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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.

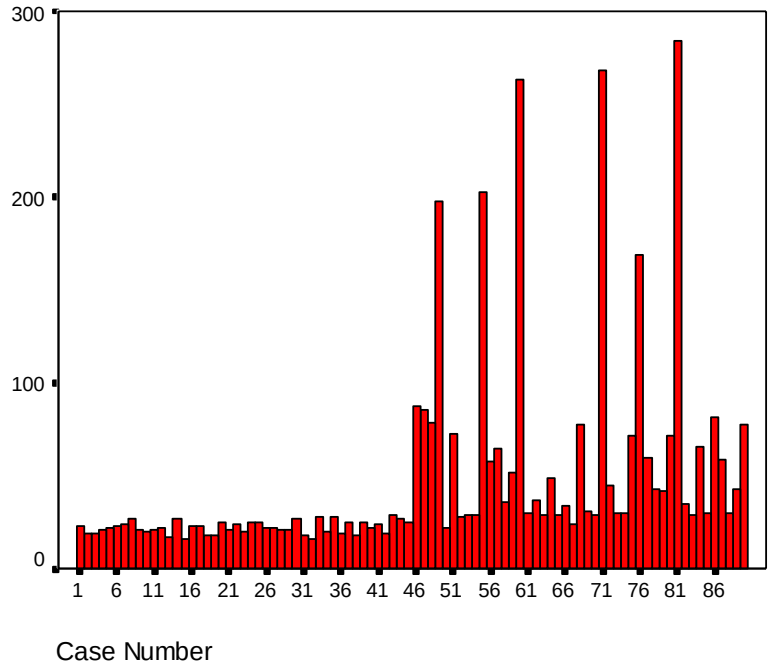
The study was to evaluate the relation if any, between the above parameters in acute phase of MI. The study compared serum concentrations of estrogens in patients and healthy subjects. Statistical analysis of the data was done Microsoft Excel was used for data entry. The statistical packages SPSS and 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

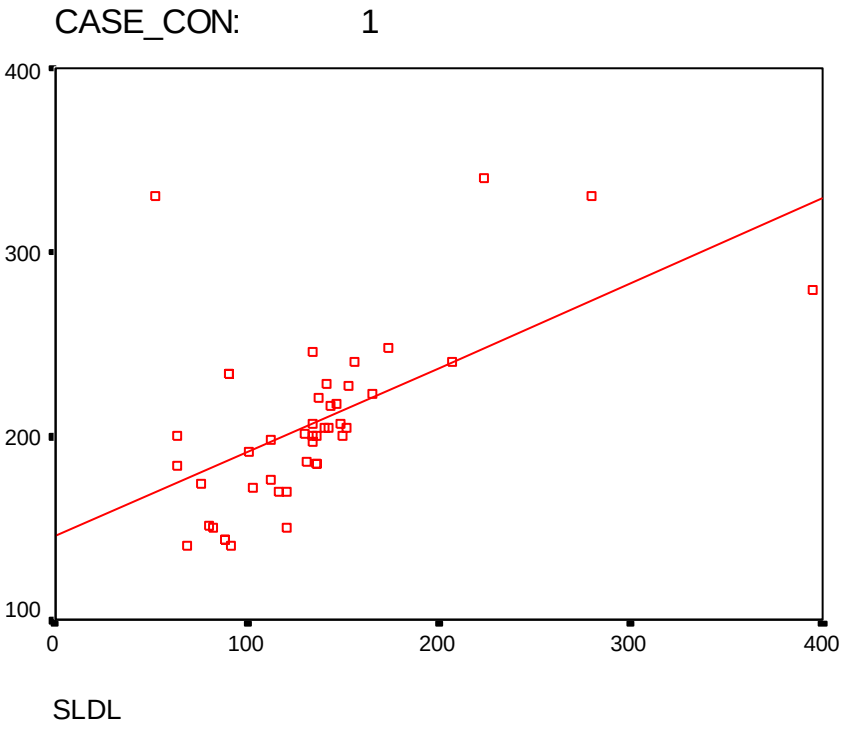
S.Estradiol positive non significant correlation with S.Triglyceride.

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

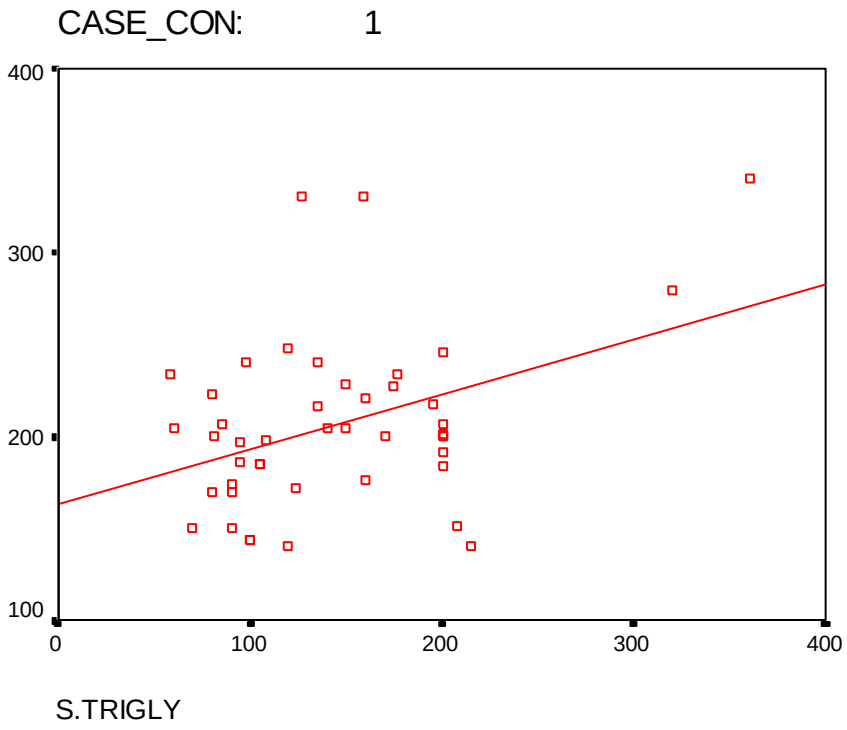
Negative and non significant correlation

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

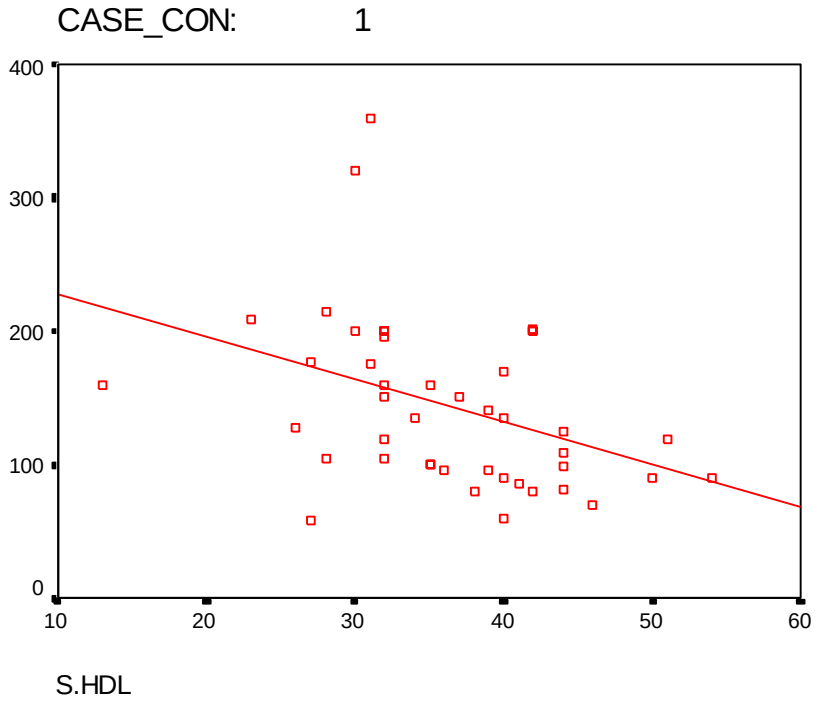
Negative non significant correlation

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

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

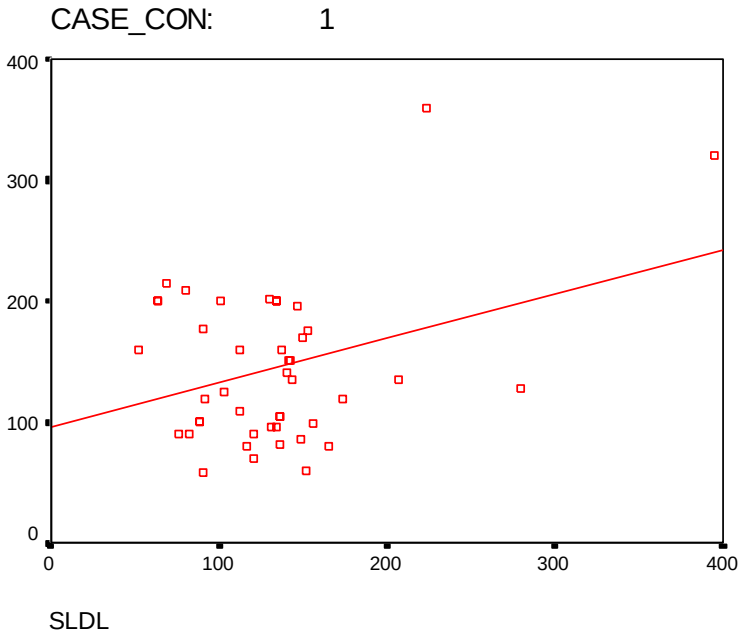
Negative significant correlation

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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PROGESTERONE INDUCED INSULIN RESISTANCE- AN ANIMAL STUDY

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ABSTRACT

BACKGROUND

The occurrence of gestational diabetes in pregnant nondiabetic women is one of the observations in humans pointing to an interaction between progesterone and insulin. Oral contraceptive pill containing norethister one has been shown to increase serum glucose concentration. In an era when progestational agents are widely used for contraception and for maintenance of pregnancy, it is important that we gain more knowledge about the hyperglycemicaction of progesterone and its effect on reproductive function.

Objectives-Insulin resistance is an important defect in the pathogenesis of noninsulin dependent diabetes mellitus (NIDDM). Insulin resistance is accepted to be a risk factor for hypertension, dyslipidemia, atherosclerotic vascular disease, coronary artery disease & stroke. Hyperinsulinemia is consideredasa marker of insulin resistance. In patients with gestational diabetes mellitus & polycystic ovarian syndrome hyperinsulinemia stimulate ovarian androgenic hormones& these products act directly on peripheral tissues to promote insulin resistance. Effect of progesterone on gestational diabetes & polycytic ovarian syndrome, and the cellular & molecular mechanism of insulin resistance is the study of interest.

