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Association Between Microalbuminuria and QT Interval Prolongation in Type 2 diabetes mellitus

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Abstract
Aims and objectives- To study the association between microalbuminuria and qt interval prolongation in type 2 diabetes mellitus.
Methods-This cross-sectional study with sample size 60 patients attending OP and IP in ACSR govt general hospital, Nellore in a period of 18 months mainly on patients with age group 50 years – 70 years of both males and females. simple random sampling method is used, Informed consent and ethical committee approval obtained. complete clinical examination is carried out. The investigations done are Complete blood picture, Blood urea,s. Creatinine, Complete urine exam, Urine microalbumins and ECG.
Results- There is a significant association between QTc prolongation and microalbuminuria. Hypertension longer duration of Type 2 DM, higher glycemic index, higher HbA1C levels, higher serum creatinine levels.
Conclusion: Most patients were in their 6^{th} and 7^{th} decade of life and male preponderance was noted. Higher duration of diabetes, higher age groups have increased risk of cardiac autonomic neuropathy. There is a significant association between QTc interval prolongation and microalbuminuria as evidenced by, more number of microalbuminuria cases seen with prolonged QTc interval. As duration of diabetes increases prevalence of microalbuminuria increases. 20% of peripheral neuropathy cases are associated with CAN and 20% of retinopathyare associated with CAN.

Keywords: Diabetes, HbA1c, Microalbuminuria, Creatinine,

INTRODUCTION

Type 2 DM is defined as FBS >= 126 mg/dl and PPBS > 200mg/dl and HbA1C >6.5%and oral glucose tolerance test showing 2hr plasma glucose value >200mg/dl. Diabetic nephropathy is a progressive kidney disease by the presence of albumin in urine and decreased kidney function. Diabetic nephropathy is defined as albuminuria >30mg/day or urinary albumin: creatinine ratio >30mg/gram or EGFR <60ml/minute/1.73 m^2. Microalbuminuria is defined as urinary albumin excretion rate 30-300 mg/gram.

QTc interval prolongation is a measure of ventricular depolarization. QTc interval more than 440milliseconds in males and more than 460milliseconds in females[1]. Both prolonged QTc interval and QTc dispersion are risk factors for malignant ventricular arrhythmias affecting patients' mortality. Prolonged QT interval is an independent predictor of cardiovascular mortality in Type2 DM[2].

Microalbuminuria is observed to be a strong predictor of proteinuria and chronic renal failure and cardiac autonomic neuropathy (CAN). Prolonged QTc interval is an indicator for CAN

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and high mortality[3].

MATERIALS AND METHODS:

Method of data collection- 60 cases of Type2 DM are selected from OP and IP department by using random sampling method. Informe consent is obtained from all the subjects who adhere to the inclusion and exclusion criteria. Selected patients are studied in detail by taking proper history and physical examination done. Mandatory investigations like CBP, Blood urea, serum creatinine, complete urine examination, FBS, PPBS, HbA!C and microalbumin in urine, ECG and 2D Echo are done.

Statistical Analysis-

Data entry and tabulation did use Microsoft Excel 2013 and SPSS Version16. Descriptive statistics include Mean, Standard deviation for Quantitative data, and Frequency, calculated for qualitative data. Nonparametric statistics, including the Chisquare test, were used to find the significant difference between the study variables.

Parametric statistics, including the t-test, was used to see the considerable difference between the study variables.

The P-value of <0.05 was considered statistically significant.

Inclusion criteria:

1. All type 2 Diabetes mellitus who are attending the Government General Hospital for one year.

Exclusion criteria:

1. History of MI/Angina
2.Clinical evidence of heart failure
3.Atrial fibrillation
4.Uncontrolled hypertension
5. Febrile illness
6. Urinary tract infection
7.History of intake of ACE/ARB/8NSAIDs
9.High serum calcium levels
10.Acute poor metabolic control
11. Smoking

RESULTS

Table1: Distribution based on age

Age Distribution	Frequency (%)
50 – 60	24 (40%)
61 – 70	26 (43.3%)
71 – 80	6 (10%)
81 – 90	4 (6.7%)
Total	60 (100%)
Mean ± SD	63.83 ± 8.48

The mean age of the participants was 63.83±8.48. The majority in the present study belonged to 61-70 years age group, i.e., 43.3%, 40% belonged to 50-60 years age group, 10% in71-80 years age group, 6.7% in 81 -90 years age group.

