Study Of Cardiovascular Risk Factors In Pre And Postmenopausal Women

Dr. Sushil Kumar*, Dr. Chinmay Shah**, Dr (Mrs.) Elvy R. Oommen***
*Associate Professor, CU Shah Medical College, Surendranagar, **Associate Professor, GMC Bhavnagar, ***Professor and Head, GMC, Baroda

Introduction: The term "menopause" literally means the last menstrual period. Menopause is a normal physiological event in women's life characterized by hormonal changes and in this way, is similar to life's other significant hormone related physiological event menarche (first menstruation).

According to WHO "menopause is the permanent cessation of menstruation resulting from loss of ovarian function. And the time following menopause is referred to as post menopause.

Menopause typically occurs in midlife, between the late 40s and early 50s (average-50 years).rather than the beginning of old age, as it is sometimes presented, menopause is the beginning of a new phase in a women's life that will bring different expectation, opportunities and experiences.

The experience of menopause varies widely from women to women and from culture to culture. All women however undergo the same basic hormonal changes during menopause. A woman's ovaries produce three types of hormone-estrogen, progesterone and androgen. These hormones play a vital role in menstruation, ovulation and pregnancy.

During perimenopause the ovaries gradually stop producing estrogen, is still produced by the adrenal glands, fat cells in small amounts. This process is usually slow and may take several years (unless the ovaries are surgically removed or affected by radiation or chemotherapy). The degree to which woman's body resounds to these normal hormonal changes varies. The loss of female hormone production can cause both acute and chronic consequents in hormone dependent tissues such as brain, bones, blood vessels and skin. So, after menopause; women are at increased risk for heart disease and osteoporosis.

The cardiovascular disease is the major cause of death of postmenopausal women in modern society. Cardiovascular disease is disorders of the heart and circulatory system. They include thickening of the arteries (atherosclerosis) that supply the heart, limbs, high blood pressure, angina and stroke.

According to American Heart Association report (2002),after menopause 70% of women eventually develop cardiovascular disease and 30% develop osteoporosis in USA.Postmenopausal women are particularly at risk and current evidence indicates that this is due to loss of protective effects of estrogen on the cardiovascular system.

In this study an attempt has been made to co-relate biochemical changes, blood coagulation, respiratory change and cardiovascular disease, in women after menopause.

The diagnosis of cardiovascular disease presents quite a challenge in women compared with men. Gender difference in the clinical presentation of cardiovascular disease and hormone related changes may contribute to the difficulties. Because the risk increases with age, there is a need for an increased awareness of the importance of cardiovascular disease as a major public health issue for older women. This study may also be useful for early diagnosis and primary prevention from cardiovascular disease in menopausal women.

Material and Method: For this study 61 healthy women were selected, in which 31 were premenopausal and 30 were postmenopausal. All premenopausal were 35 years old and above with regular menstrsual cycle and postmenopausal women had amenorrhea for a minimum period of one year due to natural menopause without any irregular bleeding up to age of 55 years.

In this study one of the parameters was lipid profile, so selection of subjects was very important. All subjects were of average middle socio –economic group. None of the subjects were obese, smokers, used alcohol, and had a history of cardio-pulmonary disease, hormonal disturbance, chronic disease or currently taking medication known to influence lipoprotein metabolism or cardiac status.

Before selection of subjects, aim of the study, plan of the investigation and its benefits were explained to motivate them to join the study. Only motivated women were included in this study. During motivation a short history was taken to know their health status. All quarries of the subjects were explained to their satisfaction. A short menstrual history was also taken to collect blood sample of premenopausal women during follicular phase (7 – 10 days) of menstrual cycle.

PLAN OF THE INVESTIGATION: All samples were collected during morning hours in between 8.30 A.M.to 10A.M. Some samples were collected at Biochemistry Department, Medical College, Vadodara & rest at a predetermined house of a subject in their society.

One day before the investigation, subjects were advised not to take anything by month after 8.30 P.M. onwards. Next day at sharp 8.30 A.M following investigation was started. Then a fixed performa was filled up to collect demographic data.

1. Measurement Of Pulse And Blood Pressure
2. Measurement Of Height And Weight
3. Measurement Of Peak Expiratory Flow Rate (Pefr).
4. Measurement Of Clotting Time
5. Platete Count
6. Assessment Of Lipid Profile

Result: The present work was carried out on 61 women, in which 31 were premenopausal and 30 were postmenopausal to find out the effect of menopause on cardiovascular risk factors. Premenopausal women were more than 35 years old with regular menstrual period and postmenopausal women had no menstrual period minimum from one year. All women were non- obese, non smoking and not having any chronic disease. Detail result is tabulated in Table 1 to Table 4

Premenopausal women acted as control. On the other hand postmenopausal acted as case. On comparing the parameters before and after menopause, it can be seen that value of systolic blood pressure increases significantly from mean value of 120.19 ± 10.53 mm Hg to 126.40 ± 8.24 mm Hg ($p=0.01$) and diastolic pressure also increases significantly from 82.88 ± 4.37 mm Hg to 86.27 ± 5.50 mm Hg ($p<0.01$). Body mass index increases but not significantly. Haemostatic changes occur after menopause; clotting time decreases just significantly ($p < 0.05$) but changes in platelets count is not significant.