MATERIALS AND METHODS

Sixty female albino rats weighing around 200 gram showing regular estrous cycle were chosen. Progesterone injections were given in varying doses and for varying periods. Control animals were given only castor oil injections. Blood was collected at the end of the experimental period, blood glucose and serum insulin was estimated along with uterine glycogen content.

RESULTS

Blood glucose and insulin levels were found to be increased, whereas uterine glycogen content decreased according to the dosage and duration of injections.

CONCLUSION

Though the hyperglycemic effect of progesterone seems to be facilitatory to reproductive function, an excessive response can lead to gestational diabetes.

KEYWORDS

Progesterone, Hyperglycemia, Hyperisulinemia, Insulin Resistance, Gestational Diabetes.

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BACKGROUND

Progesterone, secreted for the most part from the ovary in the nonpregnant female is the 'progestational' hormone which prepares the endometrium for implantation of the fertilized ovum, working along with the other ovarian hormone estrogen. After implantation, the continued presence of progesteroneis essential for the maintenance of pregnancy, for foetal growth and preparing the mammary glands for lactation.[1]

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One of the less well known effects of progesterone is its effect on carbohydrate metabolism.[2] The occurrence of impaired glucose tolerance in non-diabtic pregnant women, the so called gestational diabetes, was one of the observations in the humans, pointing to an interaction between progesterone and insulin. Though the role of other gestational hormones like Human Placental Lactogen in the genesis of gestational diabetes cannot be ruled out, progesterone has been considered as the important factor.[2,3,4]

Several reports are available on the hyperglycemic effects of progesterone and synthetic progesins. One of the earliest studies was that of Funk et al,[5] and Ingle et al.[6] Both of them obtained great increases in blood glucose levels by administration of progesterone. Oral contraceptive pill containing nor-ethister one has been shown to increase serum glucose concentration.[7]

Later studies pointed to the induction of insulin resistance by progesterone, resulting in hyperinsulinemia in addition to hyperglycemia.[8]

The sites of insulin resistance have not been worked out in detail but adipocytes and skeletal muscle are possible candidates.[9,10] Liver is another possible site of insulin resistance. Though progesterone is a hormone necessary for reproductive functions, the effects of this hormone on glucose metabolism of the reproductive organs has not been worked out so far. Nor is the physiological significance of the hyperglycemia and hyperinsulinemia established.

Hence it was decided to study the effect of the synthetic progestin 17a hydroxyl progesterone caproate on the carbohydrate metabolism of rat uterus. Uterine glycogen content of rats treated with different doses of progestin for I week, 3 week and 6 weeks was estimated.

It is hoped that the findings of the present study would answer the questions-Why should progesterone cause hyperglycemia?-What is the importance of this effect for reproductive function? Such conformation would be necessary also for a better understanding of the phenomenon of gestational diabetes and for better understanding of the phenomenon of gestational diabetes and for developing strategies for the management of this condition. Further in an era when progestational agents are widely used for contraception as well as for maintenance of pregnancy, the importance of establishing the implications of their side effects is obvious.

Halling et al noted that three women who took a contraceptive containing ethynodioldiacetate & mestranol had abnormal serum glucose levels. But this effect could not be reproduced with mestranol alone, thus suggesting a progestogen effect.

In 1969 Gold and his co-workers produced and elevation of both the blood glucose & plasma insulin levels in men treated with ethynadioldiacetate.[11]

Beck studied the effect of Progesterone in rhesus monkey at the level of 20mg inoil/day (approximately 5mg/kg/day) for 3 weeks.[2] There was no change in fasting blood glucose, insulin or growth hormone levels nor in the intravenous glucose tolerance or glucose disappearance rate. However there was a fourfold increase of the integrated 40 minute plasma insulin response. Enhancement of the plasma insulin response was also seen after tolbutamide administration in progesterone treated monkeys. Progesterone also reduced the sensitivity of monkeys to the hypoglycemic action of exogenous insulin. Another study conducted by Beck in rhesus monkey concluded that progesterone was responsible for the hyperinsulinemia of pregnancy. Kalkh off et al observed that the physiologic does of progesterone increased the secretory response of isolated rat pancreatic islet cell in response to glucose.[12]

In another study by the same workers an enhanced plasma insulin response to oral glucose has been observed in women & men given large doses of progesterone I M without associated changes in plasma cortisol or growth hormone levels.

Virkar et al studied the correlation of the clinical parameters with glucose tolerance test in woman taking oral contraceptives.[13] The women taking the combination oral contraceptives showed an impairment in carbohydrate metabolism at a much earlier age when compared to the control group and the low dosage progestogen group.

Only very few studies have been done on the effect of progesterone on glucose metabolism of uterus. Recent findings indicate that treatment with oral contraceptive lead to alteration in intermediary metabolism. The data obtained provide evidence for the assumption that the alteration found during gestation are comparable to those measured during treatment with oral contraceptive. Regarding the carbohydrate metabolism during pregnancy, alterations in glucose, pyruvate & lacate content in blood have been reported in literature.

The content and distribution of glycogen in the uterus have attracted the attention of many investigations and in most species genital tract glycogen is unique in that unlike muscle or liver glycogen, it is unaffected by either carbohydrate intake or exercise, but is controlled by ovarian steroids like estrogen and progestogens. Unlike human whose uterine glycogen content increases after ovulation, rat, mouse& hamster glycogen content begins to increase before ovulation and become very small during early proliferativestage.[14]

MATERIALS AND METHODS

Experimental Pattern

Groups of female albino rats around 200 gms showing regular 4 days cycle were chosen, fed on rat feed and Bengal gram for 2 weeks and standardized. Estrous cycle of rats was studied by examining the vaginal wash under microscope. Sixty animals showing regular 4 day cycles were chosen for the study. Progesterone injections were given in doses of 5 mg, 10 mg & 20 mg weekly to different groups for 1 week, 3weeks and 6 weeks respectively. The animals were closely watched for gastrointestinal infection and other diseases. Progesterone injections were given in the estrous phase of the cycle. Progesterone was administered intramuscularly using a preparation of 17 alpha hydroxy progesterone caproate (AHPC), 1ml of which contained 250mg of AHPC.0.1 ml of this drug was made up to 2ml with castor oil IP so that 0.04 ml contained 5mg, 0.08ml contained 10mg and 0.16 ml contained 20mg.This was administered using a tuberculin syringe intramuscularly. Control animals were given only castor oil. At the end of the experimental period blood was collected for blood glucose estimation and radioimmunoassay of insulin. Before blood collection, animals were put on fast for 18 hours. After collection of blood, the uteri of the animals were isolated and weighed. The uteri were subsequently homogenized and the glycogen content estimated. Blood was collected from the retro orbital sinus using heparinized capillary tubes and blood glucose was estimated by glucose oxidase/ peroxidase method.

Estimation of insulin was done by standard insulin radioimmunoassay kit. Tissue glycogen was analyzed by Anthrone reagent- Carrol NV et al's method.

Grouping of Animals were Done as Follows-

- Group1 (1 week treatment)- one dose only IM,
  a) Control- castor oil IM- 5 animals.
  b) 5 mg progesterone- 5 animals.
  c) 10 mg progesterone- 5 animals.
  d) 20 mg progesterone- 5 animals.
  ,
- Group 2 contained 3 week treated animals.
  a) Controls: Castor oil IM weekly for 3 weeks (5 animals).
  b) 5 mg progesterone weekly for 3 weeks (5 animals).
  c) 10 mg progesterone weekly for 3 weeks (5 animals).
  d) 20 mg progesterone weekly for 3 weeks (5 animals).

- Group 3 contained 6 week treated animals. 5mg, 10mg and 20mg of progesterone were given weekly for 6 weeks and control animals were injected with castor oil.

RESULTS

It was observed that mean blood glucose level increased invariably in all groups in accordance with the duration of administration. There was no change in control group.

The F test revealed that the difference in mean glucose level between the dosage/ control was highly significant statistically (F=17.78; df (3, 6); p-.001) Similarly the difference in the mean glucose level between duration was also significant at 5% level. So it is evident that the mean glucose level is increased if the dosage as well as the duration increases. The maximum effect was attained in the 20 mg group at the end of 6 weeks.

Sl. No.	Groups (Dosage/ Control)	Blood Glucose Level (mg/100ml)		
		1 Week Treatment	3 Week Treatment	6 Week Treatment
1	Control	46	44	46
2		44	46	46
3		46	44	44
4		48	45	43
5		46	46	46
6	5 mg	50	69	74
7		48	66	78
8		46	66	77
9		48	68	76
10		46	66	76
11	10 mg	65	882	98
12		66	84	100
13		65	82	102
14		64	84	98
15		67	86	98
16	20 mg	78	109	118
17		78	110	120
18		76	106	118
19		76	108	120
20		74	108	118

Table 1. Blood Glucose Levels

Category	Mean glucose (mg/100ml)		
	1 week	3 weeks	6 weeks
	Mean ± SD	Mean ± SD	Mean ± SD
Control	46.0 ± 1.4	45.0 ± 1.0	45.0 ± 1.4
5 mg	47.6 ± 1.7	67.0 ± 1.4	76.2 ± 1.5
10 mg	65.4 ± 1.1	83.6 ± 1.7	99.2 ± 1.8
20 mg	76.4 ± 1.7	108.2 ± 1.5	118.8 ± 1.1

Table 2. Mean blood Glucose According to Duration in Different Groups

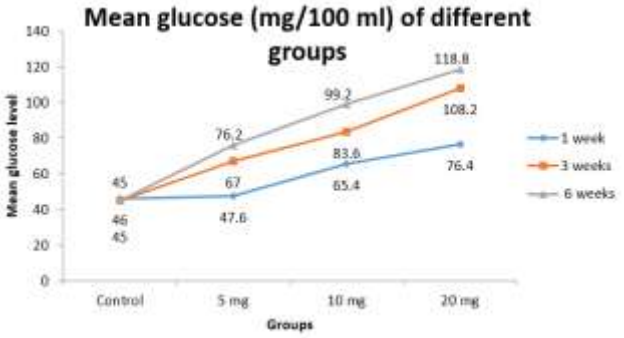

Figure 1

	Type III Sum of Squares	df	Mean Square	F	p
Between duration	6960.9	2	3480.45	1628.281	<0.001
Duration vs. Group Dosages	2904.7	6	484.117	226.487	<0.001
Error(factor1)	68.4	32	2.137		

Table 3. Anova Table for Testing the Homogeneity of Blood Glucose of Different Groups

The ANOVA table for testing the homogeneity of mean insulin revealed that the difference was significant statistically between dosages as well as between durations. Therefore it is inferred that while the dosage is changed, the mean insulin level increased irrespective of the duration. Similarly, a remarkable increase is noted if the duration is changed irrespective of the dosage. Since F test is statistically significant between groups/ control, all the three groups administered with different dosage of drugs proved to be very much effective in increasing mean insulin levels compared to control not only in the in 1 week group, but also in the 3 week and 6 week groups.

