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Endogenous Hyperestrogenemia in young Male survivors of Acute Myocardial Infarction

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Abstract:
Background*: The levels of sex hormones in coronary heart disease are of interest for several reasons. The disease is common in men and relatively rare in pre-menopausal women . The present study was designed to evaluate the possible alterations in the levels of sex hormone estradiol and lipid profile and also to elucidate the nterrelationship between them in young men in the acute phase of myocardial infarction.*
Materials and Methods*: A case control study conducted among 45 male survivors of Myocardial Infarction confirmed by electro cardio graphic changes and conclusive enzyme changes, and age matched normal control group from the healthy donors who visited the Blood bank. The quantitative data collected and the mean values were tested statistically by using Mann-Whitney U test. a non parametric test for variables and Pearson correlation test to see any association between variables*
Results*: There is an obvious increase in S. Estradiol and all levels of lipid profiles increases in patient group. The mean serum estradiol level in patients and controls were 71.862 ± 67.74 and 22.05± 3.38 pg/ml respectively The mean serum Estradiol concentrations was significantly increased in patients (p<0.001) Considering lipid profile, in the present study, statistically significant increase levels was observed only with total cholesterol and serum triglyceride levels in the patient group compared to controls.*
Conclusion: *The most reasonable source of the elevated serum estradiol levels observed in patients with coronary disease, seem to be a increased aromatization in adipose and muscle tissues converting androstenedione and testosterone to esterone and estradiol, respectively. It appears more likely that hyperestrogenemia preceedes acute MI in men*
Key Word*: Hyperestrogenemia Acute Myocardial infarction, Young male survivours of MI ,Lipids*

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I. Introduction

Myocardial infarction is the most important single cause of death in India. A difference in sex hormones has been suggested as a major predisposing factor for myocardial infarction in men. Sex based difference in incidence varies according to age. Men have a higher mortality from MI than women at all ages

Myocardial Infarction generally occurs with the abrupt decrease in coronary blood flow due to Coronary Artery Diseases (CAD) or thrombotic occlusion of a coronary artery[1]. Thrombotic occlusion occurs mostly in blood vessels previously narrowed by atherosclerosis. Increasing age, male sex, heredity or genetic predisposition are risk factors of CAD that cannot be changed. Individual response to stress, usage of too much of alcohol and type A individuality can be considered as contributing risk factors Hormone levels are possibly related to the risk of heart disease through lipoprotein levels, specifically high density lipoprotein cholesterol (HDL-C) which is a powerful protective agent Women have high levels of HDL-C than men[2].

Gender is an important determinant of CAD[3,4]. The most likely ultimate cause of this male – female difference is the sex hormone patterns. The established view is that endogenous estrogen act directly or indirectly to protect the arterial wall from atherogenic insults like LDL-C

In men estrogen is produced in significant quantities by peripheral tissue aromatization of androgenic precursors from the testis and adrenal glands[5,6,7.].Both hyperestrogenemia and hypotestosteronemia have been reported in association with MI in men by many researchers[8,9,10,11]. Hormone levels are possibly related to the risk of heart disease through lipoprotein levels, specifically high density lipoprotein cholesterol (HDL-C) which is a powerful protective agent Women are having high levels of HDL-C than men[12].

Aim of this study is to elucidate the blood levels of sex hormone estrogen and lipid profile and their interrelation in young male survivors of acute myocardial infraction in our population of rapid modernization associated with sedentary but stressful life-style, a case control study seem to be beneficial.

II. Material And Methods

The study protocol was approved by the Ethical Committee,Govt.Medical College, Thiruvananthapuram and written informed consent was obtained from all study participants. Cases and controls were interviewed. A standardized structural questionnaire was used to collect their history.

Sample size

Calculated using the formula $n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (\sigma 1^2 + \sigma 2^2)}{(\mu 1 - \mu 2)}$

Approximate sample size calculated is 45 case and 45 control= 90

Study setting:

The intensive coronary care unit and blood bank of Government Medical College hospital, Thiruvananthapuram, Kerala

Study Design:

A comparative case control study

Study population

45Young male survivors of myocardial infarction of age between 25 to 45 and age matched healthy individuals fulfilling inclusion criteria are selected as control group from blood bank of same institution

Study Duration: 1 year

Subjects & selection method

Study subjects, who were admitted consecutively in the intensive coronary care unit of Government Medical College hospital, Thiruvananthapuram constituted the study group. Diagnosis of a/c myocardial infarction was made on the basis of clinical history of ischemic pain, confirmed by electrocardiographic changes and conclusive enzyme changes.