After menopause, peak expiratory flow rate (PEFR) decreases significantly ($P < 0.01$). Major changes occur in lipid profile. In which TC, LDL and VLDL increase very significantly where as HDL decreases very significantly ($P < 0.001$).The change in serum TG increases significantly.

Table 1:- Physical characteristic of subjects.

	Numbers	Age (Years)	Height (cms)	Weight (Kg)
Premenopausal Women. (Control)	31	40.19 ± 3.46	156.19 ± 4.98	60.96 ±5.54.
Postmenopausal Women(Case)	30	51.23 ± 5.02	153.76 ± 5.70	59.61 ± 6.72.

Table 2: - Showing changes in Blood Pressure after menopause.

Parameters	Premenopausal	Postmenopausal	Changes	Significan
Systolic Blood Pressure (mmHg).	120.19 ± 10.53	126.40 ± 8.24	6.21 (+ 5.16 %)	p = 0.01.
Diastolic Blood Pressure. (mmHg)	82.88 ± 4.37	88.27 ± 5.50	5.39 (+ 6.50 %)	p < 0.01.
p>0.05 = Not significant; p<0.05 = Just significant; p<0.01= Significant; p<0.001 =Very significant.				

Table No. 3:- Showing changes in Body Mass Index, Platelets count, Clotting time and Peak Expiratory Flow Rate after menopause

Parameters	Premenopausal	Postmenopausal	Changes	Significance
Peak Expiratory Flow Rate(L / Sec.)	488.38 ± 80.04	437.66 ± 58.17	50.72 (10.38 %)	p<0.01.
Clotting Time (min.)	3.79 ± 0.94	3.32 ± 0.68	0.47 (-12.4 %)	p <0.05
Platelets count (Lakhs per cmm)	2.07 ± 0.55	2.01 ± 0.58	0.06 (-2.9 %)	p = 0.67.
Body Mass Index (Kilogram/meter^2)	24.87 ± 1.94	25.30 ± 2.61	0.43 (1.7 %)	p =0.466.
Note: - p>0.05 = Not significant; p<0.05 = Just significant; p<0.01= Significant; p<0.001 =Very significant.				

Table 4: - Showing changes in Lipid Profile after menopause.

Parameters(mg /dl).	Premenopausal	Postmenopausal	Changes after menopause	Significa
Triglyceride (TG)	140.10 ±31.28	168.03 ± 42.11	27.93 (19.93 %)	p < 0.01.
Total Cholesterol (TC)	139.90 ± 26.73	172.8 ± 23.45	32.90 (23.51 %)	p <0.001
High Density Lipoprotein (HDL)	34.61 ± 6.5	29.06 ± 4.44	- 5.55 (16.03 %)	p <0.001
Low Density Lipoprotein (LDL)	76.78 ± 24.14	109.41 ± 23.07	32.63 (42.49 %)	p <0.001
Very Low Density Lipoprotein (VLDL)	28.412 ± 6.30	34.31 ± 6.33	5.89 (20.75 %)	p <0.001
Note: - p>0.05 = Not significant; p<0.05 = Just significant; p<0.01= significant; p<0.001 =Very significant.				

Discussion: Cardiovascular disease remains the leading cause of death and disability in women, although onset in usually 10 years latter than in men. menopause, whether surgically induced or naturally occurring, carried an increased risk of CVD.The gradual decline in endogenous estrogen production that occurs with menopause is thought by many researchers to be the primary reason for the increases risk. Decreased estrogen levels have multiple detrimental effects on the vasculature, lipid profile and fibrinolytic and coagulation systems. The long term effects of these physiological changes may lead to accelerated atherosclerosis and an increase in clinically apparent cardiovascular disease.

In the present study blood pressure, peak expiratory flow rate, body mass index, platelets count, clotting time serum triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein and very low density lipoprotein were assessed in 31 premenopausal and 30 postmenopausal women. The postmenopausal data is compared with premenopausal data to know the effect of menopausal on these parameters.

Blood Pressure: In this study both systolic blood pressure and diastolic blood pressure changes increases after menopause systolic blood pressure changes from 120.19 ± 10.53 mm Hg to 126.40 ± 8.24 mm Hg (P < 0.05) and total changes is 5.16 %. This finding is supported by Staessen et al (1989), Karen et al (1989), Bonithon-Kopp et al (1990), Akahoshi et al (1996), Shelley et al (1998), Kim Sutton, Tyrrell et al (1998), Karen et al (2001) and Bulliyya G. (2001).

The diastolic blood pressure increases in this study from 82.88 ± 4.37(in premenopausal women) to 86.27 ± 5.50 (in postmenopausal women) and this change (6.50 %) is statistically significant (P<0.01). This finding is supported by Steassen et al (1989), Kim Sutton -Tyrrell et al (1998) and Do KA et al (2000).

The change in blood pressure after menopause is controversial. Some researchers have shown no change in blood pressure after menopause, Hjortland et al (1976), Shibata et al (1979),Davis et al (1994), Salomaa et al (1995), Akahoshi et al (1996) and Peters et al (1999). Natural menopause is also age related. Wen –Harn et al (1986), measures blood pressure in two groups (35-44) years and (45-54) years and find a positive relationship between age and blood pressure.

