



A STUDY OF PLASMA HOMOCYSTEINE LEVELS AND ELECTROCARDIOGRAPH FINDINGS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITHOUT CARDIOVASCULAR SYMPTOMS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background & objectives: our aim is to study the plasma homocysteine levels and ECG findings in patients with Type-2 Diabetes Mellitus without cardiovascular symptoms in a tertiary care Hospital. Our objective is to estimate FBS, PLBS, HbA1c and Lipid profile, to correlate the ECG changes with biochemical parameters, to correlate levels of plasma homocysteine with Lipid profile and HbA1c and ECG changes. **Methods & materials:** It is a Hospital-based cross sectional study conducted in 163 patients with Type-2 Diabetes Mellitus in medical wards of Sri Venkateswara medical College, Tirupati for a period of 1 year. Detailed History and physical examination are done on every patient, performed various investigations such as Fasting and post prandial blood sugar, serum creatinine, Lipid profile, plasma Homocysteine and ECG (12-Lead), ECG normal and abnormal changes and any other changes to detect signs of myocardial infarction in abnormal patients. **Results:** Most common age group is 60-69 years and most comprised in males. There is significant difference in gender wise and age wise distribution with duration of Diabetes, Cholesterol and triglycerides levels were normal in patients, most common ECG findings are T-inversions followed by LVH and ST-segment changes are recorded. Significant association between ECG with HbA1c, cholesterol, triglycerides and plasma homocysteine. **Interpretations and conclusions:** Our study concluded that plasma Homocysteine is an independent cardiovascular risk factor in diabetes patients, Diabetes patients with high HbA1c and plasma homocysteine levels are at greater risk of silent cardiac events and plasma homocysteine can be used as a surrogate marker in addition to ECG to screen for cardiac changes in diabetic patients.

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INTRODUCTION

Diabetes mellitus is gaining importance some of the most, if not probably the most, critical non-communicable diseases worldwide. Diabetes mellitus is the most familiar endocrine disease affecting humanity. Globally, Diabetes Mellitus is a significant threat to human health by 2003, it was estimated that approximately 194 million people had diabetes, and this figure is expected to rise to almost 350 million by 2025.

The prevalence in India varies from 1.7 to 9.6 % in various studies. A multi-center research done by the Indian council of medical research showed a prevalence of 1.73 percent in Indians above 15 years of age. The spectrum of fasting (FPG) and the response to an oral glucose load (OGTT-oral glucose tolerance test) varies among normal individuals. Symptoms of diabetes plus random blood glucose concentration $>200\text{mg/dl}^a$ or, Fasting plasma glucose $>126\text{mg/dl}^b$ or, Two-hour plasma glucose $\geq 200\text{mg/dl}$ during an oral glucose tolerance test¹. Autonomic dysfunction in diabetes is common.

Abnormal cardiovascular test suggesting cardiovascular autonomic neuropathy is present in 16-40% of the diabetic

population. Patients with diabetic cardiac autonomic neuropathy are more prone to sudden cardiac death, probably due to silent myocardial ischemia or infarction or due to primary malignant ventricular arrhythmias.

The ECG, which reflects the heart's electrical activity, can show abnormalities in people with diabetes more often than in non-diabetics. The more attendant factors are more common only seen in people with diabetes. In this context, the factors that modify impulse generation, conduction, nervous control of the heart, vascular supply of the myocardium, state of the myocardium, all required to be considered individually.

There is a higher prevalence of RBBB and AV block in diabetics that cannot be accounted for by the increased incidence of ischemic heart disease alone. A higher incidence of these blocks is seen independent of ischemic heart disease. Recent observations noted that corrected QT interval (QTc) in surface ECG seems prolonged in people with diabetes with autonomic neuropathy. Postulations are made that it may be one of the causes of sudden death or a compounding factor for malignant ventricular arrhythmias' predisposition. This high

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lights the importance of simple, non invasive investigations like ECG in diagnosing asymptomatic cardiac autonomic dysfunction.

Hyper homocysteinemia has received increasing attention during the past decade and has joined smoking, dyslipidemia, hypertension, and obesity as an independent risk factor for cardiovascular disease.

Besides, elevated homocysteine levels have been implicated in several other clinical conditions, including renal failure, rheumatoid arthritis, alcoholism, osteoporosis, neuropsychiatric disorders, diabetes mellitus, and complications of diabetes.

Observations inpatients with homocysteinemia led to the notion that total homocysteine (tHcy) may be involved in atherosclerosis's pathogenesis. This concept prompted many epidemiological studies that assessed the relation between moderately elevated tHcy levels and coronary artery disease.