Exclusion criteria

1. Cigerette smokers
2. Alcoholics
3. Hypertensive
4. Obese individuals, cardio-respiratory diseases, liver diseases, angina pectoris or previous incidence of MI.

Inclusion criteria

1.Young male survivors of acute myocardial infarction patients without previous history
2. Age group between 25-45 years

Study variables

1. Serum Estrogen
2. Serum. Cholesterol
3. Serum HDL-C
4. Serum LDL-C
5. Serum Triglyceride

All the variables are collected at the first day of admission of consecutive patients

Age matched healthy males who visited the Blood Bank of MCH for blood donations to their relatives were included in the control group.

- Informed consent obtained from the participants.
- Confidentiality was ensured and maintained throughout the study.
- No expenses were incurred from the patients.

III. Procedure Methodology

Venous blood samples were withdrawn on the first day of admission. Serum separated from cells by centrifugation and stored at -20° C until assay. Estimation of Serum estradiol done in Biochemistry Laboratory, Medical College Hospital, Thiruvananthapuram.

Samples for lipid parameters were collected in the fasting state. Lipid profile are quantified by enzymatic assay in Central Research Laboratory in Govt. Medical College Hospital Thiruvananthapuram

Storage of test kit and Instrumentation

Unopened test kits are stored at 2-8°c upon receipt and the microtiter plate kept in a sealed bag with desiccants to minimize exposure to damp air. Opened test kits can be used till the expiration date shown, provided it is stored as described above. A micro titer plate reader with a bandwidth of 10nm or less and an optical density range of O-3 O.D at 450nm wavelength is acceptable for use in absorbance measurement. Radioimmuno assay done according to the prescribed format and were read from Elisa reader

Cholesterol and TG quantification was determined by enzymatic assay. HDL C quantification done *by* precipitating reagent test. LDL-C was not separately estimated. It was calculated from the following formula
LDL Cholesterol = Total-cholesterol – (HDL Cholesterol +Triglycerides)

Statistical analysis

The study group selected included 45 male survivors of Myocardial Infarction, confirmed by electrocardio graphic changes and conclusive enzyme changes, from the intensive care unit of Medical College Hospital, Thiruvananthapuram. Age matched normal control group was selected from the healthy donors who visited the Blood bank of same institution. Serum estradiol and lipid profiles were estimated in both groups on first day of admission.

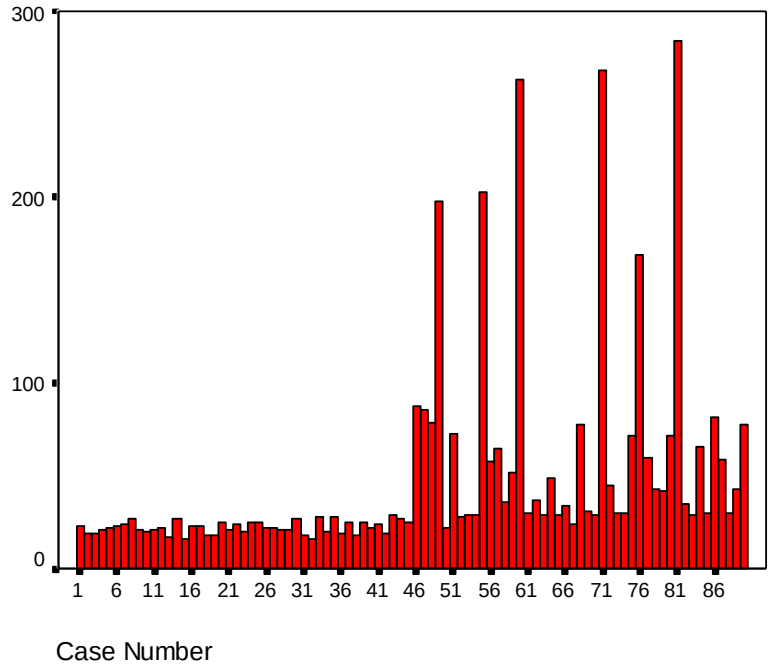
The study was to evaluate the relation if any, between the above parameters in acute phase of MI. The study compared serum concentrations of estrogens in patients and healthy subjects. Statistical analysis of the data was done Microsoft Excel was used for data entry. The statistical packages SPSS and Epi-Info were used for analysis. A 'p' value of less than 0.05 was considered statistically significant.