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Graph1: Distribution based on age

Table2: Distribution based on gender

Gender	Frequency (%)
Male	36 (60%)
Female	24 (40%)
Total	60 (100%)

Table 2 showed distribution based on gender, where 60% were male, and 40% were female in the present study.

Graph 2: Distribution based on gender

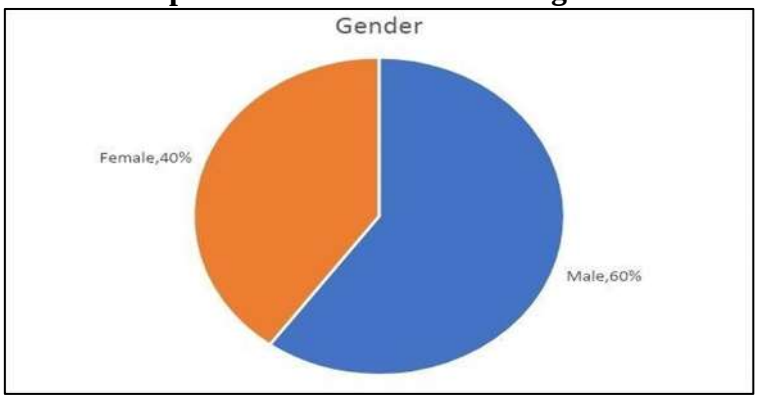

Table3: Distribution based on Family h/o Diabetes

Family h/o Diabetes	Frequency (%)
Yes	25 (41.7%)
No	35 (58.3%)
Total	60 (100%)

In the present study, 41.7% had a family history of diabetes.

Graph3: Distribution based on Family h/o Diabetes

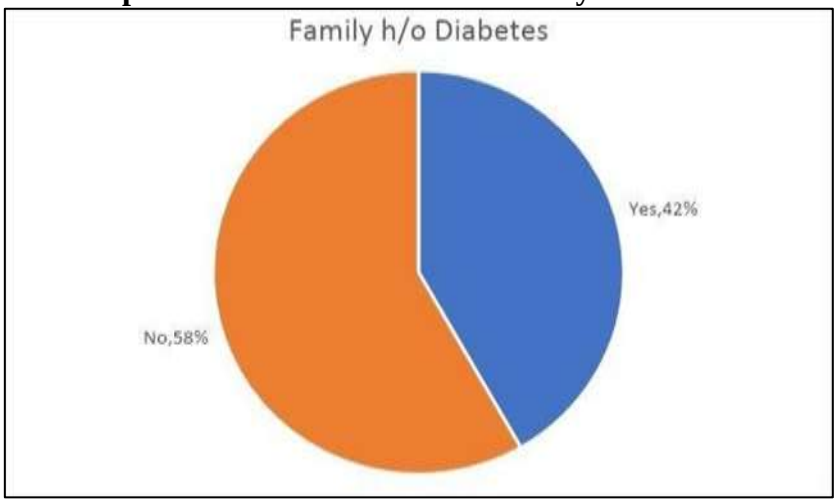

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Table4: Distribution based on the duration of diabetes

Duration of Diabetes	Frequency
5 –10	32 (53.3%)
11 –15	23 (38.3%)
>16	5 (8.3%)
Total	60 (100%)
Mean±SD	10.05 ± 3.03

Table 4 shows distribution based on the duration of diabetes where 5 - 10 years duration in 53.3%,11-15years duration in 38.3%,8.3% had a period of>16years in the present study.

The mean duration of diabetes in the present study was 10.05±3.03 years.

