrode et al., 1998). Smaller thigh circumference has also been associated with an increased risk of CAD and total death in women after controlling of waist circumference (Heitmann & Frederiksen, 2009). Thigh circumference has an inverse relation with the waist to-thigh ratio (WTR). Therefore, WHR or WTR are better predictor for CAD than waist circumference alone in women. Higher WHR or WTR was associated with the lower hip or thigh circumference. Therefore, it was observed that thigh circumference and hip circumference were negatively associated with risk of CAD after controlling waist circumference, BMI, and age in post-menopausal women. In a large prospective study of women, a significant association was observed between CAD and WHR or WTR. The higher the WHR or the WTR the greater is the association with the degree of upper body obesity (Ross et al., 1991). In contrast; hip and thigh circumference has been associated with lower body obesity (Lohman et al., 1992).

In the present study, we observed that the blood lipid levels except HDL-C significantly increased after menopause in women. A reverse trend was also observed in case of HDL-C. Similar reports were also obtained from National Cholesterol Education program (NCEP, 1993). A number of reports revealed that reduced HDL-C and higher triglycerides both are associated with the risk of CAD in post-menopausal women (Bass et al., 1993; Ernst, 1991) whereas LDL-C and TC have poor impact on CAD in this group of women (Jacobs et al., 1990; Bass et al., 1993). Reports also reveal that strong associations exist between triglycerides and other plasma lipid factors in post-menopausal women (Roeters van Lennep et al., 2002). Several studies have also demonstrated that triglyceride level has major importance in determining CAD risk in post-menopausal women (Danesh et al., 1999; Nieto et al., 1999; Murray et al., 1999). In agreement with the present study, several other publications have shown that a reduced level of HDL-C is the lead predictor for the risk of CAD in post-menopausal women than elevated levels of LDL-C if TG and TC are also elevated (Kuhn et al., 1993; Hak et al., 2000; Matthews et al., 1989; Poehlman et al., 1997; Lobo, 1991).

It was observed in the present study that Systolic Blood Pressure (SBP) increases significantly in post-menopausal women but there observed no significance difference between the Diastolic Blood Pressure (DBP) of the two groups of women. Similar findings have also been obtained from several reports (Poehlman et al., 1997; SHEP, 1991; Staessen et al., 1997). Several reports have demonstrated that isolated systolic hypertension

(SBP≥160 mmHg) is associated with an increased risk of CAD, stroke and all causes of mortality in women independent of other risk factors (Antikainen et al., 1998; Manson et al., 1991; Colandrea et al., 1970). However, the rise in prevalence of systolic hypertension is steeper for post-menopausal women (Kannel et al., 1980; Rutan et al., 1989; Stamler et al., 1989). This specific effect of menopause may be mediated via a reduction in arterial compliance (Staessen et al., 1990).

The relationship between maximal oxygen uptake (VO_2 max) and risk factors of CAD including age, SBP and DBP have been found in a study (Tobita et al., 1995). In the present study no significant difference of PFI and VO_2 max were observed between the groups of women (Table 1). A publication tried evaluated whether physical fitness is independent of any morphological parameters (Chatterjee & Mitra, 2001). They claimed that there is a positive correlation between PFI scores and maximum oxygen uptake capacity (VO_2 max). It was also found that the prevalence of CAD is lower in physically active women than women leading sedentary life. In another prospective study, it has been found that both occupational and leisure time physical activity are independently related to VO_2 max (Kishida et al., 1997). Another study reported that VO_2 max declines with age while intra abdominal adipose tissue and subcutaneous abdominal fat increases with age (Ryan & Nicklas, 1999). In fact, abdominal fat mass increases with age and this increase is greater in obese subjects (Bouchard et al., 1993). Interestingly, another study also observed that the ratio between abdominal fat and total fat is highly correlated with age (Svendsen et al., 1995).

It has been observed that reduction of weight is associated with an improvement in risk factors and favorable changes in triglycerides, HDL-C and LDL-C levels and blood pressure (Van Gaal et al., 1997; Wood et al., 1991). Physical exercise has a beneficial effect of weight reduction in the management of coronary risk factors in obese pre- and post-menopausal women (Greene & Fernandez, 2007). Weight loss can have tremendous effects. Post-menopausal women have higher rates of risk of CAD than do pre-menopausal women even though the same age. Other reports have been reached to the same results (Kannel, 1987; Gaziano, 1994). Therefore, post-menopausal women have high risk of death from CAD (Greene & Fernandez, 2007).

CONCLUSION

Based on the above information, after menopause women appear to be at an increased risk for the development of morbidity of CAD. The effect of CAD was significantly greater in post-menopausal women compared with pre-menopausal women. Although many factors can influence an individual's risk for CAD, menopause is unique to women. We found that menopause is an independent factor which contributes to the increased risk of CAD with other risk factors. It is also found that increased CAD risk leads to earlier menopause. After menopause, overweight women had higher levels of TC, LDL-C and TG, hypertension, high BMI and lower levels of HDL-C. There was a positive correlation

between CAD and hypertension, hypercholesterolemia, obesity and diabetes and a negative correlation with physical exercise. In fact, the levels of most risk factors were lower in case of physically active women. So, we prescribe exercise for both pre- and post-menopausal women. CAD risk factors are very crucial for women at the menopausal transition. It is prescribed for post-menopausal women, weight loss and lower triglycerides as a primary order of CAD risk management. The aim should be to raise HDL-C levels and lowered LDL-C levels. CAD is projected to become the number one single cause of mortality after 10 years.

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