Sl. No.	Groups (Dosage/ Control)	Insulin Levels (μIU/ ml)		
		1 Week Treatment	3 Week Treatment	6 Week Treatment
1	Control	17.8	17.6	17.6
2		16.9	17.9	17.8
3		17.5	17.5	17.4
4		17.4	17.4	17.5
5		17.3	16.9	17.6
6	5 mg	18.5	26.2	34.6
7		17.9	26.8	38.4
8		18.9	26.4	34.4

9		19.5	28.6	34.6
10		18.4	29.6	33.6
11		20.6	34.4	50.7
12		20.8	38.8	53.4
13	10 m g	22.5	36.4	54.8
14		20.7	35.8	55.8
15		20.8	36.6	56.7
16		28.7	49.8	78.4
17		26.8	50.4	75.4
18	20 mg	28.8	50.6	76.4
19		29.3	49	76.4
20		29.5	48.4	75.4

Table 4. Serum Insulin Levels

Category	Mean insulin ((μIU/ ml)		
	1 week	3 weeks	6 weeks
	Mean ± SD	Mean ± SD	Mean ± SD
Control	17.4 ± 0.3	17.5 ± 0.4	17.6 ± 0.1
5 mg	18.6 ± 0.6	27.5 ± 1.5	35.1 ± 1.9
10 mg	21.1 ± 0.8	36.4 ± 1.6	54.3 ± 2.3
20 mg	28.6 ± 1.1	49.6 ± 0.9	76.4 ± 1.2

Table 5. Mean Serum Insulin Levels According to Duration in Different Groups

	Type III Sum of Squares	df	Mean Square	F	p
Between duration	5971.306	2	2985.653	1905.533	<0.001
Duration vs. Groups Dosages	3204.975	6	534.162	340.919	<0.001
Error (factor 1)	50.139	28.886	1.736		

Table 6. Anova Table for Testing the Homogeneity of Serum Insulin Level of Different Groups

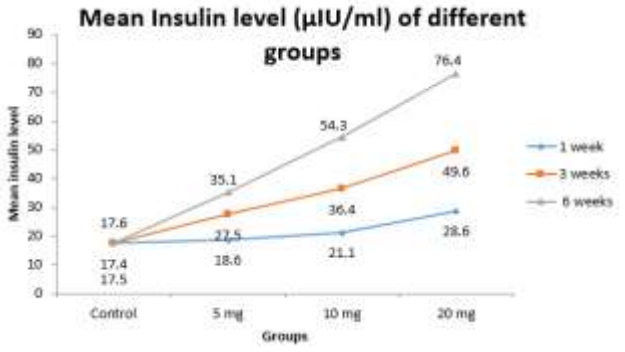

Figure 2

There is a declining trend in the tissue glycogen level if duration and dosages were increased. The difference in the reduction attained at varying dosages and at varying duration was tested statistically by computing the F ratio. In the case between dosages/ control the F ratio was 22.04 which was highly statistically significant (P<.001). A similar result was obtained when the duration was also altered.

Sl. no	Groups (Dosage/ Control)	Glycogen level (mg/gm)		
		1 week Treatment	3 week Treatment	6 week Treatment
1		0.677	0.6501	0.6642
2		0.6674	0.676	0.643
3	Control	0.6452	0.6456	0.6432
4		0.6853	0.6652	0.653
5		0.6752	0.6433	0.632
6		0.6563	0.5334	0.48214
7		0.6552	0.5342	0.4423
8	5 mg	0.6575	0.5562	0.4532
9		0.6565	0.545	0.496
10		0.6545	0.532	0.482
11		0.501	0.302	0.2572
12		0.5342	0.354	0.2642
13	10 m g	0.5332	0.324	0.295
14		0.5352	0.341	0.2567
15		0.5432	0.341	0.257
16		0.432	0.2572	0.093
17		0.412	0.2472	0.0735
18	20 mg	0.433	0.2342	0.075
19		0.412	0.256	0.073
20		0.426	0.252	0.075

Table 7. Glycogen Levels in Wet Tissue as per Duration in Different Groups

Category	Mean tissue glycogen(mg/gm)		
	1 week	3 weeks	6 weeks
	Mean ± SD	Mean ± SD	Mean ± SD
Control	0.670 ± 0.015	0.656 ± 0.014	0.647 ± 0.012
5 mg	0.656 ± 0.001	0.540 ± 0.010	0.471 ± 0.022
10 mg	0.529 ± 0.016	0.332 ± 0.020	0.266 ± 0.017
20 mg	0.423 ± 0.010	0.249 ± 0.009	0.078 ± 0.008

Table 8. Mean Glycogen Level in Wet Tissue as per Duration in Different Groups

	Type III Sum of Squares	df	Mean Square	F	p
Between duration	.424	2	.212	1301.238	<0.001
Duration vs. Groups Dosages	.150	6	.025	154.034	<0.001
Error (factor1)	.005	32	.000		

Table 9. ANOVA Table for Testing the Homogeneity of Mean Tissue Glycogen of Different Duration in Different Groups

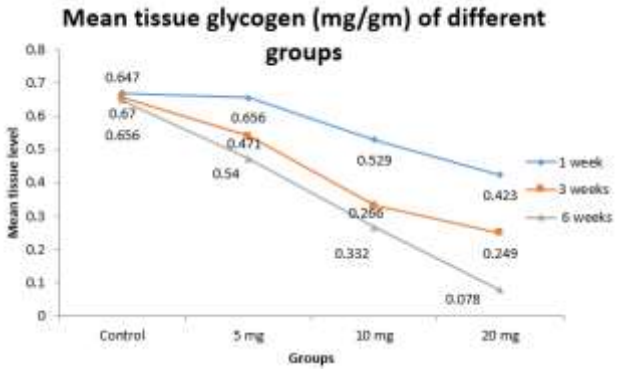

Figure 3

Therefore it is proved that the duration as well as dosage has a remarkable effect over control in reducing the tissue glycogen level. The maximum result is observed at 6 weeks time in 20mg group.

DISCUSSION

Progesterone induce hyperglycemia. However the teleologic significance of the progesterone induced hyperglycemia has not been established. One possibility is that progesterone – induced hyperglycemia is meant to increase glucose utilization and glycogen synthesis in theuterus during the progestational phase and during pregnancy.

The present study was aimed at probing into the above possibility Changes in blood glucose and insulin levels induced by administered progesterone were correlated with glycogen content and glucose utilization by the uterus in albino rats. Uterine pyruvate levels and lacate were estimated as an index of glucose utilization by the tissue.

As in the case of previous studies blood glucose levels and insulin levels were increased in the animals treated with progesterone. It had an increasing trend according to dosage and duration of progesterone treatment. The prominent findings were a reduction in uterine glycogen level and lacate level with an increase in pyruvate level during treatment with progesterone.

Blood Glucose and Insulin Levels

Like most previous studies done with natural progesterone and other progestins the present experiment have brought out the hyperglycemic effect of the progestin. 17- ahydroxy progesterone caproate. Kulkarni et al working with ethinodioldiacetate in rabbits also observed an impairment of glucose tolerance.[15] On the other hand in 1979 Merkatz et al showed that medroxy progesterone aceate did not alter glucose or insulin response.[16] In fact the plasma fasting glucose was lowered. Samad et al studied the effect of subdermal progesterone implant in overectomised sheep and no significant effect on the concentration of glucose on plasma was observed.[17]

Eigenmann and Rijnberk from their studies inferred that increase in glucose caused by progesterone is due to increase in growth hormone release.[18] This hyperglycemia will stimulate increased insulin release. Pre-treatment with ergotamine (an apha adrenergic receptor blocking agent) abolished hyperglycemic effect of progesterone implicating a role for cate cholaqmines.

The content and distribution of glycogen in the uterus have attracted the attention of many investigators. In most species genital tract glycogen is unique in that, unlike muscle or liverglycogen, it is unaffected by either carbohydrate intake or exercise, but is cantrolled by ovarian steroids. In this study, the uterine content of glycogen, pyruvate and lactate were estimated in control and in animals treated with progesterone. Uterine glycogenwas found to be reduced under the influence of progesterone. Pyruvate levels in the progesterone treated animals were higher than controls whereas lactate levels were lower.

As the estimations were done with the whole uterine tissue, the changes could have involved the endometrium or myometrium. But it is more likely that both the tissues are involved, considering the already known effects of progesterone on endometrium and myometrium.

Considering the above effect of progesterone on glycogen of human uterus, it was felt quite surprising that the rat uterine glycogen decreased under the influence of progesterone. However many previous workers have reported comparable results. Kostyo & Shea recorded decreased glycogen content in the endometrium of rat and ewe respectively during implantation and gestation periods.[19,20] Paul & Duttagupta concluded from their study that progesterone inhibits the glycogenic effects of oestrogen in the liver and uterus of ovariectomized rats.[21] Moreover progesterone by itself inhibits uterine glycogen accumulation in these animals. Reddy & Govindappa found that uterine glycogen content of albino rats decreased during implantation which may be due to progesterone.[22]

The present study indicates that the insulin resistance induced by progesterone involves the uterus as well-as least in relation to the glycogen synthesis in the uterus. Insulin favours glycogen synthesis and inhibits glycogenolysis. This effect is inhibited by progeseteroneand thus insulin resistance is induced by progesterone. This effect of progesterone is comparable to its effect on hepatocytes obtained in the previous studies in this department.

It is also possible that progesterone induced depression of uterine glycogen is mediated through the secretion of adrenaline from adrenal medulla. Other glycogenolytic hormones may be involved in the glycogen depletion of uterus. Eigenmann obtained an evaluation of growth hormone on administration of medroxy progesterone acetate, another progestin.[19] Pre-treatment with ergotamine (an adrenergic receptor blocking agent) abolished the hyperglycemic effect of progesterone implicating a role of catacholamines. Both growth hormone and catacholamines are glycogenolytic hormones.

In the present study the mean uterine pyruvate level showed an increasing trend as the duration as well as dosage of progesterone increased whereas tissue lactate level showed a declining trend. We can conclude that

progesterone increase aerobic glycolysis possibly in the endometrium myometrium- a facilitation effect on insulin action.

What could such a facilitation of aerobic metabolism mean to the myometrium? An increase in the contractility of the myometrium at the time of implantation and pregnancy would be detrimental to these processes and could lead to expulsion of the blastocyst/conceptus. Progesterone is known to decrease the excitability and contractility of myometrium.

There is evidence that glucose utilization of skeletal muscle also is not inhibited by progesterone. Davy has showed that progesterone did not alter the pyruvate and lactate content of rat diaphragm. Thus we can assume that insulin resistance brought about by progesterone does not involve in the utilization of glucose in skeletal as well as smooth muscle. In the uterine smooth muscle as well as endometrium utilization of glucose by aerobic metabolism is actually increased.