Graph4: Distribution based on the duration of diabetes

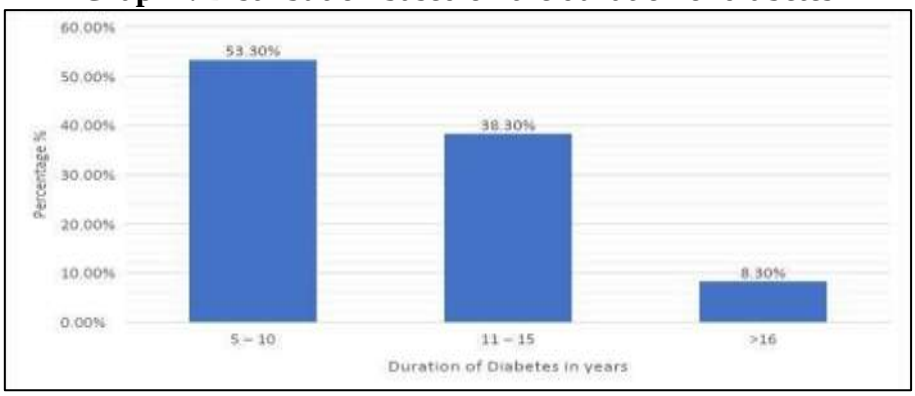

Table5: Distribution based on treatment

Treatment	Frequency (%)
Oral Hypoglycemics	25 (41.7%)
Oral Hypoglycemics +Insulin	22 (36.7%)
Insulin	13 (21.7%)
Total	60 (100%)

Table 5 shows distribution based on treatment where 41.7% of the study population were on Oral Hypoglycemics, 36.7% were on Oral Hypoglycemics and Insulin, 21.7 % were on insulin in the present study.

Graph 5: Distribution based on treatment

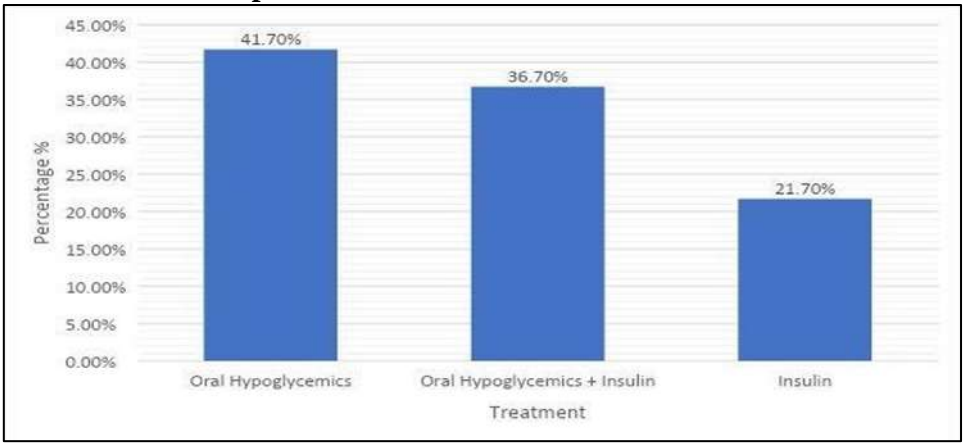

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Table 6: Distribution based on complications

Microvascular complications	Diabetic Neuropathy	16 (26.7%)
	Retinopathy	15 (25%)
	Nephropathy	27 (45%)
Macrovascular complications	Coronary Artery Disease	0 (0%)
	Cerebrovascular disease	0 (0%)
	Peripheral vascular disease	0 (0%)
Non-Vascular complications	Gastrointestinal	0 (0%)
	Genitourinary	0 (0%)
	Dermatological	0 (0%)

In the present study, 26.7 % of the Study population had Diabetic Neuropathy, 25% had changes on fundoscopy, and 45 % were diagnosed with nephropathy.

Graph 6: Distribution based on complications

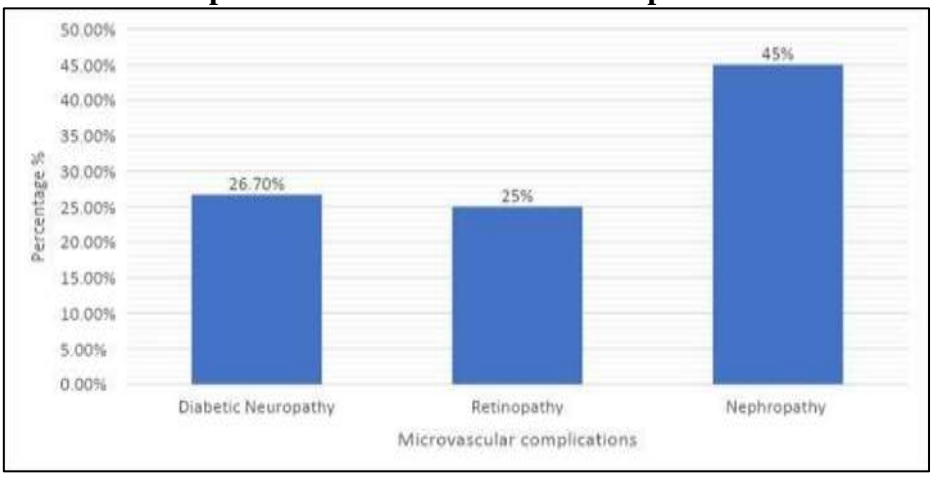

Table 7: Distribution based on Microalbuminuria

Microalbuminuria	Frequency (%)
None	33 (55%)
1 +	8 (13.3%)
2 +	12 (20%)
3 +	7 (11.7%)
Total	60 (100%)

Table 7 shows distribution based on Microalbuminuria, where 20% had 2+, 13.3% had 1+, and 11.7% had 3+Microalbuminuria in the present study.