Statistical methodology

The quantitative data collected were entered and statistical tables were constructed statistical constants like mean, std. deviation, standard error were computed and compared. The mean values were tested statistically using Mann-Whitney U test. The relationship between two variables measured at interval/ratio level.

A. Comparison of various parameters between patient with MI and controls

1. Figure I Comparison of means of S. Estradiol of control and case



The mean serum estradiol level in patients and controls were 71.862 ± 67.74 and 22.05± 3.38 pg/ml respectively The mean serum Estradiol concentrations was significantly increased in patients ($p<0.001$) Significant (2-tailed)

2. Table I Comparison of means of S. Total Cholesterol

S. Total Cholesterol	No	Mean mg/dl	Std. Deviation	Minimum	Maximum
Case	45	211.19	46.78	140	340
Control	45	156.09	38.22	74	216

P≤.000 Significant (2- tailed)

3. Table II: comparison of means of S. HDL in case and controls

S. HDL	No	Mean	Std. Deviation	Minimum	Maximum
Case	45	36.09	7.84	13	54
Control	45	33.84	8.39	11	54

P≤.162 Not significant

4. Table III Comparison of means of LDL

S. LDL	No	Mean	Std. Deviation	Minimum	Maximum
Case	45	132.73	58.52	52	395
Control	45	110.56	39.13	51	181

P≤116 Not significant

5. Table IV comparison of means of Triglyceride

Triglyceride	No	Mean	Std. Deviation	Minimum	Maximum
Case	45	144.2	63.34	58	360
Control	45	80.76	23.33	30	139

P≤.000 Significant (2- tailed)

Correlations

Correlations were done to evaluate any relationship between the sex hormone and lipid status in the patient survived

B. Corelation of various parameters between patient with MI and controls

1. Table V Correlation of S. Estradiol with S. Total Cholesterol

		S. Total Cholesterol
S.Estradiol	Pearson Correlation	-.038
	Sig. (2- tailed)	.805
	N	45

A negative non-significant correlation

2. Table VI : Correlation of S. Estradiol with S. HDL-C

		S. HDL
S.Estradiol	Pearson Correlation	.053
	Sig. (2-tailed)	.732
	N	45

Positive non significant correlation.

. **3. Table VII Correlation of S. Estradiol with S. LDL**

		S. LDL
S.Estradiol	Pearson Correlation	.168
	Sig. (2- tailed)	.269
	N	45

S.Estradiol positively correlated with serum LDL and not significant.

4. Table VIII Correlation of S. Estradiol with S. Triglyceride

		S.Triglyceride
S.Estradiol	Pearson Correlation	.143
	Sig. (2- tailed)	.350
	N	45

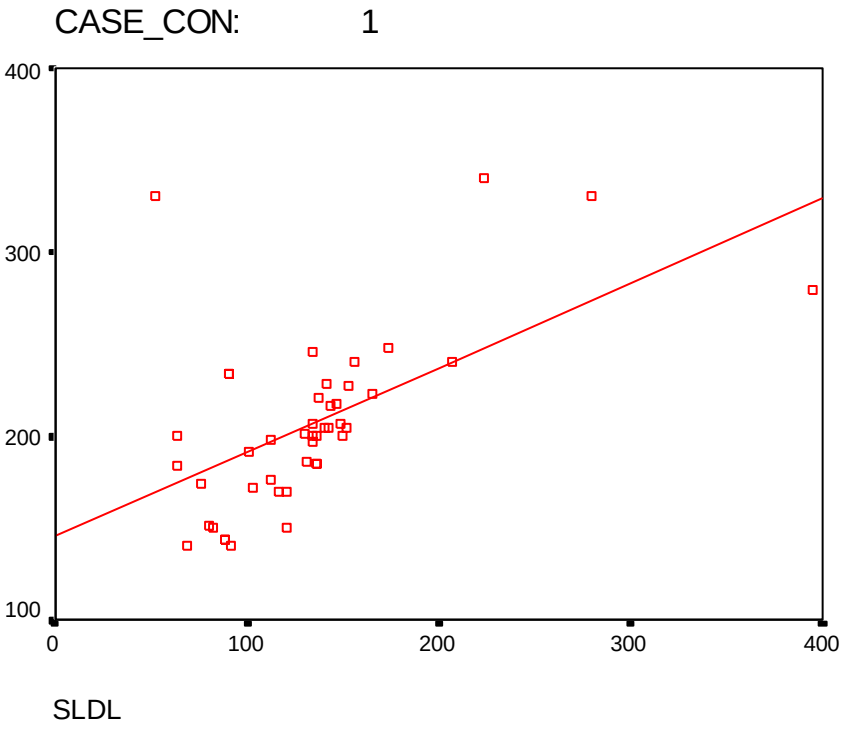
S.Estradiol positive non significant correlation with S.Triglyceride.