Reddy and Govindappa analysed glycogen metabolism in the uterus of adult female wistar albino rats. During implantation the uterine glycogen content was decreased, while free glucose and phosphorylase activity were elevated and they have attributed the changes to progesterone16. The pyruvate content increased with reduction in the lactic acid level during the course of implantation.

The above results coincide with the results of the present study. When progesterone was given in increasing doses, it decreased uterine glycogen content and increased pyruvate content. Decrease in glycogen content due to progesterone administration may be as a result of increased phosphorylase activity as discussed earlier. The pyruvate content increase due to aerobic metabolism of glucose.

CONCLUSION

1. The interaction between progesterone, insulin and blood glucose in relation to uterine carbohydrate metabolism was studied in female albino rats of reproductive age group.
2. Blood glucose and insulin levels and glycogen content of uterus were assessed quantitatively. Pyruvate and lactate levels of uterus were estimated as indicators of glucose utiisation of uterus.
3. It was observed that mean blood glucose and serum insulin levels increased proportionate to the dosage as well as duration of progesterone administration.
4. Uterine glycogen progressively decreased in a dose and duration dependent manner.
5. Uterine pyruvate content increased and lactate level decreased suggesting facilitation of aerobic glycolysis in endometrium and/or myometrium.
6. Hyperglycemia with high insulin levels, indicate persistent stimulation of beta cells by progesterone either directly or by inducing insulin resistance and hyperglycemia. Insulin resistance increase blood glucose level and the latter in turn raises insulin secretion further.
7. It is inferred that the insulin resistance induced by progesterone involves the uterus in relation to glycogen synthesis. Progesterone inhibits glycogen synthesis and promotes glycogenolysis. It may be due to increased phosphorylase activity. Progesterone- induced stimulation of growth hormone and adrenaline secretion could also account for the findings.
8. Facilitation of aerobic glycolysis by progesteronemay be intended to increase the availability of ATP for the synthetic and other reactions necessary for implantation and pregnancy. Progesterone induced insulin resistance thus spares the glycolysis of uterus.
9. Decreased lactate levels possibly prevent the feedback inhibition of phosphorylase activity and hence of glycogenolysis in the uterus.
10. This study had brought out the importance of the insulin resistance induced by progesterone to reproductive function, at least in the rats. More glucose is made available to the fetus. Also the decrease in uterine glycogen consequent to the insulin resistance, facilitates implantation. As the resistance does not involve glycolysis, availability of energy rich phosphate to the uterur is not affected.
11. Though the hyperglycemic effect of progesterone seems to be facilitatory to reproductive function, an excessive response can lead to gestational diabetes. More detailed are required before this information could help us in the prevention and management of this serious complication of pregnancy.

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A Comparative Study of ECG Changes in Patients with and Without Alcohol Use Disorder

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Abstract: ***Background****: Alcohol use is currently a widespread disorder. It affects almost all age groups. Heavy alcohol consumption can lead to cardiac arrhythmias and sudden death. Alcohol use disorder(AUD) is defined as the cluster of behavioural and physical symptoms, which include withdrawal, tolerance, and craving. Alcohol can cause ECG changes before the manifestation of cardiac disorders. Therefore, this study was undertaken which help in the earlier detection of cardiovascular disease and preventing its complications.*
Materials and Methods*: This was a comparative study involving fifty patient Alcohol Use Disorder s and fifty non-AUD patients. Patients satisfying the inclusion and exclusion criteria were selected consecutively from the Psychiatry OPD and De-addiction centre till the calculated sample size was attained. After taking an informed consent, biodata, history of alcoholism and blood pressure was recorded in a proforma. ECG was taken with CARDIART6108T machine and the parameters were noted. Three ml of blood was collected from AUD patients. Data was entered into excel sheet analysed using SPSS version 21 software.*
Results*: Patients with alcohol use disorder had prolonged duration and abnormal morphology of P wave, prolongation of QT and QTc interval, NSST and T wavechanges and shortening of TP interval. These patients also had many other statistically significant variations like presence of Q waves, presence of LVH, non – progression of R wave and LV strain pattern.*
Conclusion: *There is significant ECG changes in patients with Alcohol Use Disorder which makes them prone to cardiovascular risk. ECG changes can be due to the associated electrolyte abnormalities like hyponatremia, hypokalemia,hypomagnesaemia and hypocalcemia.*
Key Words*: Alcohol Use Disorder, Electrocardiogram, Duration of alcohol use, Serum electrolytes.*

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I. Introduction

Alcohol is a psychoactive substance which can produce dependence problems. The burden of death and disease produced by alcohol is significant across the world. Excessive consumption of alcohol remains one of the first five factors which are responsible for death ,disease and disability throughout the world.[1]

Alcohol use disorder (AUD) is a common disorder characterized by withdrawal, tolerance and craving. The incidence of AUDis increasing. One of the most commonly associated condition in patients with alcohol use is low grade hypertension[2]. Long term consequences of alcohol on cardiovascular system are systemic hypertension, arrhythmia and cardiomyopathy.[3] The prevalence of alcohol dependence among males in Thiruvananthapuram district is 38.4%.[4] It has been observed that prolongation of QT interval and non-specific ST and T changes are frequent in ECG of patients with chronic alcoholic use disorder. Prolongation of QT interval may be due to the abnormality in serum calcium level.[5]

Sinus tachycardia is seen in large number of patients with alcohol use disorder due to increased secretion of epinephrine from adrenal medulla. This mainly depends on the dose of administration of alcohol.[6] Moderate alcohol dose was found to increase the secretion of catecholamine from adrenal medulla.[7]

Alcohol abuse is a pattern of drinking which cause damage to the physical, mental and social wellbeing of the patients and also to those around them. It is having a strong relation with hypertension and the prevalence is 50-150% higher in heavy alcohol uses.[8] The impulse conduction of heart is another factor which is mainly affected in patients with chronic alcohol use. Most common rhythm disorder found is atrial fibrillation.[9]

Alcohol use disorder: **DSM – 5 criteria**:
In May 2013, the American Psychiatric Association has issued 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5).
DSM–5 combined the two DSM–4 disorders, alcohol abuse and alcohol dependence, into a single disorder called Alcohol Use Disorder (AUD) with mild, moderate, and severe sub-classifications.

The presence of 2 of these symptoms indicates an Alcohol Use Disorder (AUD).
Therefore a regular monitoring of AUD patients with ECG along with Echo and other haematological parameters could be a step in early detection of cardiovascular disease so that remedial measures can be adopted early among them, ultimately reducing the associated mortality and morbidity in the long term.

II. Material And Methods

This study was conducted in the Department of Psychiatry, Govt Medical College, Thiruvananthapuram. The participants in this study were chosen from AUD patients attending the OPD of Psychiatry and De-Addiction Centre, Govt. Medical College, Thiruvananthapuram. Fifty AUD patients and fifty non AUD patients satisfying the inclusion and exclusion criteria were recruited into the study consecutively till the sample size was attained. After taking an informed consent, the biodata and baseline characteristics of each subject were recorded using a proforma. Under aseptic precautions, 3ml of blood was collected for examination.

Study design
Comparative Cross Sectional Study.
Study setting
OPD of Psychiatry and De-addiction centre, Government Medical College, Thiruvananthapuram.
Study population
Patients having Alcohol Use Disorder confining to DSM-5 criteria.
Comparative group
Other patients without Alcohol Use Disorder attending the OPD are selected as comparative group.
Exclusion criteria:

- Known case of diabetes mellitus, hypertension, coronary artery disease and other heart disease.
- Subjects on any long-term drugs that can cause ECG changes.
- Those who are not willing to give consent.

Inclusion criteria

- Patients having Alcohol Use Disorder confining to DSM-5 criteria.

Sample size
Sample size is calculated using the formula:

$$n = \frac{2 \times \{ Z_{(1-\alpha/2)} + Z_{(1-\beta)} \}^2 \times \sigma^2}{d^2}$$

A sample size of 50 was decided upon for each group (n=50 + 50 =100)
Sampling technique
Consecutive patients attending OPD of Psychiatry and de-addiction centre, Government Medical College, Thiruvananthapuram fulfilling my study criteria is enrolled for the study.
Duration of study
1 year.
Study variables
1. Socio demographic characteristics.
2. Duration of alcohol use.
3. Blood pressure (BP): Hypertension defined as systolic BP ≥140 mm Hg and diastolic BP ≥ 90 mm Hg on two or more occasions separated by a minimum period of 3 minutes (JNC 8 Criteria).
4. ECG parameters: Heart rate, P wave, PR intervals, QRS complex, ST segment,QTC interval, QT interval, T wave, TP interval.
Data collection technique
Ethical clearance was obtained. Consecutive patients coming to study setting before the administration of any drugs and confining to the inclusion and exclusion criteria was assessed for ECG changes. The purpose and Nature of the study was explained to the selected cases and controls in detail. Informed consent was obtained. The information about the history was collected using a Proforma.
Data collection tool
Structured proforma was used to collect the clinical history and to confirm the diagnosis. BP of the subjects was recorded using a standardised sphygmomanometer. Twelve lead ECG was recorded by using a standardized ECG machine.

Statistical analysis
Data was entered in to Microsoft Excel data sheet. Quantitative variables were expressed as mean and standard deviation and qualitative variables were expressed as percentage. Statistical test of significance: Comparison of quantitative variables analysed using unpaired t test. Comparison of qualitative variables analysed using chi square test. Statistical test of significance for non- parametric variables include Mann-

Whitney U test and Kruskal Wallis test. A P value of <0.05 was considered statistically significant and a P value <0.01 was considered very significant. Analysis of data done using SPSS version 21.

Ethical considerations

Institutional Ethics Committee clearance was obtained.,Informed consent obtained from the participants. Confidentiality was ensured and maintained throughout the study.No expenses were incurred from the patients.

III. Results

This study was conducted with a view to compare the changes in ECG parameters associated with Alcohol Use Disorder patients with other non AUD patients

Age distribution of patients Among the patients studied 34% were under the age of 40 and another 34% were in the age group of 41-50. 32% were greater than 50 years of age. Among the comparative group 20 percent were under the age of 40 years, 44% comes under the age group of 41-50. 36% comes under the age roup of greater than 50. Mean ± SD in Patients with alcohol use disorder is 44.8 ± 12 and in Patients without alcohol use disorder is 47.6 ± 8.2 t = 1.33, 0.186

Comparison of blood pressure

1. Comparison of systolic blood pressure

Table .2. Comparison of SBP based on groups

Group	Mean	SD	N	t	P
Patients with alcohol use disorder	139.6	12.6	50	5.93	p<0.01
Patients without alcohol use disorder	127.6	6.6	50		

The mean systolic blood pressure of patients with alcohol use disorder (N=50) was 139.6mm of Hg (SD 12.6) and those without alcoholic use disorder (N=50) was 127.6mm of Hg (SD =6.6).The difference was statistically significant.(p<0.01)

2. Comparison of diastolic blood pressure

Table 2: Comparison of DBP based on group

Group	Mean	SD	N	t	P
Patients with alcohol use disorder	89.3	8.4	50	4.4	p<0.01
Patients without alcohol use disorder	83.4	4.5	50		

The mean diastolic blood pressure of patients with alcohol use disorder (N=50) was found to be 89.3 mm of Hg (SD=8.4) and those without alcohol use disorder (N=50) was found to be 83.4mm of Hg (SD=4.5).The difference was statistically significant.(P<0.01). The difference was significant.