Estrogen increases the release of Nitric Oxide which is a vasodilator. On the other hand estrogen also stimulates the production of prostacycline within the arterial endothelial cells, which induces a vasodilatory effect and a consequent fall in blood pressure. Estrogen also decreases the production of thromboxane A_2 by platelets which is vasoconstrictor in nature. Cheang et al (1994). So after menopause in absence of estrogen vasodilator effect disappears and thus peripheral resistance increases and diastolic blood pressure increases.

Estrogen also stimulates the synthesis of renin in liver, which is the rate limiting step of the renin angiotensin aldosterone system. This system causes vasoconstriction and increases blood pressure (Meldrium et al; 1983).

A balance between there two opposing effects may occur in the vessels and may explain the contradictory reports of B.P after menopause in many results. Another mechanism was proposed by John Ciriello (1997) that estrogen may exert its beneficial effects on the circulation by altering the function to central neuronal circuits that are involved in the control of blood pressure. This possibility stems from the recent evidence that circulating steroid molecules exert potent effects on a variety of neuronal structure controlling non-reproductive functions. They investigated that the effects of estrogen on the function of neurons in circumventricular organs. Circumventricular organs are structures within the brain that lack a functional blood brain barrier. Therefore, substances within the circulation have access to neurons without crossing the blood brain barrier. The subfornical organ is a circumventricular organ through which angiotensin II exerts an effect on central neuronal circuits that control blood pressure. Activation of subfornical organ neurons leads to elevated blood pressure by causing the release of arginine vasopressin from the posterior pituitary and by activating the sympathetic nervous system. They discovered that in the female rat, many of the neurons within the subfornical organ that contain Angiotensin -I receptor, the receptor through which angiotensin-I exerts its effects on the neuronal

membrane, also contain the estrogen receptor in ovariectomized female rats have a higher resting discharge rate than neurons in estrogen treated, ovariectomized rats. Further more, the response of these subfornical organ neurons to circulating angiotensin-I in the ovariectomized female is greater than that in the estrogen treated animals. Finally increased levels of estrogen within the circulation attenuate the spontaneous discharge rate of subfornical organ neurons and inhibit the response of these neurons to angiotensin-I. Similar effects of estrogen were observed on the blood pressure responses to systemic administration of angiotensin -II. These observations suggest that estrogen may have a cardio protective effect in the female by inhibiting central neuronal system that are activated by systemic changes in angiotensin- II such as in high renin dependent renovascular hypertension. The lack of this estrogen in the postmenopausal women may account for the higher incidence of arterial hypertension or higher blood pressure.

Peak Expiratory Flow Rate: The respiratory parameter peak expiratory flow rate decrease after menopause by 10.38% from the premenopausal value 488.38 ± 80.04 L / min. to postmenopausal value 437.66 ± 58.17 L / min. This change of PEFR in postmenopausal women is significant ($p < 0.01$).

According to Sznajid et al (1989) in female after 32 years PEFR value decreases with age by 6 L / min. per year. The decrease in PEFR after menopause is due to two reasons. First it is due to aging and second is due decreased level of progesterone. Pulmonary changes due to aging are decrease in lung compliance with increased rigidity, lowered diaphragm and loss of internal alveolar surface area. Residual volume increases in aging due to less vigorously ascent of diaphragm and decreased elastic recoil. All combined are responsible for a slowly progressive fall in PEFR. (Columbia University report).

After menopause progesterone level decreases this alters the contractility of the smooth muscle and increases the hydration of the airways mucosa. Because progesterone is important in regulation of microvasular leakage in airways. This is also a reason for premenstrual asthma and decrease in PEFR. (Beynon and Garbett, (1988).

Progesterone has been shown to have widespread smooth muscle relaxant effect and therefore may have a bronchodilator action. (Premkumar and Walter; 1993). The above studies are well compared with the results of our studies.

Lipid Profile: Menopause is associated with potentially adverse changes in lipids and lipoprotein, independent of any effects of aging. (Stevenson et al;1993). In postmenopausal women the lipid and lipoprotein values changes in the direction of increased atherogenicity and towards mole value (e.g. LDL-C rises HDL-C falls). During the sixth decade of life women develop even higher LDL-C levels than men. These changes increase the incidence of CVD seen in postmenopausal women (Peter Oster; 1982).

Triglyceride: In the present study the plasma level of triglyceride in postmenopausal women increases from 140.09 ± 32.48 mg/dl of premenopausal control to 160.03 ± 42.11 mg/dl. Total change is 27.93 mg/dl or 19.93% and this change is statistically significant ($p<0.01$).

The results of several studies are summarized in this table.