5. Table:IX Correlation of S. Total Cholesterol with S. HDL

		S HDL
S. Total Cholesterol	Pearson Correlation	-.076
	Sig. (2- tailed)	.619
	N	45

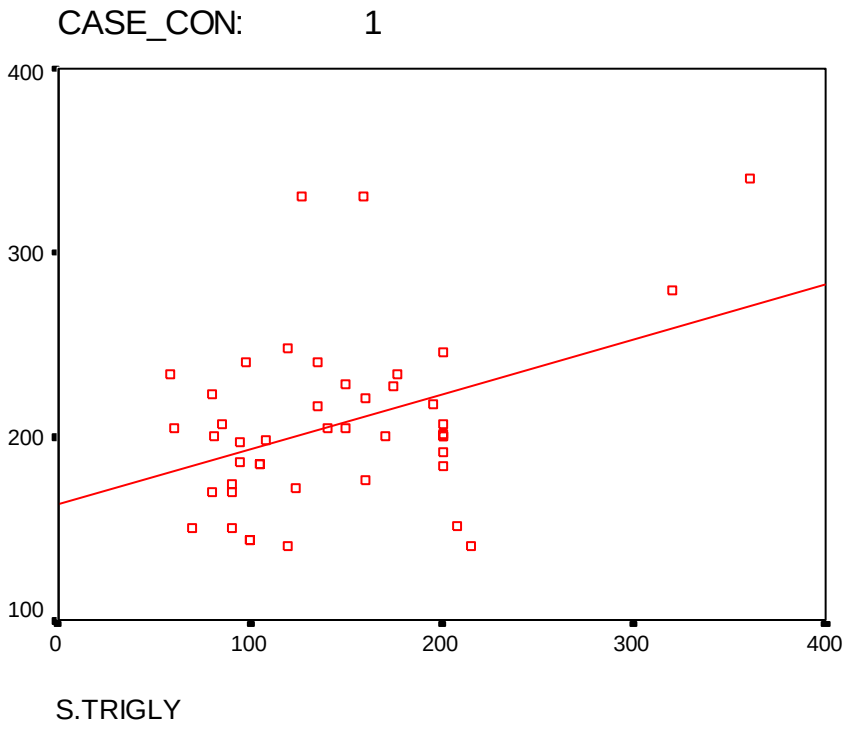
Negative and non significant correlation