Comparison of ECG changes in patients with and without alcohol use

1. Comparison of heart rate based on groups

Table 3: Comparison of Heart rate based on group.

Group	Mean	SD	N	t	P
Patients with alcohol use disorder	84.4	7.0	50	4.79	p<0.01
Patients without alcohol use disorder	79.4	2.2	50		

In this study the mean heart rate of the patients with alcohol use disorder was 84.4 beats per minute (SD=7) and those without alcohol use disorder was 79.4 (SD=2.2) beats per minute.t=4.79,P<0.01.

2 .comparison of rhythm based on groups

No rhythm abnormality was found in patients with alcohol use disorder. 100% of the subjects were having normal rhythm (N=50).In comparative group also the rhythm was normal. There is no significant difference in the rhythm between AUD patients and comparative group. (P=1.0).(Mann-Whitney U Test)

3. Comparison of morphology of p wave

Table 4: Comparison of morphology of P wave in lead II based on group

Morphology of P wave in lead II	Patients with alcohol use disorder	Patients without alcohol use disorder	Z#	P

	Count	Percent	Count	Percent		
Normal	46	92.0	50	100.0	2.03*	0.042
Abnormal	4	8.0	0	0.0		

Mann-Whitney U Test *: - Significant at 0.05 level

Only 8% (N=4) of the AUD patients had abnormal morphology of P wave while 92% (N=46) of them had normal morphology. In comparative group (N=50) no abnormality was detected in P wave morphology. The difference was statistically significant at P value <0.05.

4. Comparison of duration of P wave in lead II

Table 5 : Comparison of duration of P wave in lead II expressed in seconds based on group

Group	Mean	SD	N	T	P
Patients with alcohol use disorder	0.11	0.02	50	2.67**	0.009
Patients without alcohol use disorder	0.10	0.01	50		

**: - Significant at 0.01 level

The mean duration of P wave in patient with alcohol use disorder was 0.11s (SD=0.02) and in patients without alcohol use disorder was 0.10 seconds (SD=0.01). The difference was statistically significant at P value <0.01.

5. Comparison of duration of PR interval in lead II

In this study no significant difference in the duration of PR interval was found between the AUD group and comparative groups. In patients with alcohol use disorder the mean duration of PR interval was 0.15 s (SD=0.03) and in patients without alcohol use disorder also the mean PR interval duration was 0.15s (SD=0.02).The P value is 0.287.

6. Comparison of duration of QRS complex in lead II.

The mean duration of QRS complex in patients with alcohol use disorder was 0.10 s (SD=0.03).In comparison group also the mean QRS duration was found to be 0.10s (SD=0.02).No significant difference was observed between the duration of QRS complex in both groups. P value =0.494.

7. Comparison of duration of QT interval in lead II

Table 6: Comparison of duration of QT interval in lead II expressed in seconds based on group

Group	Mean	SD	N	T	P
Patients with alcohol use disorder	0.36	0.04	50	3.76	p<0.01
Patients without alcohol use disorder	0.34	0.02	50		

In the present study mean duration of QT interval in patients with alcohol use disorder (N=50) was 0.36 seconds (SD=0.04) and in other group (N=50) was 0.34 seconds (SD=0.02).This difference was statistically significant at p value < 0.01.

8. Comparison of corrected QT interval based on groups.

Table 7: Comparison of corrected QT interval based on groups.

Group	Mean	SD	N	t	P
Patients with alcohol use disorder	0.43	0.05	50	4.9	p<0.01
Patients without alcohol use disorder	0.39	0.02	50		

In the present study mean duration of QTc interval in patients with alcohol use disorder was 0.43 seconds (SD=0.05) and in comparison group was 0.39 seconds (SD=0.02).This difference was statistically significant at p value < 0.01

9. Comparison of ST segment based on groups.

Table 8 : Comparison of ST segment based on group

T Wave	Patients with alcohol use disorder		Patients without alcohol use disorder		Z#	P
	Count	Percent	Count	Percent		
Normal	44	88.0	49	98.0	1.98*	0.048

Tall wave	2	4.0	1	2.0		
Inverted T wave	4	8.0	0	0.0		

Mann-Whitney U Test *: - Significant at 0.05 level

Among the study group 88 % of the patients had normal ST segments (N=44). 6 % (N=3) had ST segment elevation and another 6% (N=3) had ST segment depression. Among the comparison group 98% (N=49) of them had normal ST segment and 2 % (N=1) had ST segment elevation .This difference was statistically significant at a P value < 0.05.

10. Comparison of T wave based on groups

Table9: Comparison of T Wave based on groups

T Wave	Patients with alcohol use disorder		Patients without alcohol use disorder		Z#	P
	Count	Percent	Count	Percent		
Normal	44	88.0	49	98.0	1.98*	0.048
Tall wave	2	4.0	1	2.0		
Inverted T wave	4	8.0	0	0.0		

Mann-Whitney U Test *: - Significant at 0.05 level

In the present study 88 % of the patients with AUD had normal T wave (N=44). 4 % (N=2) had tall T wave and 8 % (N=4) had inverted T wave. Among the comparison group only 2% (N=1) had tall T wave while 98 % (N=49) of the subjects had normal T wave. The difference was statistically significant at P value < 0.05

11. Comparison of duration of TP interval.

Table10: Comparison of duration of TP interval in lead II expressed in seconds based on groups.

Group	Mean	SD	N	t	P
Patients with alcohol use disorder	0.33	0.03	50	3.03**	0.003
Patients without alcohol use disorder	0.34	0.01	50		

**: - Significant at 0.01 level.

Among the AUD group the mean duration of TP interval in patients with alcohol use disorder was 0.33 seconds (SD=0.03) and those without alcohol use disorder was 0.34 seconds (SD=0.01). The difference was statistically significant at P value < 0.01 level.

2. Comparison of other abnormalities in ecg based on groups.

Table11:Comparison of others based on group

Others	Patients with alcohol use disorder		Patients without alcohol use disorder		Z#	P
	Count	Percent	Count	Percent		
Negative	40	80.0	50	100.0	3.31	p<0.01
Presence of Q waves	2	4.0	0	0.0		
Presence of LVH	2	4.0	0	0.0		
Non progressive R wave	1	2.0	0	0.0		
RSR pattern	4	8.0	0	0.0		
LV strain pattern	1	2.0	0	0.0		

Mann-Whitney U Test

Among the patients with alcohol use disorder 80%(N=40) of them did not have any other abnormalities.4% (N=2) of them had the presence of Q waves and another 4 %(N=2) had LVH.2 %(N=1) of them had non progression of R wave, 8%(N=4) of them had RSR' pattern, 2 %(N=1) of them had LV strain pattern. Among controls no other abnormalities was detected. These findings were statistically significant at P value <0.01.

IV. Discussion

The present study was conducted in a view to compare the ECG parameters of the patients with alcohol use disorder to those who do not have this disorder.Alcohol use has got complex effects on cardiovascular functioning. One of the most important acute effect of alcohol on heart is negative inotropic effect.This can later

lead to irregular and ineffective contractions of myocardium with very fast heart rate called as tachyarrhythmia.[10]

Studies have shown that alcohol has shortened the effective refractory period and also slowed down the intra atrial conduction .It also prolonged the HV interval and shortened the sinus node recovery time. Alcohol also causes stimulation of sympathetic nervous system and promotes adrenaline secretion from the adrenal medulla. There is also a significant reduction in short term heart rate variability.[11]

Distribution of age and sex

In the present study the mean age of the patients with alcohol use disorder was found to be 44.8 (SD=12). Only male patients were included in this study. One reason for this is females in our society won't disclose the data due to social stigmas attached to them.[12]

Effect on blood pressure

In the present study the mean systolic blood pressure of patients with alcohol use disorder (N=50) was 139.6 mm of Hg (SD 12.6) and diastolic blood pressure was 89.3 mm of Hg (SD=8.4) .Systolic BP of the comparison group was (N=50) was 127.6mm of Hg (SD =6.6) and diastolic BP was 83.4 mm of Hg (SD= 4.5). Recent cross sectional studies are concentrating to find the effect of alcohol use on the blood pressure. It has been found out that even moderate alcohol consumption have raised the blood pressure. A systematic review of alcohol interventiona studies have confirmed that alcohol restriction reduced both diastolic and systolic blood pressure [13],[14].Alcohol decreases the baroreceptor reflex sensitivity by interacting with nucleus of tractus solitarius and rostral ventro lateral medulla. It also affects ANS. There is increased sympathetic nervous system activation and discharge of sympathetic amines. Due to direct stimulation of ACTH release in regular alcohol users there is increased cortisol secretion. The mineralocorticoid activity of cortisol leads to raised blood pressure .Alcohol also causes vasoconstriction of blood vessel due to increased intracellular calcium and increased vascular sensitivity to nor epinephrine.. The role of vasoconstrictor substances like endothelin1, nor epinephrine and angiotensin II were also proposed to have role in the mechanism for alcohol induced hypertension.[15]

Heart rate

In this study the mean heart rate of the patients with alcohol use disorder was 84.4 beats per minute (SD=7) and those without alcohol use disorder was 79.4 (SD=2.2) beats per minute. Similar finding was shown in another study.. They generated a hypothesis which states that sinus tachycardia and respiratory sinus arrhythmia can lead to Holiday Heart Syndrome.[84,85]The proposed mechanism by which the alcohol increase the heart rate is increased sympathetic activity and decreased parasympathetic activity.[16,17]

Rhythm

Atrial arrhythmias are common in patients with Alcohol Use Disorder, due to arrhythmogenic effect of ethanol..[18] Sudden stoppage of alcohol intake results in beta adrenergic stimulation and increase in catecholamine level and patients are prone to arrhythmias.[19] Despite higher incidence of atrial arrhythmias in patients consuming alcohol we got normal rhythm for all patients .This may be because the patients have paroxysmal tachyarrhythmia which may be absent during the recording of ECG. However the patients gave history of palpitation and breathlessness. Some studies have proved that the amount of alcohol intake should be greater than 3 to 5 drinks per day to cause AF in men.[19,20] Another study by Koskinen et al concluded that alcohol was associated with increased incidence of atrial fibrillation but not any other form of supraventricular arrhythmias. They also found out that heavy drinking was associated with ventricular arrhythmias and sudden death.[21,22]

Morphology and Duration of P wave

30 seconds prolonged than non-alcoholics (0.10s) .Abnormal morphology of P wave was found in 8% of the patients with alcohol use disorder while no abnormality was detected in non-alcoholics. These findings were similar to another study conducted by Sengul et al.[23] The prolongation of P wave is associated with development of atrial fibrillation. This relationship was also established in many other clinical studies.[25,26,27]

PR interval

In the present study the mean duration of PR interval is 0.15s.There was no difference between the cases and controls. However the relation between PR interval and alcohol intake remain inconsistent. Prolongation of PR interval is associated with conduction disturbances.[27,29] Some other studies have showed shortening of PR interval in alcoholics. Shortening of PR interval is associated with re-entrant tachycardia.[28]

QRS interval

In the present study no significant differences were present between the cases and control group regarding QRS duration. This was similar to the findings present in another study conducted by Ramanna et al.[30] Previous studies have shown that QRS prolongation leads to increased chance of arrhythmias.