Workers	Changes observed after menopause in plasma level of TG
Present study	Increases significantly (P<0.01).
Lindquist & Bengtsson (1980)	Increases significantly
Notelovitz et al (1983)	Not significant.
Baird et al (1985)	Increases 25 mg/dl (P<0.001).
Karen et al (1989)	Increases P≤0.05.
Siddle et al (1990)	Increases P<0.001.
Farish et al (1990)	Not significant
Jensen et al (1990)	Increases significantly (P<0.05).
Kalavathi et al (1991)	Not significant.
Razay et al (1992)	Increases by 27.54 mg/dl.
Stevenson et al (1993)	Increases significantly P<0.005
Davis et al (1994)	No change.
Wakatsuki & Sagara (1995)	Not significant
Salomaa et al (1995)	Not significant
Kim Sutton-Tyrrell et al (1998)	Increases significantly P=0.002
Peters et al (1999)	No change
Do KA et al (2000)	Increases by 27.54 mg/dl.
Torng et al (2000)	Increases P<0.001.
Li-Ching Lyu et al (2001)	Not significant.
Note - p>0.05 = Not significant; p<0.05 = Just significant; p<0.01= significant; p<0.001 =Very significant.	

The results of plasma TG level after menopause is contradictory but more agree on this point that after menopause plasma TG level increases except Davis et al (1994) and Peters et al (1999) who report no change. Kalkhoff et al (1982) proposed that progestin enlarge adipocyte cell size but do not affect cell number. This means by which depot TG storage is enhanced may reside in the stimulation of lipoprotein lipase, an enzyme that promotes hydrolysis of circulating plasma TG and fat cell uptake of free fatty acids derived from this process. Estrogen reduces adipocyte rise and adipose lipoprotein lipase activity, while promoting increased hepatic synthesis and release of TG rich VLDL. In the liver, progesterone partially reduces the estrogen effect on TG entry into the plasma component.

According to this mechanism in postmenopausal women both estrogen and progesterone plasma level decreases. So due to less estrogen adipocyte cell size increases and lipoprotein lipase activity increases. This causes release of TG from adipocyte. The decreased level of plasma progesterone in liver causes release of TG from liver. Hence plasma level of TG increases after menopause. The above studies are well compared with the results of our studies.

Total Cholesterol: In this study plasma total cholesterol level increases from (premenopausal value) 130.90 ± 26.73 mg/dl to (postmenopausal value) 172.80 ± 23.45 mg/dl. The increase in plasma total cholesterol level (23.51%) after menopause is significant, (P<0.001). The plasma levels of total cholesterol observed after menopause by other workers are:-

Workers	Changes observed after menopause in plasma level of TC
Present study	Increases significantly (P<0.001).
Hjortland et al (1976)	Increases.
Shibata et al (1979)	Increases.
Baird et al (1985)	Increases 25mg/dl (P<0.001) in white women but in black women no change observed.
Karen et al (1989)	Increases significantly (P<0.05).
Jensen et al (1990)	Increases significantly (P=0.001).
Kalavathi et al (1991)	Increases by 15.10 mg/dl.
Deminovic et al (1992)	Increases significantly in white women by 13 mg/dl (P<0.002) but in black women increases by 5.4 mg/dl.
Razay et al (1992)	Increases by 38.67mg/dl.
Lobo et al (1992)	Increases significantly (P<0.001).
Beresteijn et al (1993)	Increases by 42.53 mg/dl (19%).
Davis et al (1994)	Increases by 16.62 mg/dl.
Stevenson et al (1995)	Increases significantly (P<0.001).
Salomaa et al (1995)	Increases by 8.9%.
Akahoshi et al (1996)	Increases significantly.
Wakatsuki et al (1997)	Increases significantly (P<0.005).
Peters et al (1999)	Increases by 10%
Carr M C et al (2000)	Increases significantly (P<0.05).
Torng et al (2000)	Increases significantly (P<0.001).
Li-Ching et al (2001)	Increases significantly by16.19mg/dl (P<0.001).
Ariyo & Villalanca (2002)	Increases by 15 %.
Note - p>0.05 = Not significant; p<0.05 = Just significant; p<0.01= significant; p<0.001 =Very significant.	

All results show that after menopause plasma total cholesterol increases. There is only one exception when Hamman et al (1975) worked on Pima Indian. They observed that in Pima Indian women the plasma total cholesterol level changes from 182 ± 5 mg/dl in premenopausal women to 180 ± 5 mg/dl in postmenopausal women. This change was not significant. It has been suggested that this is due to the diet of Pima Indians, which is generally lower in cholesterol and environmental factors may play an additional role.

Besides genetic determinants dietary cholesterol, dietary fat, total caloric intake, alcohol consumption, cigarette smoking and physical activity are known to influence concentrations of lipid in women. Some of the strongest determinants of lipids in cholesterol and lipoprotein concentrations in women are sex hormones, including estrogen and progestin. (Bush et al;1988)

Middelberg et al (2002) reported that postmenopausal women showed larger genetic variance for most lipids, apart from apo B and lipoprotein (a). In premenopausal women TC, LDL & HDL all showed an influence of the shared environment (22 % to 34 %), which after menopause decreases in HDL and completely disappeared in TC and LDL. Generally there was no indication that different genes influence lipids before and after menopause.

Total Cholesterol level includes levels of HDL, LDL and VLDL.After menopause plasma level of LDL and VLDL increases, but plasma level of HDL decreases. The increase in plasma LDL and VLDL levels is more than decrease in HDL level. So the net effect is plasma level of total cholesterol increases after menopause.