6 Figure II. correlation of S. Total cholesterol with S.LDL



Positive significant correlation

7.Figure III: Correlation of S. Total Cholesterol with S. Triglyceride



Positive non-significant correlation

8. Table: X Correlation of S. HDL with S. LDL

		S. LDL
S. HDL	Pearson Correlation	-.070
	Sig. (2- tailed)	.649
	N	45

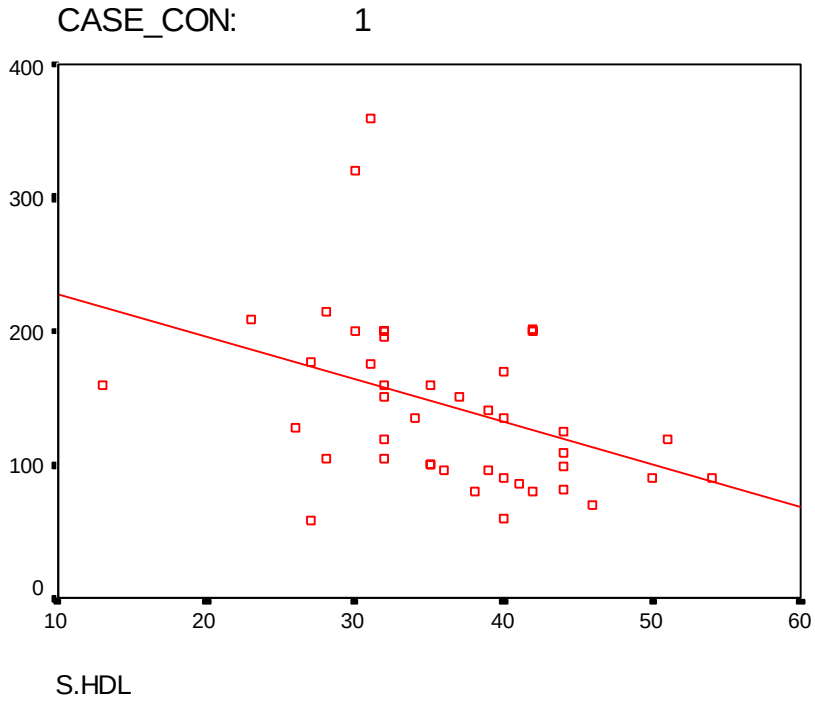
Negative non significant correlation

9. Table XI: Correlation of S. HDL with S. Triglyceride

		S.Triglyceride
S. HDL	Pearson Correlation	-.395
	Sig. (2- tailed)	.007**
	N	45

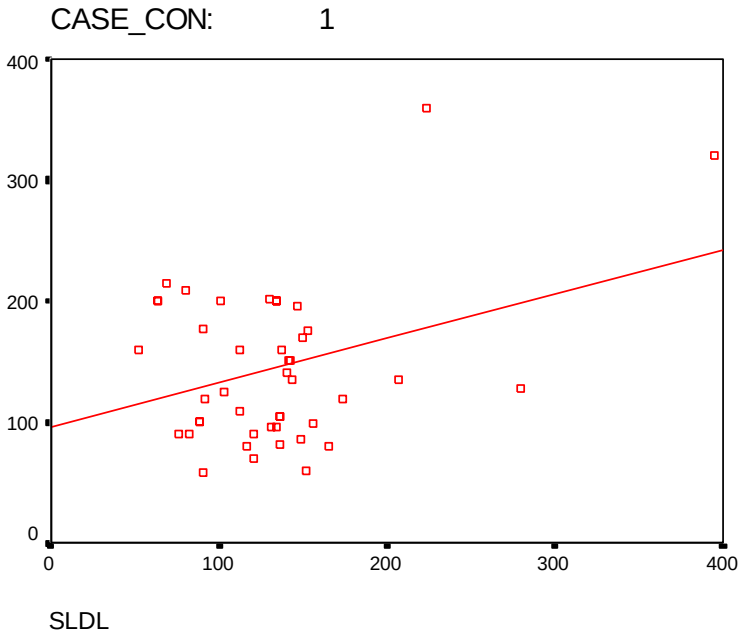
Negative significant correlation

Figure IV. Correlation of S. HDL with S. Triglyceride



Negative significant correlation

10. Figure V. Correlation of S. LDL with S. Triglyceride



Positive and significant correlation

IV. Discussion

The present study was designed to evaluate the possible alterations in the levels of sex hormones estradiol and lipid profile and also to elucidate the interrelationship between the steroid hormones and lipoproteins in young men in the acute phase of myocardial infarction.

Earlier studies have suggested that hyperestrogenemia may play a role in the development of MI in young men[4,9,10]. Since estrogen administration in men had been reported to lead to MI and venous thrombosis, it was hypothesized that hyperestrogenemia in men may be related to MI by underlying thrombosis[,11,12,13,]

Comparison of means of S. Estradiol in case and controls

The mean serum estradiol level in patients and controls were 71.862 ± 67.74 and 22.05± 3.38 pg/ml respectively The mean serum Estradiol concentrations was significantly increased in patients ($p<0.001$)

Myocardial infarction is usually the result of two processes, coronary artery disease and thrombosis[15]. Each process has its own etiological factors. The finding of abnormal levels of sex hormones in men with CAD has led to the hypothesis that alterations in the sex hormone levels may represent an important risk factor for MI. Most investigators found significantly elevated endogenous esterone and or estradiol levels,

It is of interest that hyperestrogenemia has also been implicated in coronary spasm[8] and ventricular arrhythmias[9]; factors that may accompany coronary thrombosis formation.