QT and QTc interval

Ethanol prolongs the repolarisation time and increases the QT interval.[31] In the present study also we got QT interval (0.36s) and QTc (0.43s) as prolonged similar to study conducted by Priyadarshini et al.[28] QT interval prolongation was one of the frequent ECG finding in patients with alcohol use disorder.[32,33] This can lead to polymorphic ventricular tachycardia. QTc prolongation is also a predictor of sudden cardiac death in alcoholics.[34] Alcohol affects the amount of calcium entering the voltage gated calcium channels during the plateau phase of action potential. It thus prolongs the ventricular repolarisation which depends on the reduction in L-type calcium currents and increased outward potassium current.[35] Inhibition of HERG channel resembling the delayed rectifying potassium channels by ethanol also prolongs QT interval.[36]

ST segment

In the present study 6% of the patients had ST segment elevation and another 6% had ST segment depression compared to normal. This was a statistically significant difference. These findings were similar to many other studies.[37,38] ST segment deviation either elevation or depression from isoelectric line is a predictor of coronary problems in asymptomatic individuals.[39] Many authors have observed that ethanol have the ability to produce acute coronary events.[40,41]

T wave changes

7 study published in journal of medical reports stated that there are characteristic T wave changes during alcohol withdrawal. The patient developed features of acute coronary ischaemia.[42] Similar changes in T wave were also reported by another studies.[43,44] Thus people with Alcohol Use Disorder is having elevated risk of coronary artery disease.[29]

TP interval

In patients with alcohol use disorder TP interval was reduced (0.33s) compared to normal (0.34s) which was statistically significant. These findings were similar to other study conducted by Venkatesh G. The decrease in TP interval may be due to the presence of increase in heart rate.[44]

Other abnormal findings in ECG

In present study we found many other statistically significant variations. RSR' pattern in 8% of AUD patients compared to nil in comparative group. Various conduction abnormalities including RBBB was seen in various studies.[46,47] Some other ECG findings like presence of pathological Q waves, non-progressive R wave and LV Strain pattern is seen in few. Though it is statistically significant clinical significance is doubtful. May be their presence is unlikely to be different from their frequency in the general population. In our study most of the cardiac diseases are excluded. So these findings suggest that the ECG abnormalities are indicator of masked cardiac disease which may become evident later. ECG abnormalities may precede the development of myocardial impairment as suggested by Priest et al.[45]

V. Conclusion

The present study attempted to compare ECG changes in patients having alcohol use disorder with that of patients who don't have this disorder . On statistical analysis of the parameters, patients with alcohol use disorder have increased heart rate, increased blood pressure, prolonged duration and abnormal morphology of P wave, prolongation of QT and QTc interval, non specific ST and T wave changes and shortening of TP interval compared to the comparison group. These patients also had many other statistically significant variations like presence of Q waves, presence of LVH, non – progression of R wave and LV strain pattern though the clinical significance is doubtful. There was no statistically significant difference in PR interval and QRS duration.

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Serum Electrolyte Abnormalities on ECG in patients With and without Alcohol Use Disorders-A Cross sectional Comparative study

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Abstract:
Background *The burden of death and disease produced by alcohol is significant. Alcohol can cause ECG changes before the manifestations of cardiac disorders. It causes various electrolyte abnormalities. This study was undertaken with a hope of early detection of cardiovascular disease among Alcohol Use disorder (AUD) patients and preventing its complications. The basic significance of this study is it helps in counseling and convincing the patient to stop alcohol. Present study is aimed to assess the impact of duration of alcohol use and serum electrolyte abnormalities on ECG*
Materials and Methods*: A comparative study involving fifty AUD patients and fifty non-AUD patients satisfying the inclusion and exclusion criteria from the Psychiatry OPD and De-addiction centre till the calculated sample size was attained. After taking an informed consent and bio data, history of duration of alcoholism was recorded in a proforma. ECG was taken and the parameters were noted. Three ml of blood was collected from study subjects and serum electrolyte estimation was done in fully automated analyzer. Data was entered into excel sheet analyzed using SPSS version 21 software.*
Results*: There was no significant relation between duration of alcohol use and ECG changes. Serum sodium level showed a positive relation with P wave morphology, serum calcium level showed positive relation with QTc and serum magnesium showed a positive association with ST segment changes*
Conclusion: *A regular monitoring of AUD patients with ECG and other haematological parameters helps in early detection of cardiovascular disease so that remedial measures can be adopted early and can reduce the associated mortality and morbidity in the long term.*
Key Word*: Serum electrolytes, Alcohol Use Disorder, Electrocardiogram, Duration of alcohol use.*

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I. Introduction

Alcohol has been implicated in the burden of multiple diseases predominantly diabetes mellitus, cardiovascular disorders, GIT problems, epilepsy and other neuro-psychiatric disorders. It is also responsible for the major fraction of injuries due to accidents.

Alcohol use disorder (AUD) is a common disorder characterized by withdrawal, tolerance, craving, failure to fulfill major role at work, having persistent social or interpersonal problems, use in those situations in which it is physically hazardous etc.

DSM – 5 criteria: In May 2013, the American Psychiatric Association has issued 5th edition of the Diagnostic and Statistical Manual of Mental Disorders[2] (DSM–5).

DSM – 5 criteria combined the two DSM–4 disorders, alcohol abuse and alcohol dependence, into a single disorder called Alcohol Use Disorder (AUD) with mild, moderate, and severe sub-classifications.

The presence of 2 of these symptoms indicates an Alcohol Use Disorder (AUD).

The severity of the AUD is defined as:

Mild: The presence of 2 to 3 symptoms.

Moderate: The presence of 4 to 5 symptoms.

Severe: The presence of 6 or more symptoms

The prevalence of alcohol dependence among males in Thiruvananthapuram district is 38.4% [1] .It has been observed that prolongation of QT interval and non-specific ST and T changes are frequent in ECG of patients with chronic alcoholic use disorder. Most of the ST-T changes in chronic alcoholic use may be a manifestation of associated electrolyte abnormalities[10]Abnormalities of potassium[3] calcium [4] magnesium[6] are usually observed in patients with chronic alcohol use and these may lead to ECG changes. Alcohol impair the contractile function

of heart by interfering with the calcium uptake and binding by sarcoplasmic reticulum. Prolongation of QT interval may be due to the abnormality in serum calcium level[5]

Alcohol abuse is a pattern of drinking which cause damage to the physical, mental and social wellbeing of the patients and also to those around them. It is having a strong relation with hypertension and the prevalence is 50150% higher in heavy alcohol uses.[16]This is usually a transient hypertension and becomes normal, few days after withdrawal. The interaction between various electrolytes has been described to have a role in the generation of hypertension[7]

Therefore a regular monitoring of AUD patients with ECG along with other haematological parameters could be a step in early detection of cardiovascular disease so that remedial measures can be adopted, ultimately reducing the associated mortality and morbidity in the long term.

Primary objective

- To study the association of duration of alcohol use and ECG changes.
- To assess the serum electrolytes (serum sodium, potassium, calcium, magnesium) level and its association with ECG changes in patients having Alcohol Use Disorder.

II. Material And Methods

This study was conducted in the Department of Psychiatry, Government Medical College, Thiruvananthapuram. The subjects participating in this study were chosen from AUD patients attending consecutively in the OPD of Psychiatry and De-Addiction center, Government Medical College, Thiruvananthapuram. Fifty AUD patients and fifty non AUD patients satisfying the inclusion and exclusion criteria were recruited till the sample size was attained. After taking an informed consent and bio data of each subject were recorded using a proforma. Under aseptic precautions, 3ml of blood was collected for examination.

Study design

Comparative Cross Sectional Study.

Study setting

OPD of Psychiatry and De-addiction centre, Government Medical College, Thiruvananthapuram.

Study population

Patients having Alcohol Use Disorder confining to DSM-5 criteria.

Comparative group

Other patients without Alcohol Use Disorder attending the OPD are selected as comparative group.

Study subjects

Exclusion criteria:

- Known case of diabetes mellitus, hypertension, coronary artery disease and other heart disease.
- Subjects on any long-term drugs that can cause ECG changes.
- Those who are not willing to give consent.

Sample size

Sample size is calculated using the formula:

$n = 2 \times \{ Z_{(1-\alpha/2)} + Z_{(1-\beta)} \}^2 \times \sigma^2$

Therefore a sample size of 50 was decided upon for each group

Sampling technique

Consecutive patients attending OPD of Psychiatry and de-addiction centre, Government Medical College, Thiruvananthapuram fulfilling study criteria is enrolled for the study.

Duration of study

1 year.

Study variables

- Duration of alcohol use.
- ECG parameters: Heart rate, P wave, PR intervals, QRS complex, ST segment, QTC interval, QT interval, T wave.

3. Serum electrolytes (sodium, potassium, calcium, magnesium).

Normal range: Sodium: 135-145 mmol/L[8]

: Potassium: 3.6-5 mmol/L[8]

: Calcium: 8.5-10.5 mg/dl[8]

: Magnesium: 1.82-2.43 mg/dl[8]

Data collection tool
Structured proforma was used to collect the clinical history and to confirm the diagnosis..

Recording of ECG
CARDIART 6108 T is the electrocardiograph machine used to record the ECG of both the cases and controls. Twelve lead ECG was recorded by using a standardised ECG machine.

Serum electrolytes (Na, K, Ca, Mg)
Serum sodium and potassium ions estimation done by Ion selective electrode method, serum magnesium estimation done using End point method and serum calcium estimation was done using Arzenazo III method in the Central lab, Department of Biochemistry, Government Medical College, Thiruvananthapuram.