METHODS AND MATERIALS

It is a Hospital-based cross sectional study conducted in 163 patients with Type-2 Diabetes Mellitus in medical wards of Sri Venkateswara medical College, Tirupati for a period of 1 year from the date of the ethical committee approval (16/2/2019 – 15/2/2020). Detailed History and physical examination are done on every patient, performed various investigations such as Fasting and post prandial blood sugar, serum creatinine, Lipid profile, plasma Homocysteine and ECG (12-Lead). The following ECG abnormalities were explicitly looked for: ST-segment elevation or depression, T-wave aberrations (inversion or tall T-wave), bundle branch block, LVH, arrhythmias, prolonged QT, and other changes to detect signs of myocardial ischemia in asymptomatic patients.

Inclusion criteria: Patients of Type 2 diabetes mellitus without cardiovascular complaints, patients who are willing to give valid informed written consent, patients who are above 30 years of age.

Exclusion criteria: Type 2 Diabetes mellitus with concomitant diseases or conditions affecting lipid levels like chronic liver disease and hypothyroidism.

RESULTS

Table I Demographic characteristics of the study participants (n=163)

Variable	Categories	Number	Percentage
Age	30-39 years	14	8.6%
	40-49 years	31	19.0%
	50-59 years	26	16.0%
	60-69 years	55	33.7%
	>=70 years	37	22.7%
Gender	Male	113	69.3%
	Female	50	30.7%

Nearly 34% of the study participants were aged between 60-69 years age group. The gender-wise distribution shows 69.3% were male.

Table II Blood Sugar levels among the study participants (n=163)

Variable	Category	Number	Percentage
Fasting Blood Sugar	Normal	12	7.4%
	Elevated	151	92.6%
Post-Prandial Blood Sugar	Normal	4	2.5%
	Elevated	159	97.5%
HbA1c	Normal	22	13.5%
	Elevated	141	86.5%

Blood sugar levels Normal levels 7.4 % subject in FBS, 2.5% subject in PPBS and 13.5% participants had normal in HbA1c, whereas in elevated levels 92.6 % comprises of FBS, 97.5% comprises of PPBS and 86.5% participants had elevated in HbA1c.

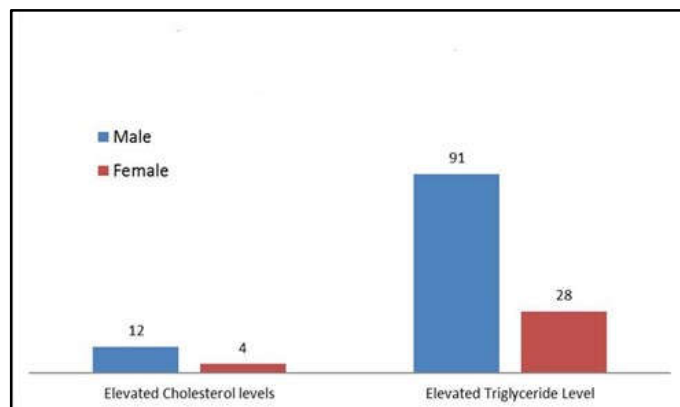


Figure 1 Gender wise distribution of serum lipid levels (n=163)

Males comprises of 12% in elevated cholesterol levels and 91% in elevated triglycerides levels whereas in females 4% comprises of elevated cholesterol levels and 28% in elevated triglycerides levels.

Table III Description of the ECG findings in the study participants (n=163)

ECG findings	Number	Percentage
Normal	27	16.60%
Tinversions	41	25.10%
LVH	23	14.10%
STchanges	23	14.10%
QS complex	17	10.40%
RBBB/LBBB	14	8.60%
QT prolongation	12	7.30%
SinusTachycardia	11	6.70%
AVHRT/AVRT	5	3.10%

The commonest abnormality was T wave inversion, which was present in 25.1% of the participant's Electro car diogram. In 6.1% of the patients had more than one abnormal finding in their electro cardiogram.

There was no significant difference in the occurrence of abnormal ECG findings between males and females (p=0.743). As the age increases, the occurrence of abnormal ECG findings also increased, but this change was not statistically significant in our study between males and females (p=0.200). Cardiac abnormality was common in 1-5 years group and more than 10 years from the first diagnosis of Diabetes Mellitus. This difference was not statistically significant in our study population (p=0.807).

