

A CORRELATIVE STUDY OF ESTROGEN AND LIPID PROFILE IN PRE-MENOPAUSAL AND POST-MENOPAUSAL WOMEN

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Abstract

Background and Objective: The effect of the hormonal changes associated with menopause on the serum lipid levels may play an important role in most cardiac related disorders associated with menopause. The aim of the present study was to investigate the correlation between the lipid profile and estrogen level in premenopausal and postmenopausal women.

Materials and Methods: The premenopausal females of 25 - 35 yrs in their follicular phase of menstrual cycle were selected and two groups of post menopausal women, <10 yrs of menopause and >10 yrs of menopause were selected. About 6ml of blood sample was drawn for the estimation of estrogen and 4ml of blood for the estimation of lipid profile. The data were expressed as Mean \pm SD. The correlation of estrogen level with lipid profile was done using correlation test and P value less than 0.05 was considered significant.

Results: HDL cholesterol was found to be significantly declined in postmenopausal ($p < 0.01$) as compared to premenopausal women ($p < 0.01$) with less than 10 years of menopause whereas there was no significant correlation in postmenopausal women ($p < 0.01$) with less than 10 years of menopause. The correlation of estrogen level with other parameters of lipid profile didn't exhibited any significant correlation ($p > 0.1$) in all the three groups.

Conclusion: Estrogen may be the protective factor that is causing lesser incidence of these diseases in premenopausal women.

Keywords: Premenopausal Women, Postmenopausal Women, Lipid Profile, Estrogen level.

1. Introduction:

Menopause is a physiological phenomenon wherein the permanent cessation of menstruation takes place. Menopause is primarily due to exhaustion of stocks of oocyte or primordial follicle in the ovary with a consequent fall in oestrogen and progesterone secretion causing the cessation of cyclical endometrial development and hence menstruation.

The post menopause was thought to be an oestrogen deficient state and it applies to the whole of a woman's, life after menopause. But in post menopause, the ovarian stroma continues to secrete androgen and a proportion of androgen from ovary and adrenal cortex is converted peripherally into oestrogen, so that not all postmenopausal women are oestrogen deficient and develop long term effects of menopause which include increased bone loss leading to osteoporosis and atherosclerosis. Several factors have been considered to predispose to atherosclerosis. After Rudolph Virchow stressed that lipid was an important constituent of atheromatous lesions¹, studies were done in this matter and it is now clear that elevated levels of certain types of lipoproteins substantially increase the risk of atherogenesis in individual patients.

Menopause may occur before complete exhaustion of oocyte in the ovary. The remaining oocyte becomes insensitive to stimulation. By climacterium we mean vegetative crises associated with woman's decline in fertility. Climacterium and menopause are usually two events that are usually coincident but are different in nature. While menopause is external or symptomatic phenomenon the climacterium is a fundamental and profound phenomenon affecting the entire body and of a more or less extended period in a woman's sexual life^{2,3}.

Menopause is an unavoidable change that every woman will experience, assuming she reaches middle age and beyond. It is helpful if women are able to learn what to expect and what options are available to assist the transition, if that becomes necessary. Menopause has a wide starting range, but can usually be expected in the age range of 42-58 years⁴. An early menopause can be related to cigarette smoking, higher body mass index, racial and ethnic factors, illnesses, chemotherapy, radiation and the surgical removal of the ovaries, with or without the removal of the uterus⁴.

Various studies suggest that gonadal hormones exert an important influence on circulating lipids and lipoproteins. Oliver MF in 1950 reported that

progesterone either had no effects or produced an opposite effect caused by administering oestrogen on plasma lipids and lipoproteins by interfering with binding sites of other steroid hormones including oestrogen⁵.

Of the female sex hormones Oestrogens have been hypothesized to protect against cardiovascular disease. So it is very important now to divert an increasing amount of attention to alleviate long term effects of oestrogen deficiency. Oestrogen replacement therapy remains one of the most significant factors in the prevention of ischemic heart disease in women⁶.

Numerous studies have suggested that the magnitude of risk reduction is in the order of 50 percent⁸⁻¹⁰. The benefits are best seen among current users of hormone replacement therapy and particularly those with existing risk factors of ischemic heart disease. It has been postulated that cardiovascular benefits of oestrogen are mediated through action on lipoprotein metabolism and direct effect on vessel wall. Hence the present study was conducted to correlate the level of oestrogen and lipid profile pre and postmenopausal women.