Graph 7: Distribution based on Microalbuminuria

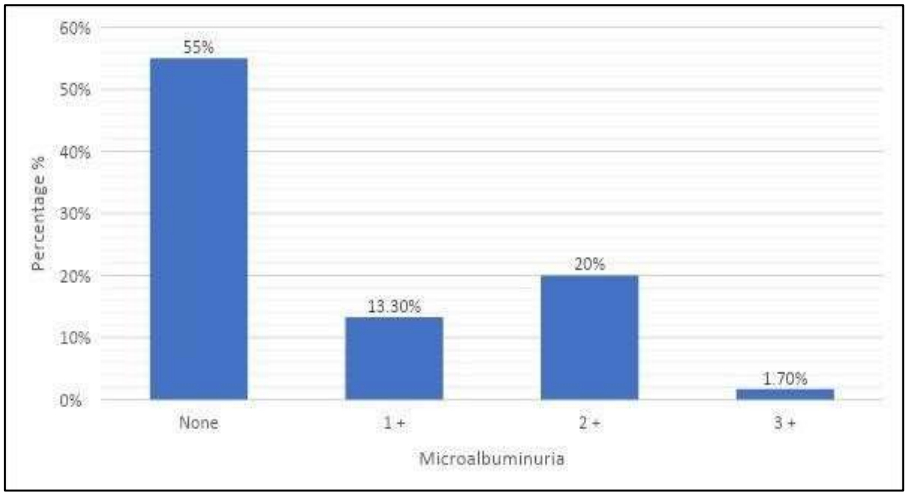

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Table 8: Distribution based on ECGQTc Prolongation (>440msec)

ECGQTc Prolongation (>440msec)	Frequency (%)
Yes	22 (36.7%)
No	38 (63.3%)
Total	60 (100%)

Table 8 shows distribution based on QTc prolongation (>440msec) where in the present study, the prevalence of QTc prolongation was 36.7%.

Graph 8: Distribution based on ECGQTc Prolongation

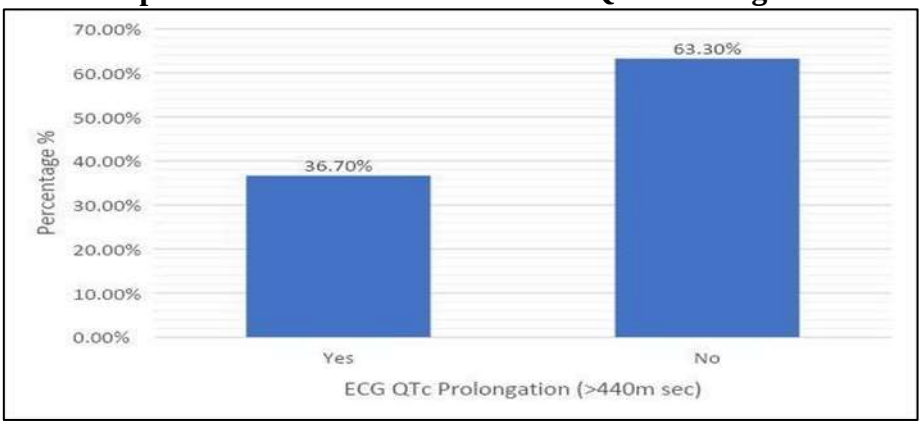

Table 9 : Association of Prolonged QTc and Age

PROLONGED QTc

Age distribution	Yes	No	
50 -60	11 (18.3%)	13 (21.7%)	24 (40%)
61 -70	8 (13.3%)	18 (30%)	26 (43.3%)
71 -80	2 (3.3%)	4 (6.7%)	6 (10%)
81 -90	1 (1.7%)	3 (5%)	4 (6.7%)
Total	22 (36.7%)	38 (63.3%)	60 (100%)
ChiSquare test=1.52,p=0.67 (Not significant)			

Table 9 shows distribution based on Age and QTc prolongation, where the majority is seen in 50 - 60yearsage group, i.e.,18.3%, followed by13.3%in 61-70yearsagegroup.
There was no significant difference between Age and Prolonged QTc as the p-value calculated to be
>0.05.