It has been reported that obesity, drug intake and cigarette smoking can cause hormonal imbalance in men with coronary artery disease[10.] As the above risk factors were strictly excluded in the present study group, the possible sources of the marked elevation of serum estradiol observed in our data should be considered significant. Either an increase in the production rate or decrease in the metabolic clearance rate of this hormones could produce the above results.

In healthy men, most of the estradiol are derived secondarily from the aromatization of androstenedione and testosterone respectively, in the peripheral tissues[6,14,]. Normal serum estradiol concentration in the adult male is around 20-30 pg/ml (70-110pmol/l) with a production rate of around 45 μg/day. The plasma estradiol is also bound to SHBG but with only half the affinity of testosterone.

Total plasma estradiol levels in healthy adult men do not vary significantly with age. Decrease in precursor levels is compensated by an increase of fat mass and tissue aromataze activity with age [6,14].The higher level of estradiol in younger patients with MI demonstrated in this study, might be related to alterations occurring in the peripheral conversion of testosterone to estrogen at an earlier age than usual.

This is most reasonable because in normal men it is the only known mechanism that increases both estrogens proportionately. The adrenal cortex secretes esterone but not estradiol, whereas the testicle secretes estradiol but relatively little esterone. So, only increased peripheral aromatization causes rise in both hormones proportionately.

The heart has been termed a 'target organ' for estradiol; Auto radiographic studies have demonstrated estrogen receptors in the coronary arteries[15]. Elevated levels of estradiol might influence the pathophysiology of myocardial infarction by precipitating myocardial ischemia and angina pectoris. The potential mechanism by which elevated estradiol levels could lead to myocardial ischemia includes enhanced adrenergic activity[1,9] and cardiac sympathetic stimulation, platelet aggregation [14,15,16,] , increased coronary artery smooth muscle tone leading to coronary vasospasm[17] and adverse effects on lipoprotein metabolism[18].

Estradiol has been reported to have effects that could (1)increase the synthesis of adrenergic neurotransmitters (2)inhibit the enzymatic degradation of adrenergic neurotransmitters and (3)potentiate the synthetic activity of adrenergic neurotransmitters[19,20,21]. These observations suggest that estrogens act as adrenergic stimulants and are significant in the context of the numerous report of the beneficial effect of adrenergic blocking agents in the treatment of angina and ventricular arrhythmias [6,22]

Addition of noradrenalin to in vitro sertoli cell culture resulting in increased aromatization of testosterone to estradio[23] further elevated noradrenaline levels in the patients with acute MI has been reported. Therefore, the observed changes were probably due to increase in the causes of aromatization of testosterone [26].

It is of interest that hyperestrogenemia has been implicated in coronary spasm and ventricular arrhythmias, that may accompany coronary thrombosis formation. Rather than mediating a protective action on the heart. Jaffe [8] has suggested that estrogen might induce an increase in coronary artery smooth muscle tone. When he compared the pretreatment exercise test results with after two weeks of estrogen treatment, greater ST segment abnormalities were noted [8].

It appears more likely that hyperestrogenemia preceedes MI in men for the following reasons: (1)The association of hyperestrogenemia with diabetes mellitus, hypertension, hypercholestrolemia,and or smoking which are major risk factors for MI in men who had not had an MI, (2)evidence for feminization preceding the MI and (3) induction of MI by the administration of estrogen[24].

Further evidence for a role of endogenously produced estrogen in normal male cardiovascular health comes from a condition in which a deficiency occurs in the enzyme responsible for the aromatization which converts a ring in the androgens to the corresponding phenolic ring characteristic of estrogens.[25] In a recent preliminary study demonstrated a potential role for endogenous sex hormones in vascular reactivity in elderly men taking the aromatase inhibitor testolactone for benign conditions for prolonged periods[25]

It is difficult to know whether the abnormal findings in survivors of Myocardial Infarction are a cause or a result of the acute event[26]. Whatever explanations, there is a remarkably clear separation of estradiol levels between normal individuals and young men surviving from acute Myocardial Infarction.