2. Materials and Methods:

In the present study, the Premenopausal females of 25 - 35 yrs in their follicular phase of menstrual cycle were selected and two groups of post menopausal women, <10 yrs of menopause and >10 yrs of menopause were selected. All subjects selected were non vegetarians and free from any endocrine disorder and are not taking any lipid lowering drugs. Vegetarian's subjects suffering from any endocrine disorder and taking any lipid lowering drugs were excluded. The subjects were advised to come after overnight fasting and blood samples were taken for estimation of lipid profile and serum estrogen.

Under all aseptic precautions 6ml of blood sample was drawn from antecubital vein and was collected in two clean dry bottles. 2ml blood sample was collected in one bottle for Estrogen estimation and 4ml plain blood sample was collected in other bottle for lipid profile.

Estimation of lipid profile was done using the kit provided by Auto span. HDL cholesterol and Total Cholesterol and triglyceride estimation was done commercially available kit. Serum estradiol level was estimated quantitatively by Enzyme immuno Assay.

Estimation of total cholesterol in serum by modified Roeschlau's method¹¹. Estimation of Triglycerides in Serum was done by the method of McGowan *et al*¹². Estimation of HDL

cholesterol in serum was done by Method by Burstein *et al*¹³.

Calculation of VLDL and LDL was by Friedewald formula¹⁴ were, VLDL cholesterol= Triglycerides / 5 and LDL cholesterol = Total cholesterol- (HDL cholesterol + TG/5). Serum Oestrogen Estimation was done by Pathozyne Estradiol (E2) kits are designed for the measurement of total estradiol in human serum or plasma.

2.1 Statistical Analysis: The data were expressed as Mean \pm Standard Deviation. Baseline parameters were compared using Student 't' test. Correlation of lipid profile with estrogen between case and controls was performed by the correlation test. P value less than 0.05 was considered significant.

3. Result:

In the present study, influence of Estrogen on circulating levels of Total Cholesterol, Triglycerides, HDL Cholesterol, VLDL Cholesterol, LDL Cholesterol, TC/HDL ratio and LDL/HDL ratio were studied.

The results were tabulated and the Mean and Standard Deviation (SD) of Age, Total Cholesterol, Triglyceride, Low Density Lipoprotein, Very Low Density Lipoprotein, High Density Lipoprotein, TC/HDL and LDL/HDL in premenopausal group of subjects, in postmenopausal group of subjects with less than 10 years of menopause and postmenopausal women with more than 10 years of menopause were given in Table-1 and 2. The correlation of all the parameters of lipid profile in all three groups of subjects with estrogen was given in table-3.

The correlation of estrogen level with HDL cholesterol was found to be significantly declined in postmenopausal ($p < 0.01$) as compared to premenopausal women ($p < 0.01$) with less than 10 years of menopause whereas there was no significant correlation in postmenopausal women ($p < 0.01$) with less than 10 years of menopause. The correlation of estrogen level with other parameters of lipid profile didn't exhibited any significant correlation ($p > 0.1$) in all the three groups.

4. Discussion:

It was well established that Atherosclerosis which predisposes to coronary artery disease cerebral thrombosis and other various illnesses is a metabolic disorder involving lipid and lipoprotein metabolism. The incidence of atherosclerosis and its complications increase

with increase in Total Cholesterol, and Low density Lipoprotein cholesterol where as the incidence decrease with increase of HDL cholesterol.

Premenopausal women are found to be protected against cardiovascular disease by their typically lower Low Density Lipoprotein levels and higher High Density lipoprotein levels compared with men of same age. The increased risk of coronary artery disease following menopause points to the relation between endocrine influences on lipid profile especially when other risk factors like blood pressure, blood sugar and body weight are normal. Of the two sex hormones in females progesterone either had no effect or produced an effect opposite to that of estrogen on lipid and lipoprotein metabolism. Estrogens have a major beneficial effect on cholesterol metabolism and appear substantially to reduce the risk of atherosclerosis and cardiovascular disease in postmenopausal women.