Table IV Association of abnormal ECG with Serum HbA1c levels in the study patients :(n=163)

Categories	Abnormal ECG	Normal ECG	p-value (Chi-Square test)
Serum HbA1c levels	Elevated	121 (85.8%)	20 (14.2%)
	Normal	15 (68.2%)	7 (31.8%)
			0.039*

Elevated Serum HbA1c levels were significantly associated with a higher risk of abnormal ECG findings. This risk was found to be 2.82 times with 95% C.I. of 1.02 – 7.79 times (p < 0.05 level).

Table V Association of abnormal ECG with serum cholesterol in the study patients :(n=163) (Fisher Exact test)

Categories		Abnormal ECG	Normal ECG	P-value+
Serum Cholesterol Levels	Elevated	16 (100%)	0	0.047*
	Normal	120 (81.6%)	27 (18.4%)	

Elevated Serum Cholesterol levels were significantly associated with a higher risk of abnormal ECG findings (p <0.05 level).

Table VI Association of abnormal ECG with serum triglycerides in the study patients: (n=163)

Categories		Abnormal ECG	Normal ECG	P-value (Chi-Squaretest)
Serum Triglycerides level	Elevated	106 (89.1%)	13 (10.9%)	0.001**
	Normal	30 (68.2%)	14 (31.8%)	

Elevated Serum Triglycerides levels were significantly associated with higher risk of abnormal ECG findings. This risk was found to be 3.81 times with 95% C.I. of 1.62–8.96 times (p <0.01level).

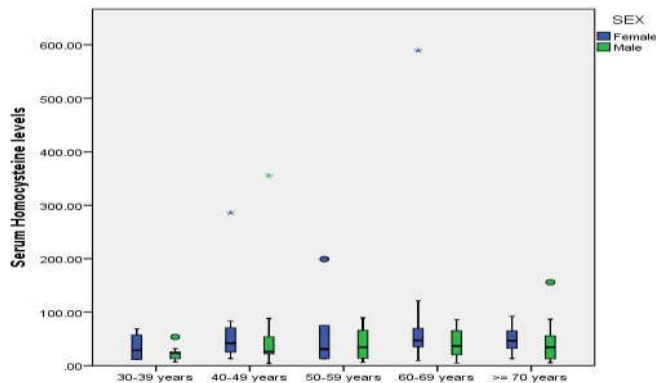


Figure II Gender and age-wise distribution of Homocysteine levels (N=163)

There is no statistical significant with gender and age wise distribution of homocysteine levels and also with duration of diabetes mellitus and hbA1c levels. Among total 19.6% of the participants had normal homocysteine levels.

Table VII Association of Elevated Serum Homocysteine levels with ECG findings in the study patients :(n=163)

Categories		Elevated Serum Homocysteine levels	Normal Serum Homocysteine levels	p-value (Chi Squaretest)
ECG Findings	Abnormal	122 (89.7%)	14 (10.3%)	<0.001***
	Normal	9 (33.3%)	18 (66.7%)	

The higher the Homocysteine values, the greater were the chances of abnormal ECG findings (p<0.001level).The level was 17.43 times higher, with the 95% Confidence interval (C.I) ranging from 6.59 times to 46.10 times. This risk was also statistically significant when the values were adjusted for age, gender, and duration since the first diagnosis, HbA1c level, and lipid levels. This is depicted in Table 17. The adjusted ODDs ratio was found to be 17.97(95% C.I= 6.01–53.73).

DISCUSSION

Diabetes is a significant risk factor for cardiovascular disease. It is associated with premature atherosclerosis due to endothelial vasomotor dysfunction, effects of advance glycation products, adverse effects of circulating free fatty acids, and increased systemic inflammation. These commonly present like coronary artery disease, chronic heart failure, or arrhythmias due to diabetic cardiomyopathy.

In the current study of 163 subjects the mean age was 58.42 years. The Least age group was 30 years and highest age group was 81 years and majority of subjects being in the age group of 60-69 years and followed by >70 years. When compared with similar studies conducted by SahilGupta^{et al.}², Avinash^{et al.}³, and Bendigeri^{et al.}⁴ showed a mean age group of 50 years, 61 years, and 53years respectively.

Male predominance with Diabetes mellitus is more, in our study gender distribution among subjects in which male subjects comprised of 69.3% were females accounted for 30.7 % compared with cross sectional study by Gupta *et al.*² showed a similar male preponderance of 62%.

Duration of diabetes mellitus among participants majority of subject come under the group of 1-5 years (36.2%), 31.9% in 6-10 years and 20.2 % subject had long lasting diabetes with duration of >10years. There is no significant correlation of duration of diabetes with age and gender. This can also be explained by the fact that diabetes is a significant cause of morbidity as age increases.