Data collection technique
Ethical clearance was obtained. Patients coming to study settings before the administration of any drugs and confining to the inclusion and exclusion criteria was assessed for ECG changes. The purpose and Nature of the study was explained in detail. Informed consent was obtained. The information about the history was collected using a Proforma.

III. Procedure Methodology

Estimation of serum electrolyte
Under aseptic precautions 3ml of blood was collected for doing the serum electrolyte estimation. The blood was immediately centrifuged and serum was used for estimation of electrolytes. The estimation was done using fully automated analyser Beckmann Coulter AU 680.Caliberation of the machine for doing calcium and magnesium was done using system calibrator.

Statistical analysis

Analysis
- Data was entered in to Microsoft Excel data sheet.
- Quantitative variables were expressed as mean and standard deviation and qualitative variables were expressed as percentage.
- Statistical test of significance: Comparison of quantitative variables analysed using unpaired t test. Comparison of qualitative variables analysed using chi square test. Statistical test of significance for non-parametric variables include Mann-Whitney U test and Kruskal Wallis test.
- A P value of <0.05 was considered statistically significant and a P value <0.01 was considered very significant.
- Analysis of data done using appropriate statistical software SPSS version 21.

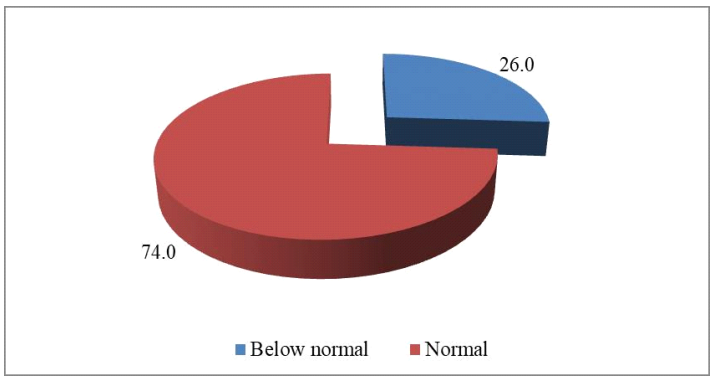
Ethical considerations
- Institutional Ethics Committee clearance was obtained.
- Informed consent obtained from the participants.
- Confidentiality was ensured and maintained throughout the study.
- No expenses were incurred from the patients.

IV. Results

This study was conducted with a view to compare the changes in ECG parameters associated with Alcohol Use Disorder patients with other non AUD patients attending study setting.

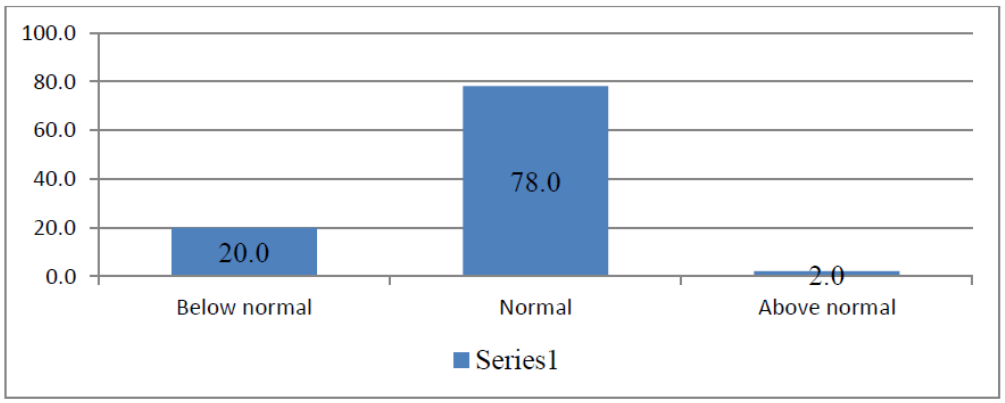
Serum electrolytes among patients with alcohol use disorder
Serum electrolyte was estimated in patients with alcohol use disorder. The association of ECG changes with the serum electrolytes was later compared. Also the changes in ECG parameters were compared with the duration of alcohol use.

- **Percentage distribution of the sample according to level of serum sodium (Fig. I)**



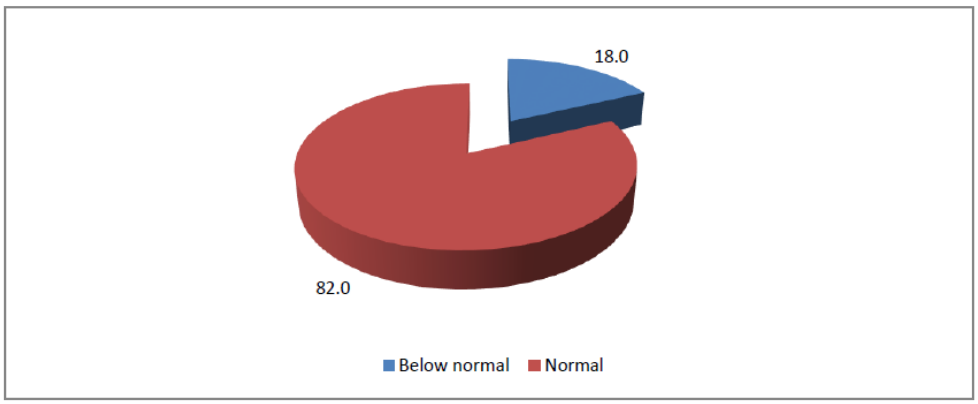
Among the patients assessed the mean serum sodium level was found to be 135.9(SD=2). 26% (N=13) of the subject had a value below normal and 74 % (N=37) of the subject had normal value.

Percentage distribution of the sample according to level of serum potassium (Fig 2)



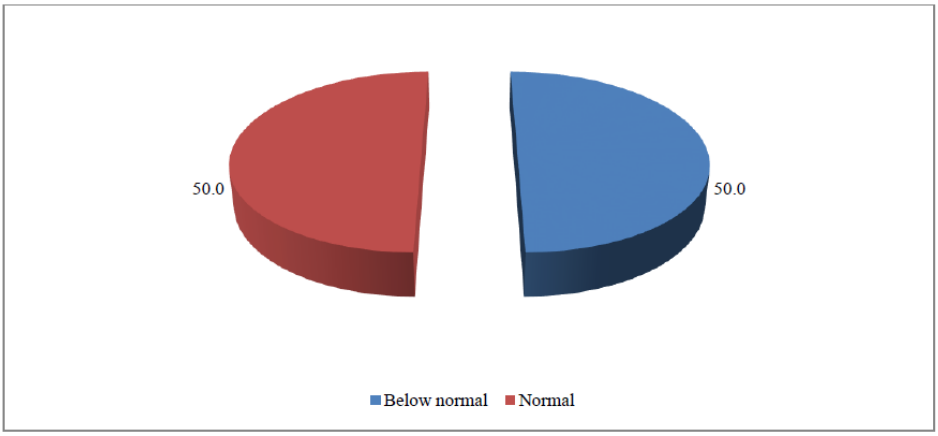
Among the study subjects the mean value of serum potassium obtained was 3.9(SD=0.5) .78% (N=39) of the subject had normal value .Only 20% (N=10) of the subject had values below normal. 2% (N=1) had values above normal.

- **Percentage distribution of the sample according to level of serum calcium (Fig 3)**



The mean value of serum calcium obtained in AUD patients was found to be 9.1(SD= 0.6). 82% (N=41) of them had normal value and 18 % (N=9) had a value lower than normal.

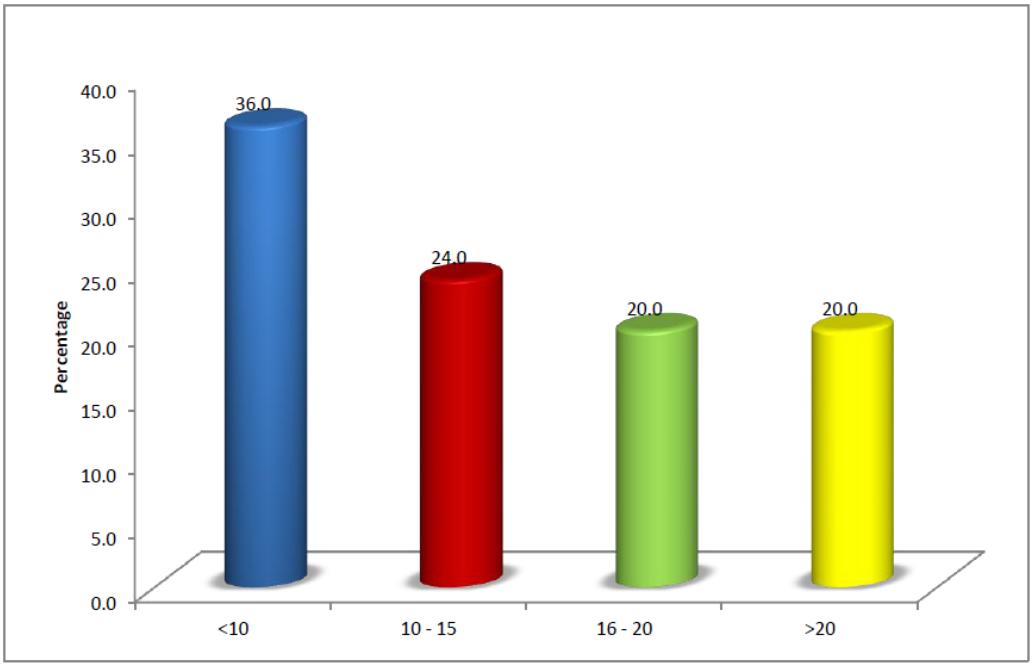
- **Percentage distribution of the sample according to level of serum Magnesium.(Fig 4)**



The mean value obtained among alcoholic patients was 1.8 (SD=0.3).The percentage distribution was 50:50, that is 50 % (N=25) of the patients had a value below normal and another 50% (N=25) had normal value.

B. Association of duration of alcohol use and ECG changes

1 Percentage distribution of the sample according to duration of alcohol use (Fig: 5)



To find out the association between duration of alcohol and ECG changes in AUD patients were classified into four groups . Not statistically significant.(P value =0.364).

2. Association of heart rate with duration of alcohol use

There is no significant relation between duration of alcohol use and heart rate. Here the r value is 0.027 and P value is 0.854 that is the change in heart rate is independent of the duration of alcohol use.

- **Comparison of T Wave based on duration of alcohol use (Table II)**

T Wave	<=15		>15		^{2}	P
	Count	Percent	Count	Percent		
Normal	27	90.0	17	85.0	3.41	0.182
Tall wave	2	6.7	0	0.0		
Inverted T wave	1	3.3	3	15.0		

Not statistically significant. (P value =0.182).

C. Association of serum electrolytes with ECG changes among alcohol use disorder (AUD) patients

- **Potassium with ECG changes among AUD patients**

Table iii: Association of Potassium with ST segment among alcohol use disorder patients.