Coincident with loss of estrogen, female LDL level rise at the time of menopause to exceed those of men. It has been suggested that loss of estrogen at menopause causes this increase in LDL. Post menopausal estrogen replacement has been found to lower LDL. By contrast HDL levels decline only 5% at menopause. Hence it was said that endogenous estrogen protect against cardiovascular disease mainly by its effects on LDL rather than HDL. But exogenous estrogen protect by raising HDL and lowering LDL. The influence of estrogen on blood levels of various lipoprotein fractions is the topic of current interest.

Present study suggests that estrogen exert a negative correlation with serum total cholesterol. Niklila *et al* reported that ethenyl estradiol hastens turn over or catabolism of cholesterol¹⁵. Edward *et al* was of the opinion that estrogen appears to increase the biosynthesis of cholesterol but rate of excretion is increased to an even greater extent that it causes a lowering of serum cholesterol¹⁶. Hence the lower level of serum total cholesterol in premenopausal women can be due to the presence of estrogen in circulation.

Estrogen shows a positive correlation with high density lipoprotein cholesterol. The primary function of HDL is in cholesterol exchange and etherification. HDL initiates the transport of cholesterol from peripheral tissues back to liver for subsequent catabolism and excretion; this process was referred as reverse cholesterol transport¹⁷. LCAT esterifies cholesterol and the substrate required is HDL. The cholesterol esters are transferred to LDL and VLDL and then back

to liver. The cholesterol in HDL would be finally deposited in liver where lipoprotein would be degraded and esterified cholesterol would be hydrolysed¹⁸. The body cholesterol pool was negatively correlated with plasma HDL-C concentration¹⁹. HDL transport cholesterol from arterial wall thus retards progression of atherosclerosis. Also HDL inhibits the uptake of cholesterol rich LDL by arterial smooth muscle cells²⁰. Thus it was seen that high levels facilitates the process of reverse cholesterol transport and would foster the efficient removal of tissue cholesterol and its subsequent elimination from the body by liver. Low levels of HDL would lead to excessive accumulation of cholesterol in the tissues and may impair normal clearance of cholesterol from the arterial wall and so accelerate development of atherosclerosis. HDL also inhibits the uptake of cholesterol rich LDL by arterial smooth muscle cell²⁰ and thus reduces the peripheral uptake of LDL.

A separate HDL receptor has now been identified and cloned. It was found primarily in endocrine glands that make steroid hormones and in liver. It is shown that treatment with gonadal hormones or hormonal derivatives exert a marked effect on serum HDL cholesterol. Estrogen treatment is associated with increased levels of HDL cholesterol²¹⁻²⁵. The presence of estrogen receptors in liver suggests that the beneficial effect of estrogen on lipoprotein metabolism is due in part to direct hepatic action. Allaupovic *et al* suggested that estrogen would specifically increase the hepatic production of HDL cholesterol. Recent studies also suggest that estrogen can increase the number of HDL receptors in liver²⁶.

Low Density Lipoprotein levels show a negative correlation with estrogen in all groups of subjects studied various studies suggest that when the activity of LDL receptors (more properly referred to as ApoB - Apo E receptors) is high concentration of LDL is low in blood. So there is an inverse relationship between concentration of LDL cholesterol and LDL receptors in liver²⁷. LDL receptor interaction constitutes an important biochemical mechanism for the regulation of cholesterol content which is mainly contained in the LDL fraction. In the liver and most other tissues Low Density Lipoproteins are taken up by receptor mediated endocytosis. Estrogen increases the catabolism of circulating LDL probably by increasing the number of LDL receptors in liver.

The triglyceride and VLDL shows a negative correlation with oestrogen. The role of sex

hormones on triglyceride level is reported by many workers. Probably there is a more efficient removal mechanism. Menopause whether included surgically or spontaneous is accompanied by an increase in serum cholesterol, triglyceride, and changes in lipoprotein distribution and heightened risk of cardiovascular diseases. Elevation of plasma cholesterol has been observed in first post menopausal decade in the healthy women. It has been suggested that this rise may be explained on an endocrine basis and related to decrease in estrogenic activity. Recent studies suggest that estrogens may reduce cardiovascular disease by ways other than their beneficial changes in lipoprotein levels. Increasing evidence from both animal and human studies demonstrates that estrogen improves blood flow, prevent oxidation of LDL which would reduce its atherogenicity, alters prostaglandin metabolism which cause vasodilatation. These changes may be a direct effect of estrogen on vessel wall because estrogen receptors have been found in the muscularly of arteries in cardiovascular tissue. Mikkola *et al* also suggested that 17 estradiol may potentiate the antioxidant effect of Vitamin E²⁸. Although there are still contraindications to estrogens, many of them have become relative contra indications because benefits of estrogen therapy outweigh the risks involved.