The question of whether or not marked estradiol elevations precede acute Myocardial Infarction cannot be answered from this study[4]. However the fact that elevation in estradiol level similar to those seen in men

immediately after acute Myocardial Infarction were observed in those with unstable angina and those in whom Myocardial Infarction was ru led out, suggests that estradiol elevation may precede the occurrence of the infarction.

Comparison of means of Lipids in case and controls

In the present study, the blood lipid levels show a statistically significant increase observed only with total cholesterol (Table I) and serum triglyceride levels (Table No. IV) (p=.000) in the patient group compared to controls. The HDL level also showed a moderate rise though not statistically significant.

Conceptually, it might be argued that circulating cholesterol originate from predominantly three sources - peripheral cholesterol synthesis, hepatic cholesterol synthesis and intestinal cholesterol absorption, but liver normally serves as the main regulatory organ that determines LDL - C blood levels[29]. Dietary cholesterol is absorbed in intestine as chylomicrons rich in triglyceride. The endothelial lipoprotein lipase remove triglyceride from them to form chylomicron remnants which are taken up by the liver[29].

This transport of cholesterol from peripheral arteries to the liver is thought to be important in the development of atherosclerosis and further development of ischemic heart disease[31].

Decreased cholesterol to the liver may increase hepatic LDL receptor activity and thus reduce circulating LDL-C blood levels, which in turn is associated with reduced risk of CHD[29].Hormone levels are possibly related to risk of heart disease through lipoprotein

In conclusion, high estradiol levels with unfavorable lipid profiles (rise in triglyceride, total cholesterol and LDL) observed in the cases in the present study might be the underlying factor that precipitated MI.

Correlation of sex hormones and Lipid profile

S. estrogen had negative correlation with total cholesterol (Table No .V) and positively to LDL (Table No VII.) and triglyceride (Table No VIII.). None of these correlation reached the level of statistical significance. Further, the correlation analysis gave the following results:

1. Total cholesterol positively correlated to LDL (Figure II) ($P \leq .000$) and Triglyceride (Fig.III) ($P = .132$)

2. Total cholesterol negatively correlated to HDL ($P \leq .619$).

3. HDL correlated negatively to triglyceride ($P \leq .007$), and LDL ($P \leq .649$).

4. Triglyceride level positively correlated to LDL ($P \leq .023$) whereas the correlation to HDL was negative ($P \leq .007$).

From the above correlation results, it is evident that an increase in blood total cholesterol causes a significant rise in LDL, the well known atherogenic factor. The associated higher TG level also seemed to produce similar effect. Further, the observed negative correlation of HDL to TG, Total Cholesterol and LDL can lead to high LDL levels. Total Serum Cholesterol, which is a powerful predictor of CAD in young men and women, has been shown to have diminishing important as age advances.

Men of all ages are at risk than similarly aged women. Although this disparity is widely thought to originate in greater level of endogenous estrogen in women, direct evidence supporting this hypothesis is lacking[17,32]. The possibility that endogenous androgens have adverse effects on cardiovascular risk in men has received the attention, and the existing evidence conflicts[27,28].. Morbidity and mortality data indirectly support the adverse effects of androgens.

Additionally, the increase in HDL cholesterol may be primarily attributed to an increase in the appropriate concentration compared with an increase in the cholesterol content in each HDL particle. Furthermore, the increase in HDL cholesterol might be limited to a specific subtraction of HDL [2]

Asymptomatic men with coronary artery disease have a lower HDL cholesterol level and higher total cholesterol level and cholesterol/HDL cholesterol ratio than those without the disease. The relation of the ratio to the presence of arteriosclerosis appears to be strong regardless of age. This ratio is a superior predictor of coronary artery disease when compared with the level of either total cholesterol or HDL cholesterol alone. Another study results also indicate a possible role of estradiol in promoting the development of atherogenic lipid milieu in men with CAD [28,30].

V. Conclusions

In conclusion, the present study shows that attack of acute Myocardial Infarction in men can alter the sex hormone levels. Whether hormonal changes show enhanced aromatization of testosterone to estradiol or were due to some other unknown mechanisms, requires further study.

a. Myocardial Infarction is associated with hyperestrogenemia and Lipid profile which is altered in myocardial Infarction, though the exact mechanism is unclear.

b. This study strongly suggests routine estimation of estrogen and lipid levels in the younger age group men with family history of MI at younger age group helps in the early detection of risk for MI..

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