Graph 9: Distribution based on Age and QTc prolongation

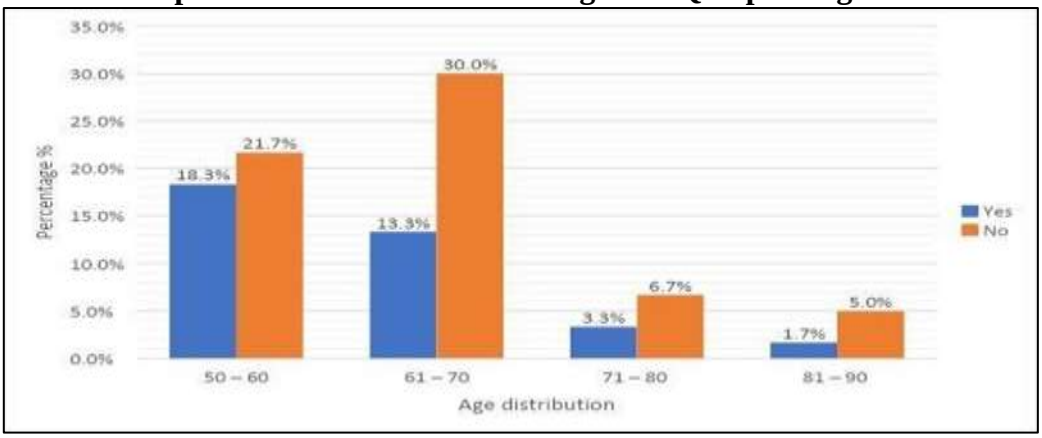

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Table10: Association of Prolonged QTc and Gender

PROLONGED QTc

Gender distribution	Yes	No	
Male	18 (30%)	18 (30%)	36 (60%)
Female	4 (6.7%)	20 (33.3%)	24 (40%)
Total	22 (36.7%)	38 (63.3%)	60 (100%)
Chi Square test=6.77, p=0.009(Statistically significant)			

Table 10 shows distribution based on Gender and Prolonged QTc, where 30% with Prolonged QTc were male, and 6.7% were female. There was a statistically Significant difference observed between the Gender and Prolonged QTc as the p-value calculated to be<0.05.

Graph10: Distribution based on Gender and Prolonged QTc

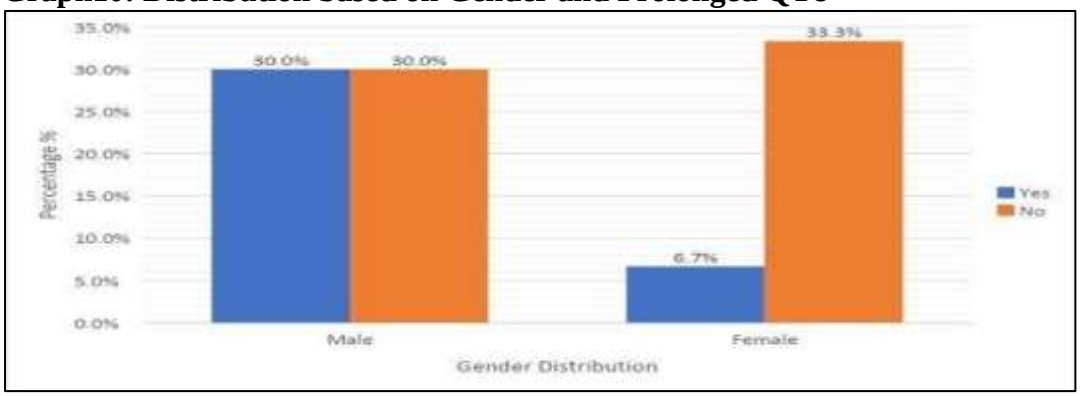

Table 11: Association of Prolonged QTc and Family H/O DM

PROLONGED QTc

Family H/O DM	Yes	No	
Yes	14 (23.3%)	11 (18.3%)	25 (41.7%)
No	8 (13.3%)	27 (45%)	35 (58.3%)
Total	22 (36.7%)	38 (63.3%)	60 (100%)
Chi Squaretest =6.78, p=0.009(Statistically significant)			

In the present study, There was a statistically significant difference observed between the Family H/O Diabetes and Prolonged QTc as the p-value calculated to be <0.05. 23.3% with family H/O diabetes had Prolonged QTc.