Conclusion:

A reduction in Total Cholesterol, LDL, VLDL, TG, LDL/HDL, TC/HDL and increase of HDL cholesterol, are protective factors as far cardiovascular and cerebrovascular diseases are concerned. Thus estrogen may be the protective factor that is causing lesser incidence of these diseases in premenopausal women. After menopause, this lipid pattern is changed and cardio protective effect of estrogen is lost. The preponderance of evidence from epidemiologic studies indicates that estrogen replacement prevents the development of heart disease in menopausal women.

References:

1. Abraham G.E. Ovarian and adrenal contribution to peripheral androgen during menstrual cycle. *Clinical endocrinol Metabol* 1973; 36: 207-11.
2. Castelll W.B., Doyle J J. Godon T. HDL cholesterol and other lipids in coronary heart disease. *Circulation*, 1977; 55. 767-71.
3. Connor W.E, Stono D.B, Hodges R.E. The interrelated effects of dietary cholesterol and fat upon human serum lipid levels. *J.Clinical investigation*, 1964; 43:1691 - 1696.
4. Gordon T, Kanne E.B, Castelli W.P, Dawber T.R. Lipoprotein cardiovascular disease and death. The Framingham study; *Arch. Intern Med*, 1981; 141: 1128.
5. Oliver M.F & Boyd G.S. Influence of sex hormones on the circulating lipids and lipoprotein in coronary sclerosis. *Circulation*, 1961; 13, 82-85.
6. Silfen SL, Ciaccia AV, Bryant HU. Selective estrogen receptor modulators: tissue selectivity and differential uterine effects. *Climacteric*, 1999 2 (4) : 268 - 83.
7. Berliner J. Atherosclerosis: basic mechanism oxidatory inflammation and genetics. *Circulation*. 1995; 91: 24-28.
8. Sang.T, B.K, Armstrong, D.T and Whitfield, J.F. Steroid Biosynthesis by isolated human ovarian follicular cells in vitro. *J.Clin. Endocrinol. Metab*, 1980; 3: 1407 – 1411.
9. Hennekens CH. Increasing burden of cardiovascular disease current knowledge and effective direction for research on risk factors. *Circulation*, 1998; 97: 1095-98.
10. Evan R, Simpson. Estrogens. Reproductive Endocrinology, *Surgery & Technology*, Vol.1 1996; Page No.477-79.
11. Roeschlau W.A, Carter G.D. Estradiol Assays: Application and guidelines for the provision of clinical, biochemistry service. *Ann. Clin. Biochem*. 1988; 25: 466 – 483.
12. Mc Gowan P.C., Madden J.C., Brenner P.F., Wilson J.D and Siteri.P.K. Origin of oestrogen in normal men and women with testicular feminisation. *J. Clin. Endocrinol. Metabolism*. 1979; 49: 905-10.
13. Burstein M, Scholnic H.R, Mortin R. HDL cholesterol and other lipids in coronary heart disease. *Lipid Research*, 1970; 32: 12.
14. Friedewald W.T, Levy RI and Friederickson DS. Clinical chemistry. 1972; 18: 499- 502.
15. Nikhila EA. Effect of Phytoestrogen in post menopausal women. *Scand. J.Clinical Lab. Invest*. 1953; 66. 431-38.
16. Edward P. Morris, Janice Rymer. Update on risk-benefit ratio of hormone replacement therapy in menopause. *Recent advances in Obstetrics & Gynaecology*. Chap 12. Page No. 161 - 175.
17. Siteri P.K, Murain J.T, Hammon G.L, Nisker J.A, Raymoure E.J and Kuhn R.W. The