High Density Lipoprotein: The present study shows that the plasma level of HDL-C decreases from 34.61 ± 6.5 mg/dl (premenopausal controls) to 29.06 ± 4.44 mg/dl (postmenopausal cases). The total change (16.03%) is statistically significant (P<0.001). Summary of previous studies is:-

(85)

Workers	Changes observed after menopause in plasma level of HDL
Present study	Decreases significantly (P<0.001).
Karen et al (1989)	Decreases significantly (P<0.05).
Jensen et al (1990)	Decreases significantly (P<0.05).
Siddle et al (1990)	Decreases significantly (P<0.001).
Kalavathi et al (1991)	Decreases significantly (P<0.01).
Stevenson et al (1993)	Decreases significantly (P<0.001).
Davis (1994)	No change.
Salomma et al (1995)	No change.
Wakatsuki (1995)	Decreases but not significantly
Lobo et al (1995)	Decreases significantly (P<0.001).
Peters et al (1999)	No change.
Do KA et al (2000)	Decreases by 1.93 mg/dl.
Kim C I et al (2000)	Decreases significantly (P<0.001).
Li-Ching Lyu et al (2001)	Decreases significantly (P<0.05), total change is 6.8 %.
Note - p>0.05 = Not significant; p<0.05 = Just significant; p<0.01= significant; p<0.001 =Very significant.	

This summary shows that after menopause plasma HDL-C level decreases except Davis et al (1994), Salomaa et al (1995) and Peters et al (1999). Do KA et al (2000) reported that the rate of decrease of plasma HDL- C in postmenopausal women was maximum around 9 months after menses ceased, with an instantaneous estimate of slope of 21.26 mg/dl per year.

Edmunds and Lip (2000) proposed that the estrogen induces inhibition of hepatic lipase which destroys HDL-C so after menopause this inhibition disappears and destroy HDL-C. Hence in postmenopausal women HDL-C level decreases.

Kalavathi et al (1991) proposed that estrogen exerts its action on hepatic lipase also known as Heparin Releasable Hepatic lipase (HRHL) to influence the metabolism of HDL. Hepatic lipase is located on the luminal surface of the hepatic endothelial cells. Hepatic lipase binds to HDL_2 in preference to those in HDL_3 or LDL. Hepatic lipase is a relatively specific HDL_2 phospholipase and that it may act in the hepatic uptake of cholesterol and in the conversion of HDL_2 to HDL_3. HDL_3 accepts cholesterol from tissues and is converted to HDL_2 which is then internalized in the liver. Estrogen decreases the hepatic lipase activity and thereby increases the plasma HDL_2 level. The precise mechanism by which estrogen regulate the activity of hepatic lipase remains unknown. Probably they repress the synthesis of the enzyme protein or they could bind to the enzyme and cause conformational changes which decrease the enzyme activity. This mechanism shows how after menopause, estrogen level decreases the HDL-C level. So the above observations are in agreement with our results.

Low Density Lipoprotein: Our study shows the increased level of plasma LDL-C level in postmenopausal cases (109.4 ±23.068 mg/dl) from premenopausal controls (78.78 ± 24.14 mg/dl). This increase of 32.63 mg/dl (42.49%) in LDL-C level is the maximum change observed than other lipoprotein and this is very significant change (P<0.001). The changes in plasma LDL-C level after menopause reported by other workers are:-

Workers	Changes Observed after menopause in LDL
Present study	Increases significantly (P<0.001).
Karen et al (1989)	Increases significantly (P<0.05).
Siddle et al (1990)	Increases significantly (P<0.001).
Jensen et al (1990)	Increases significantly (P<0.001).
Farish et al (1990)	Increases 19%,after 18 months of menopause.
Kalavathi et al (1991)	Increases significantly (P<0.05).
Lobo et al (1992)	Increases significantly (P<0.001).
Stevenson et al (1993)	Increases significantly (P<0.001).
Davis et al (1994)	Increases by 13.92 mg/dl.
Cheang et al (1994)	Increases by 40 %.
Salomaa et al (1995)	Increases by 15.46mg/dl or 11.4%
Wakatsuki et al (1997)	Increases significantly (P<0.01).
Peters et al (1999)	Increases by 14 %.
Do KA et al (2000)	Increases by 9.66mg/dl.
Torng et al (2000)	Increases significantly (P<0.001).
Carr M C et al (2000)	Increases significantly (P<0.05).
Li-Ching Lyu et al (2001)	Increases significantly by 20.4% (P<0.001).
Ariyo and Villablanca (2002)	Increases by 25%.
Note - p>0.05 = Not significant; p<0.05 = Just significant; p<0.01= significant; p<0.001 =Very significant.	

All reports show that after menopause LDL-C level increases and there is no controversy.Wakatsuki et al (1997) proposed that a decreases plasma concentration of estrogen after menopause enhances lipoprotein lipase activity which leads to an increase in the plasma concentration of LDL.

Arca et al (1994) suggested that hypercholesterolemia in postmenopausal women is due to impairment of the LDL receptor. Estrogen stimulates the synthesis of LDL receptors and lowers the plasma level of LDL-C and this effect may reduce the incidence of CVD in premenopausal women.

Ambraham & Villablanca (2002) reported that metabolic studies suggest that the reduction in LDL-C levels with hormone replacement therapy is result of enhanced hepatic lipoprotein uptake, accelerated conversion of hepatic cholesterol to bile acids, and increases expression of LDL-C receptors on hepatocytes. This result in augmented clearance of LDL-C particle from plasma. They also added that the oxidation and subsequent phagocytosis to LDL-C by macrophages result in formation of foam cells, which are key to the development of atherosclerosis.