ST segment	Mean ± SD	Median	^{2}$	P
Normal	3.9 ± 0.5	3.8	0.37	0.831
Elevated	3.8 ± 0.3	4.0		
Depressed	3.6 ± 0.5	3.9		

$ Kruskal Wallis Test-The association was not statistically significant.

B. Potassium and T wave

Table iv: Association of Potassium with T wave among alcohol use disorder patients

T wave	Mean ± SD	Median	^{2}$	P
Normal	3.9 ± 0.5	3.8	0.77	0.681
Tall wave	3.8 ± 0.1	3.8		
Inverted T wave	3.9 ± 0.2	3.9		

$ Kruskal Wallis Test not significant

C.Potassium and QTc in AUD patients

There is no significant relation between the serum potassium and corrected QT interval. Here the r value is -0.109 and P value is 0.450.

2. Association of serum Calcium level and ECG changes

A. Calcium and QTc (Fig :5)

r = -0.358*, p = 0.011 *: - Significant at 0.05 level

It was observed that as the value of calcium decreases there is an increased duration of QTc interval.

3. Association of S. Magnesium with ECG changes in AUD patients.

Table v. Serum magnesium and ST segment in AUD patients

• ST segment	Mean ± SD	Median	^{2}$	P
Normal	1.9 ± 0.3	1.9	6.74*	0.034
Elevated	1.9 ± 0.2	2.0		
Depressed	1.3 ± 0.3	1.3		

B. Serum Magnesium and T wave

Table vi : Association of magnesium with T wave among Alcohol Use Disorder patients

T wave	Mean ± SD	Median	^{2}$	P
Normal	1.8 ± 0.3	1.9	4.73	0.094
Tall wave	2 ± 0.5	2.0		
Inverted T wave	1.6 ± 0.1	1.5		

$ KruskWallis Test not significant *: -

C. Serum magnesium with corrected QT interval

Not significant

4. Association of serum sodium with ecg changes

A. Serum sodium and morphology of P wave

Table vii : Comparison of level of serum sodium based on Morphology of P wave in lead II

Level of serum sodium	Normal		Abnormal		^{2}	p
	Count	Percent	Count	Percent		
Below normal	10	21.7	3	75.0	5.43*	0.020
Normal	36	78.3	1	25.0		

*: - Significant at 0.05 level

B. Serum sodium and T wave

Table viii : Comparison of level of serum sodium based on T Wave

Level of serum sodium	Normal		Tall wave		Inverted T wave		^{2}	P
	Count	Percent	Count	Percent	Count	Percent		
Below normal	12	27.3	1	50.0	0	0.0	2.04	0.360
Normal	32	72.7	1	50.0	4	100.0		

No significant relation

C. Serum sodium and QRS complex

r = 0.104, p = 0.470 not significant

V. Discussion

The present study was conducted in a view to compare the ECG parameters of the patients with alcohol use disorder to those who do not have this disorder. Alcohol use is a socio psycho economic burden to economically lower strata of people in Kerala as elsewhere. Alcohol use has got complex effects on cardiovascular functioning. One of the most important acute effect of alcohol on heart is the weakening of myocardium (negative inotropic effect).This can later lead to irregular and ineffective contractions of myocardium with very fast heart rate called as tachyarrhythmia [9.]

Duration of alcohol use and electrocardiogram

In the present study the effect of duration of alcohol use on ECG parameters (heart rate, ST segment and T wave) was also done. Among the patients who had history of alcohol use of less than 15 years, 93% of them had normal ST segment and 90 % had normal T wave. 3.3 % had ST elevation and another 3.3 % had ST segment depression. 6.7% had tall T wave and 3.3 % had inverted T wave. While in patients with greater than 15 years of alcohol consumption 80% had normal ST segment, 10 % had elevated ST .wave. The heart rate was persistently elevated in both the age groups. However the findings are not statistically significant.

Sinus tachycardia and non -specific ST-T wave changes were common in patients with increased duration of alcohol use. Greater the duration of alcohol use greater will be the cardiovascular risk [10,11,12] .

Effect of serum calcium level on ECG changes

In the present study 18% of the subjects were having low serum calcium level. The mean value obtained was 9.1±0.6. Several studies have shown that hypocalcaemia is one of the common electrolyte abnormality found in patients with chronic alcohol use [13]. One of the reason for hypocalcaemia is that patients with alcohol use are having high values of calcium fractional excretion than normal. Ethanol also decreases the activity of Na^+-K^+ ATPase pump and decreases tubular absorption of Calcium [14.] Hypomagnesaemia along with suppressed secretion of parathyroid hormone results in further decreased calcium absorption in these patients [15,16.] Respiratory alkalosis in these patients results in parathyroid resistance leading to hypercalciuria which further leads to hypocalcaemia [17.]

The hypocalcaemia may contribute to the ECG changes in alcoholics. In the present study the relation of QTc prolongation with serum calcium was analysed and found out that QTc prolongation is associated with low serum calcium levels. This was similar to many other studies, [19,18] . Some studies have proved that severe hypocalcemia can be seen in chronic alcoholics and this causes QTc prolongation [20,21] QTc reflects impaired ventricular conduction [22] .

Effect of serum magnesium level on ECG changes

50% of our study population had hypomagnesaemia. One of the causes of hypomagnesaemia related to decreased magnesium intake is alcoholic dependence. Alcohol withdrawal syndrome causes redistribution of magnesium from extracellular to intracellular space. Proposed causes of increased magnesium entry into the cells were a) respiratory alkalosis b) excessive catecholamine release during alcohol withdrawal. Exogenous catecholamine also causes significant intracellular magnesium shift. Another reason is spurious that lipolysis in alcohol withdrawal causes mobilisation of FFA which binds magnesium and precipitate hypomagnesaemia. Gastro intestinal loss is another reason [23,24]

Another cause may be due to direct diuretic effect of ethanol [25]. Recently a study suggested nearly 21% of chronic alcoholics have hypomagnesaemia due to reversible tubular defect [26]. Transient hypoparathyroidism was reported as one of the cause for hypomagnesaemia during alcohol intoxication [16].

Clinical manifestation of magnesium depletion causes widening of QRS complex, prolongation of PR interval, inversion of T wave, U waves sensitivity to digitalis and digoxin and predisposition to various arrhythmias. Hypomagnesaemia is usually associated with hypophosphatemia, hypokalemia and hypocalcaemia. Significant ECG changes in our study were ST depression and T wave inversion. Statistically significant ST

depression is noted when magnesium is less than 1.3 mg/dl. T wave inversion was found when magnesium value is less than 1.6mg/dl. Corrected QT interval was prolonged but there was no statistically significant association with hypomagnesaemia.

Seeling compared the electrocardiographic patterns of magnesium depletion appearing in alcoholic heart disease. Magnesium plays a significant role in maintaining myocardial integrity. Magnesium depletion leads to disruption of the myocardium at cellular level and mitochondria. Serum level of magnesium is not a reliable indicator of muscle magnesium. Hence ECG changes with serum magnesium gives a better idea about myocardial injury. Though ECG improvement after magnesium therapy is not done in our study, many study showed in improvement [28,29].

Tachycardia and other ECG changes resembling those of hypokalaemia or with only primary ST changes have been reported by Flink and collaboraters [30,31].

Effect of serum potassium level on ECG changes

Twenty percentages of our subjects were having potassium values below normal. Most common sign of chronic alcohol consumption include precipitous decrease in plasma concentration of Phosphate , Magnesium, Potassium and chloride within first 24 to 36 hours after admission[34].Fifty percentage of population with alcohol use disorder will develop hypokalemia[33,34] Similar to any other electrolyte abnormalities potassium deficit also occurs due to decreased intake and gastrointestinal loss. Another cause is that there will be increased urinary loss of potassium. If the patient is having clinical symptoms like vomiting and ketoacidosis, there will be increased loss of urinary potassium due to coupling of increased mineralocorticoid levels and increased delivery of sodium to distal nephron. Coexisting magnesium deficiency also increase the chance of hypokalemia[34]There is increased insulin secretion in these patients which leads to intracellular shift of potassium. Another proposed mechanism of hypokalaemia in alcoholics is the autonomic hyperactivity and development of respiratory alkalosis[35].

Normally at a value of 3.5 meq /L there will be ST segment depression and prominent U wave will be present immediately after T wave resulting in a falsely prolonged QT interval. At a value of 2.5 meq/L PR interval will be prolonged, ST segment is depressed and T wave is inverted. QT interval remains normal. The mean value of potassium in our study was 3.9±0.5 meq/L. There was no statistically significant relation between the serum potassium and ECG findings

Effect of serum sodium level on ECG changes

In the present study 26% of the subjects were having hyponatremia (N=50). Hyponatremia is common among alcoholics. In another study by Liami 17.3% of their subjects were having hyponatremia related to alcohol use and it is the third common electrolyte abnormality[37].

In patients with AUD there will be hypertriglyceridemia and there will be marked increase in the non-aqueous phase of plasma which results in pseudohyponatremia due to fall in sodium concentration when compared to total volume[38] Another cause for hyponatremia is hypovolemia which will stimulate ADH secretion resulting in increased water intake and water retention[39]. In those who had excess consumption of beer , there will be decreased excretion of free water due to decreased excretion of urinary solutes[40]. This results in dilutional hyponatremia. SIADH and Cerebral salt wasting syndrome which are alcohol induced are other reasons for hyponatremia[41,42]

In present study 23 % of patients with hyponatremia in alcoholics had abnormal P waves which were statistically significant. Hyponatremia is one of the dyselectrolemia which have the least ecg changes. Hyponatremia decreases phase zero of the action potential[43]. P wave alternans was reported in a case of hyponatremia. In that study they further concluded that fluctuating P wave morphology should raise suspicion about biochemical or other derangement[44]. Other ECG changes in the present study did not show any statistically significant correlation with hyponatremia.

VI. Conclusion

The present study reveals the effect of duration of alcohol use and the electrolyte derangement on the ECG changes in patients with and without AUD

There was no significant relation between duration of alcohol use and ECG changes though NSST changes are more in those with greater duration of alcohol use. Serum sodium level showed a positive relation with P wave morphology. Serum calcium level showed positive relation with QTc .Serum magnesium showed a positive association with ST segment changes. No significant relation was seen in Potassium with ST segment, T wave and QTc, Magnesium with T wave and QTc and Sodium with QRS and T wave.

From the above findings it is concluded that there are significant ECG changes in patients with Alcohol Use Disorder compared to comparative group. This could be due to the direct effect of ethanol on heart or due to

underlying electrolyte abnormality .This indicates that patients with AUD are at higher risk of cardiovascular disease. Earlier detection of ECG changes can prevent cardiovascular morbidity.

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There are no conflicts of interest for this study

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