- serum transport of steroid hormones. *Rec. Prog Horm. Res.* 1988; 38: 457 – 460.
18. Sharma.V.N, Alpna Ram. The good, the bad, the ugly and the deadly Cholesterol. *South Asian Journal of Preventive Cardiology* 1998; 2: 52 - 58.
 19. Miller CJ. and Miller NE. High density lipoproteins and atherosclerosis. *Lancet*, 1975; 2: 103-8.
 20. Ono H, Sasaki Y, Bamba E. Cerebral thrombosis and microcirculation of the rat during estrous cycle after ovariectomy. *Clin. Exp. Pharmacol Physiol.* 2002; 29 (1 - 2): 73-78.
 21. Berliner. Atherosclerosis- basic mechanism of oxidative inflammation and genetics. *Circulation* 1995); 91: 248-50.
 22. Sujith Sreenivas, M.R.Chandran. Vit.E as a prophylaxis in coronary artery disease. *South Asian Journal of Preventive Cardiology.* 1999. Vol.3: 117 - 118.
 23. Vermulin A, Verdonok L. Sex hormone concentration in post menopausal women. *Clin. Endocrinology.* 1978; 9: 59-62.
 24. Vasudevan DM and Sreekumari.S. Cholesterol, Lipoprotein and cardiovascular disease. Text book of Biochemistry.2001; 3rd Edn. Page no. 144-48.
 25. Tapiero H, Ba GN, Tew KD. Estrogens and environmental estrogens. *Biomed Pharmacother.* 2002; 56(1): 36 – 44.
 26. Allaupovic P, Howard R.P & Furman R.H. Effect of estrogen and androgen and on and better lipoprotein combination in human subjects. *Circulation.*1963; 28: 64-67.
 27. Ganz.P. Vasomotor and vascular effects of hormone replacement therapy. *Am J Cardiol.* 2002; 90 (1A): 11-16.
 28. Mikkola TS, St. Clair RW. Estradiol reduces basal and cytokine induced monocyte adhesion to endothelial cells. *Circulation.* 2002; 41 (1): 313 -1 9.

Table – 1: The age, various lipid parameters and estrogen level in different groups.

	AGE	ESTROGEN	TC	HDL	VLDL	TG	LDL
Group-1	29±3.19	150.8±32.2	130.6±33.83	62.3±28.4	10.86±6.41	54.3±19.8	82.61±30.06
Group-2	56±3.11	9.24±2.87	196.4±56.52	36.3±12.3	14.3±7.35	71.60±16.75	148.88±54.89
Group-3	69±4.35	3.04±1.92	197.7±44.75	52.9±12.49	13.63±5.72	67.7±18.9	130.7±43.9

The values are expressed as Mean ± Standard Deviation.

Table – 2: The ratio of total cholesterol and LDL cholesterol in different groups.

	TC/HDL	LDL/HDL
Group-1	2.54 ± 0.876	1.5 ± 0.65
Group-2	5.74± 2.45	4.49± 2.14
Group-3	4.5 ± 2.7	3.19± 2.48

The values are expressed as Mean ± Standard Deviation.

Table-3: The correlation of various lipid parameters with estrogen in three different groups.

Parameters	Subject	Correlation Coefficient (r)	P value	Statistical Significance
Serum Estrogen and Serum TC	Premenopausal	-0.235	>0.1	NS
	Post menopausal<10 Yrs MP	-0.2245	>0.1	NS
	Post menopausal >10 Yrs MP	-0.1544	>0.1	NS
Serum Estrogen and Triglycerides	Premenopausal	-0.1548	>0.1	NS
	Post menopausal<10 Yrs MP	-0.2136	>0.1	NS
	Post menopausal >10 Yrs MP	-0.1276	>0.1	NS
Serum Estrogen and HDL	Premenopausal	0.4675	<0.02	HS
	Post menopausal<10 Yrs MP	0.4065	<0.01	HS
	Post menopausal >10 Yrs MP	-0.032	>0.1	NS
Serum Estrogen and LDL	Premenopausal	-0.0149	>0.1	NS
	Post menopausal<10 Yrs MP	-0.2157	>0.1	NS
	Post menopausal >10 Yrs MP	-0.057	>0.1	NS
Serum Estrogen and VLDL	Premenopausal	-0.1569	>0.1	NS
	Post menopausal<10 Yrs MP	-0.2133	>0.1	NS
	Post menopausal >10 Yrs MP	-0.1365	>0.1	NS

The values are expressed as Mean ± Standard Deviation.

Note: NS- Non Significant, HS - Highly Significant