Ikenoue et al (1999) observed that the diameter of LDL particles was significantly reduced in the naturally (25.29 ± 0.19 nm) and surgically (25.29 ± 0.2 nm) menopausal women compared with the premenopausal women (25.88 ± 0.22 nm) Carr M C et al (2000) and Wakatsuki et al (1997) reported that smaller the density of LDL particle higher the risk of CHD. The plasma level of TG is closely related to the rise of LDL particles in that the diameter of LDL particles is decreased in subjects with the hypertriglyceridemia. The above observations are in consonance with our study.

Very Low Density Lipoprotein: The plasma VLDL level in the present study increases in postmenopausal women (34.3 ± 6.33 mg/dl) from their premenopausal control (28.41 ± 6.30 mg/dl) this change (20.25%) is significant (P<0.001). The changes in plasma VLDL level observed in other studies are:-

Workers	Changes observed after menopause in VLDL.
Present study	Increases significantly ($p<0.001$).
Jensen et al (1990)	Increases significantly ($P<0.05$).
Siddle et al (1990)	Increases significantly ($P<0.05$).
Kalavathi et al (1991)	Increases but not significantly.
Razay et al (1992)	Increases by 5.49 mg/dl.
Wakatsuki et al (1997)	Increases but not significantly.
Kim Sutton-Tyrrell (1998)	Increases significantly ($P<0.005$).
Do KA et al (2000)	Increases by 6.02 mg/dl.
Li-Ching Lyu et al (2001)	Increases 11.4% but not significant.

The workers agree on one point that plasma VLDL increases after menopause. Wakatsuki et al (1982) proposed that VLDL a substrate for LDL is secreted by the liver. An enhance in VLDL secretion is due to an enhanced postheparin plasma lipoprotein lipase activity. In the present study clotting time decreases from 3.79 ± 0.93 (premenopausal value) to 3.32 ± 0.68 min (postmenopausal value). This change (12.40%) is statically significant (P=0.02). Hager et al (1989) and Poonam sethi et al (2001) reported that clotting time decreases with age. But no work has been done recently to establish a relationbetween clotting time and menopause.

After menopause the haemostatic balance shifted towards a latent hypercoagulable state (Notelovitz et al;1984 and Ford et al; 1996). In postmenopausal women plasma fibrinogen level and activity increases significantly. Meade et al (1983),Scarabin et al (1993), Lindoff et al (1993) Marcia L.(1995) Scarabin et al (1997) and Edmunds and Lip (2000),. The fibrinogen is an important determinant of blood viscosity and blood flow, which increases cardiovascular risk. Lip GY (1995). Clotting time depends upon both intrinsic and extrinsic clotting. So any change in both changes clotting time. After menopause thrombin time decreases. Notelvitz and Kitchens (1981) and Notelvitz et al (1984).

Stachowiak et al (2000) observed significantly shortened in APTT (which reflect intrinsic pathway) and TT (which reflect common pathway) in postmenopausal women. Postmenopausal women have significantly higher (but within normal range) and factor VII level and activity (and outside the normal range), Meade et al (1983), Scarabin et al (1993) Salomaa et al (1995), and. Scarabin et al (1997). These change may cause shortening of clotting time. But the result of clotting time is contradictory. Many researches have reported that there is no significant change in extrinsic and extrinsic system after menopause. (Notelvitz and Kitchens, 1981; Notelvitz et al, 1984 and Lindoff et al,1993).

The results of relation between clotting time and hormone replacement therapy are also contradictory. Brechm H (1964) and Amris et al (1967) have reported acceleration of clotting time. While, Abrams (1966), Beller et al (1967) and Cortes et al (1987) have reported no change in clotting time after hormone replacement therapy. Nilsson et al 1967 has observed that hormone replacement therapy shorten the clotting time. Platelets count in this study decreases from 2.07 ± 0.55 in premenopausal women to 2.01 ± 0.58 in postmenopausal women by 2.9 % but this change is not significant (P=0.67).

Notelvitz; and Kitchens (1981) also found that after menopause the change in platelet count is not significant. He observed that platelet count, in premenopausal women, 3 months before and after surgical menopause and after natural menopause does not change significantly. Carter et al (1991) reported that premenopausal platelet count was higher than postmenopausal platelet count.

Platelet count increases with hormone replacement therapy is reported by many researchers. Amris et al (1967), Ygge J.(1969), Poller (1978), Morris Noteloviz et al (1981), Eberhard and Mammen (1982), Ford et al (1994) and Mendoza et al (1997). Negrev N (1990) reported that in female rat estradiol hormone increases highly the number of thrombocytes. Estradiol increases highly the formation of specific humoral regulator of thrombocytopoiesis thrombocytopoietin.The stimulating effect of estriol and progesterone is most probably non specific .i.e. thrombocytopoietin independent. As the estriol activates proliferation of megakaryocytes greatly, but the progesterone stimulates the differentiation of these cells.