Blood glucose levels such as FBS, PLBS and HbA1c with mean values of FBS of 150.14±37.93mg/dl, mean PPBS of 206.66±56.82mg/dl and mean HbA1c of 6.92±1.28%. The higher the values indicates poor glycemic control in patients due to insufficient pancreatic stores of insulin, decreased physical activity, decreased peripheral glucose utilization and age on in cretin release can contribute to the above observation which correlates with similar studies conducted by Broughton^{et al.}⁵, Shimokata^{et al.}⁶, Muller^{et al.}⁷, and Zavaroni^{et al.}⁸.

Lipid levels while estimating it was found that 90% of the study participants had normal serum levels of cholesterol in contrast to serum triglyceride levels where only 27% of the subjects had values in the normal range. Males had higher serum cholesterol levels than females. There is no significant correlation with distribution of lipids with age and gender.

In the present study conducted among 163 asymptomatic diabetic patients, 27% of them had a normal ECG while the rest had one ECG abnormality or the other. In another cross-sectional study conducted by Seller *et al.*¹⁰ In 635 African-American diabetic patients, the most common ECG finding was isolated ST- Tab normalities in 23% of their study group, followed by poor R wave progression, incomplete LBBB, and left axis deviation. In the current study, among the 136 subjects with abnormal ECG changes, 95 were males and the rest females. There is no statistically significant between ECG with age and gender. Similar findings were observed in studies conducted by Khane *et al.*¹², Campbell *et al.*¹³, and Mihalick *et al.*¹⁴.

In the present study, a maximum number of patients with abnormal ECG findings had a disease duration of 1-5years, followed by the duration group of 6-10 years. This indirectly implies that as the duration of diabetes increases, the number of patients with abnormal ECG findings also increased, and it was statistically significant. Similar observations were made by Gupta *et al.*² and DeSantiago *et al.*¹¹, where they demonstrated that the number of people with a long duration of diabetes had increased cardiovascular events.

Our study shows that the number of patients who had abnormal ECG changes had higher HbA1c levels, which was significant statistically (p-value: 0.039). Studies conducted by Padmaja Desai *et al.*¹⁵ correlates with our above observation of ECG

significantly correlating with HbA1c levels. Studies conducted by Nathan *et al.*¹⁶ and Khaw *et al.*¹⁷ underline the importance of HbA1c levels in predicting future adverse cardiovascular events.

Our present study shows that abnormal findings on ECG correlated significantly with derangements in lipid profile, including values of serum cholesterol (p-value:0.047) and serum triglycerides (p-value:0.001). Similar studies on the relationship of lipid profile with ECG done by Soliman *et al.*¹⁸, Das *et al.*¹⁹, and Mukhopadhyay *et al.*²⁰.

On measuring the plasma homocysteine levels in 163 diabetic patients in our study, it was found that the mean homocysteine level was $48.38 \pm 60.41 \mu\text{mol/L}$. It was significantly raised compared to the normal upper cut off value of $13.9 \mu\text{mol/L}$. Similar raised mean values of serum homocysteine levels were observed in studies conducted by Bansal *et al.*⁹, Balu *et al.*²¹, Chico *et al.*²², and Hofmann *et al.*²³

Our study found that males had a higher level of homocysteine than females, but this was not statistically significant (p-value: 0.229). Similar observations were found in studies conducted on homocysteine levels in diabetic patients by Jacques *et al.*²⁴, Xu *et al.*²⁵, and Cohen *et al.*²⁶. There is no correlation between Levels of Homocysteine with age and duration of diabetes, lipid profile and with HbA1c levels.

In our present study, the plasma homocysteine levels and the occurrence of abnormal ECG findings positively and significantly correlated with each other. The p-value of <0.001 obtained using the statistical method of Chi-square test indicates that both the parameters have a highly significant statistical significance. Plasma homocysteine is considered an independent cardiovascular risk factor owing to its atherogenic and thrombogenic effects. It is proven to increase the risk of cardiovascular adverse events by 1.6 times in diabetic individuals, as noted in a study conducted by Hogeveen *et al.*²⁷. A retrospective study conducted by Leng *et al.*²⁸ on 400 patients found a positive correlation between raised plasma homocysteine levels and an increased QRS complex duration on ECG. It supports our above finding of ECG correlation with homocysteine levels.

CONCLUSION

In our study we concluded that plasma homocysteine is an independent Cardiovascular risk factor in diabetic patients, diabetic patients with high HbA1c and plasma homocysteine levels are at greater risk of silent cardiac events and plasma homocysteine can be used as a surrogate marker in addition to ECG to screen for cardiac changes in diabetic patients.

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