In the present study body mass increases in postmenopausal women (25.30 ± 2.61 Kg/m^2) than their premenopausal control (24.87 ± 1.94). But the total change (0.43 Kg/m^2) is not significant (P=0.46).Do KA (2000) found the overall increase between 3 years before and 3 years after menopause is 0.12 Kg/m^2. But Li – Ching et al (2001) found no significant change (P=0.79) in BMI in postmenopausal women. Similar finding was observed by Hjortland et al (1976), Shibata et al (1979), Siddle et al(1990), Davis et al (1994), Wakatuski and Sagara (1995), Akahoshi et al (1996) Peters et al (1999), and Torng et al (2002).

Wing et al (1991) observed that there were no significant difference in weight gain of women who remain premenopausal and those who had a natural menopause after 3 years. Blumel J E (2001) worked on 271 premenopausal Chilean women. After 5 years he reevaluated and found that women who experienced menopause and those who did not experience menopause had a similar weight increase. Likewise weight gain was similar in those who did or did not use hormone replacement therapy. While Akahoshi et al (1996) concluded that BMI is related to age at menopause and the greater the BMI, the later the age at menopause.

Razay et al (1992), Akahoshi et al (1996), and Kim Sutton-Tyrrell et al (1998) found that BMI increases after menopause.

Jousilahti et al (1996) proposed that body weight is determined by many factors, such as genetic, behavioral, cultural, socio- economic status, psychological, Physical activity and smoking. Some researchers suggested that decrease in resting metabolic rate, physical activity may increase the body weight after menopause.

Pochlman et al (1995) proposed that the loss of estrogen production after menopause is associated with an accelerated loss of lean mass in perimenopausal women. It is well known that the estrogen potentate growth hormone recreation, the loss of this potentiation could be a factor in the loss of an important trophic effect on skeletal muscle. Another possibility is that estrogen modulates the activity of cytokines leading to a more catabolic milieu. For example production of interleukin – 6 is inhibited by estradiol and loss of estrogen could lead to greater interleukin-6 activity, this change may have catabolic consequences.

Summary and Conclusion: The values for systolic blood pressure and diastolic blood pressure increases after menopause. In which systolic blood pressure increases significantly ($P<0.05$) and diastolic blood pressure changes very significantly ($P<0.01$). Peak expiratory flow rate changes very significantly ($P<0.01$). In lipid profile serum triglyceride, serum total cholesterol, serum low density lipoprotein and serum very low density lipoprotein increases and serum high density lipoprotein decreases. Except TG ($P<0.01$), all changes in lipid profile were very very significant ($P<0.001$). Clotting time decreases significantly after menopause ($P<0.05$). No significant changes were observed in platelets count and body mass index. On the basis of the present study it can be concluded that the hormonal changes after menopause brings changes in the haemostatic, blood pressure and lipid profile towards atherogenicity and increases the risk of cardiovascular disease.

The most potentially adverse changes have been found in lipid profile in postmenopausal women. Primary prevention and early detection can prevent the mortality and morbidity of women. Many researches have been done and many researches are going on in this field. More results are awaited. A recent development published in Washington post on 14th November 2002 by David Brown that elevated concentrations of C- reactive protein (CRP) appear to identify individuals at increases risk of cardiovascular disease even when their cholesterol levels are normal. Women with above average C- reactive protein and below average LDL levels had more heart attacks and strokes than women with below average C - reactive protein and above average LDL.

References:

[1] Abrams AA. (1966): Sequential estrogen and progestogen therapy. A clinical evaluation. Am J Obstet Gynecol; Dec 1; 96(7):1005-10.
[2] Akahoshi Masazumi, MD, PhD; Midori Soda, MD; Eiji Nakashima, MS; Katsutaro Shimaoka, MD; Shinji Seto, MD, PhD; Katsusuke Yano, MD, PhD (1996):Effects of Menopause on Trends of Serum Cholesterol, Blood Pressure, and Body Mass Index. Circulation; 94:61-66.
[3] Amris CJ, Starup J. (1967): The coagulation mechanism in oral contraception. Acta Obstet Gynecol Scand.; 46(1):78-91.
[4] Amy C. Bales, MD. (2000): In search of lipid balance in older women. New studies raise questions about what works best. Postgraduate Medicine;vol 108 ; no 7 ; December:57-72.
[5] Andersen LF, Gram J, Skouby SO, Jespersen J (1999): Effects of hormone replacement therapy on hemostatic cardiovascular risk factors. Am J Obstet Gynecol; Feb; 180(2 Pt 1):283-9.
[6] Annika Rosengren, Lars Wilhelmsen,Elsa Eriksson, Bo Risberg,berg, Hans Wedel (1990): Lipoprotein (a)and Coronary heart disease: a prospective case control study in a general population sample of Middle afed men. BMJ; 301:1248-51.
[7] Arca M, Vega G L,Grundy S M. (1994):Hypercholesterolemia in postmenopausal women. Metabolic defects and response to Low dose lovastatin. JAMA; Feb 9; 271(6):453-9.
[8] Ariyo Abraham A., MD, MPH; Villablanca Amparo C., MD (2002): Estrogens and lipids. Can HRT, designer estrogens, and phytoestrogens reduce cardiovascular risk markers after menopause? Postgraduate Medicine; Vol. 111; No 1; January: 23-30.
[9] Ashton WD, Nanchahal K, Wood DA. (2001): Body mass index and metabolic risk factors for coronary heart disease in women. Eur Heart J; 22: 46-55.
[10] Ashton WD, Nanchahal K, Wood DA. (2001): Body mass index and metabolic risk factors for coronary heart disease in women. Eur Heart J; Jan; 22(1):46-55.
[11] Baird DD, HA Tyroler, G Heiss, LE Chambless and CG Hames (1985): Menopausal change in serum cholesterol. Black/white differences in Evans County, Georgia American Journal of Epidemiology; Vol 122, Issue 6; 982-993.
[12] Barrett-Connor E, Bush TL (1991): Estrogen and coronary heart disease in women. JAMA; Apr; 10; 265(14):1861-7.
[13] Barrett-Connor Elizabeth, MD (1997): Sex Differences in Coronary Heart Disease Why Are Women So Superior? The 1995 Ancel Keys Lecture. Circulation; 95:252-264.
[14] Bass KM, Newschaffer CJ, Klag MJ, Bush TL (1993): Plasma lipoprotein levels as predictors of cardiovascular death in women. Arch Intern Med; 153:2209-2216.
[15] Beller FK, Porges RF. (1967): Blood coagulation and fibrinolytic enzyme studies during cyclic and continuous application of progestational agents. Am J Obstet Gynecol; Feb 15;97(4):448-59.

[16] Beresteijn EC van, JC Korevaar, PC Huijbregts, EG Schouten, J Burema and FJ Kok (1993): Perimenopausal increase in serum cholesterol: a 10-year longitudinal study. American Journal of Epidemiology, Vol 137, Issue 4: 383-392.
[17] Beynon H.L.C, N.D. Garbett (1988): Severe Premenstrual Exacerbations of Asthma; Effect of Intramuscular Progesterone. Lancet; 1988; Aug, 13; 2(8607):370-2.
[18] Blumel JE, Castelo-Branco C, Rocangliolo ME, Bifa L, Tacla X, Mamani L. (2001): Changes in body mass index around menopause: a population study of Chilean woman. Menopause; Jul-Aug; 8(4):239-44.
[19] Bonithon-Kopp C, Scarabin PY, Darne B, Malmejac A, Guize L Int J (1990): Menopause-related changes in lipoproteins and some other cardiovascular risk factors.Epidemiol Mar;19(1):42-8.
[20] Bringer J.(1992): Norgestimate: a clinical overview of a new progestin. Am J Obstet Gynecol; Jun; 166(6 Pt 2):1969-77.
[21] Bulliyya G. (2001): Risk of coronary heart disease in women after menopause. J Indian Med Assoc, Sep; 99(9):478-80, 482.
[22] Bush TL, Barrett-Connor E, Cowan LD, Criqui MH, Wallace RB, Suchindran CM, Tyroler HA, Rifkind BM. (1987): Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. Circulation; 75:1102-1109.
[23] Bush TL, Fried LP, Barrett-Connor E. (1988): Cholesterol, lipoproteins, and coronary heart disease in women. Clin Chem, 34(8B):B60-70
[24] Campos H, McNamara JR, Wilson PW, Ordovas JM, Schaefer EJ (1988): Differences in low density lipoprotein subfractions and apolipoproteins in premenopausal and postmenopausal women. Clin Endocrinol Metab; Jul; 67(1):30-5.
[25] Carlson LA, Bottiger LE. (1972): Ischaemic heart-disease in relation to fasting values of plasma triglycerides and cholesterol. Stockholm prospective study. Lancet; Apr 22; 1(7756):865-8.
[26] Carr MC, Kim KH, Zambon A, Mitchell ES, Woods NF, Casazza CP, Purnell JQ, Hokanson JE, Brunzell JD, Schwartz RS. (2000): Changes in LDL density across the menopausal transition. J Investig Med, Jul; 48(4):245-50.
[27] Carter JM, Siebers RW, Wakem PJ, Waken PJ. (1991): Platelet indices: intra-individual variation in pre- and post-menopausal females. Med Lab Sci, Jul;48(3):242.
[28] Carter JM, Siebers RW, Wakem PJ, Waken PJ. (1991): Platelet indices: intra-individual variation in pre- and post-menopausal females. Med Lab Sci Jul;48(3):242. Waken PJ[corrected to Wakem PJ]
[29] Castelli WP, Doyle JT, Gordon T, Hames CG, Hjortland MC, Hulley SB, Kagan A, Zukel WJ. (1977): HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study.. Circulation; May;55(5):767-72.
[30] Chang CJ, Wu CH, Yao WJ, Yang YC, Wu JS, Lu FH. (2000): Relationships of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women. Int J Obes Relat Metab Disord: Dec; 24(12):1699-704.
[31] Cheang A, Sitruk-Ware R, Samsioe G. (1994):Transdermal oestradiol and cardiovascular risk factors. Review.Br J Obstet Gynaecol. Jul; 101(7):571-81.
[32] Collins Lynell C., MD, FCCP and Alan Peiris,MD.(1993): Bronchospasm secondary to replacement estrogen therapy. Chest; 104; 1300-02.Columbia University .www.hora.cpmc.columbia.edu/dept/dental