Graph 11: Family H/O Diabetes and Prolonged QTc

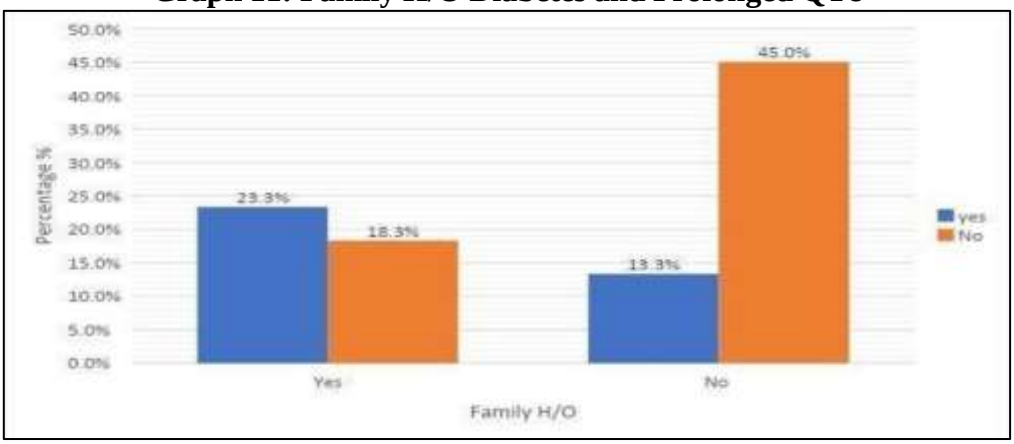

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Table 12: Association of Prolonged QTc and Duration of Diabetes

PROLONGED QTc			
Duration of Diabetes in years	Yes	No	
5 - 10	11 (18.3%)	21 (35%)	32 (53.3%)
11 - 15	7 (11.7%)	16 (26.7%)	23 (38.3%)
>16	4 (6.7%)	1 (1.7%)	5 (8.3%)
Total	22 (36.7%)	38 (63.3%)	60 (100%)
Chi Square test= 4.50, p=0.10 (Not Statistically significant)			

There was no significant difference between Duration of Diabetes and Prolonged QTc as the p-value calculated to be>0.05. 18.3% had Prolonged QTc with a duration of diabetes in years within 5 – 10 years, 11.7% with prolonged QTc had a course of diabetes within 11-15 years.

Graph 12: Duration of Diabetes and Prolonged QTc

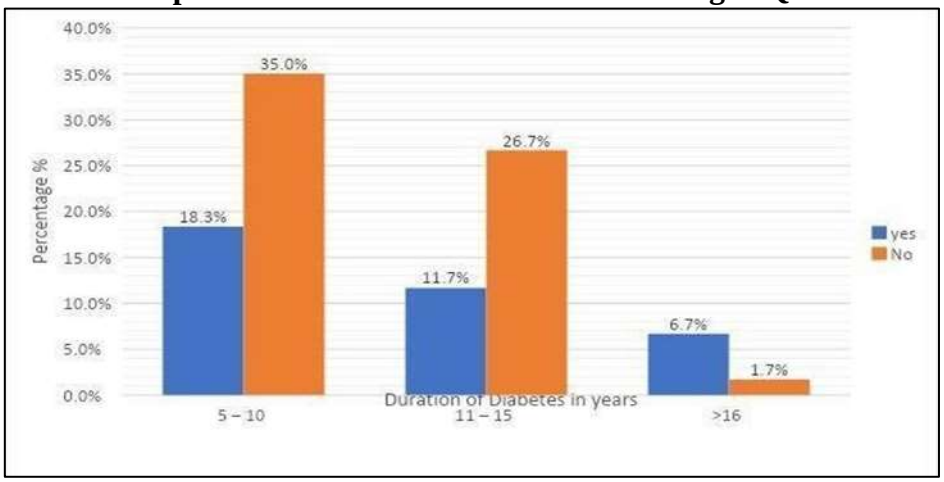

Table 13: Association of Prolonged QTc and Diabetic neuropathy

PROLONGED QTc			
Diabetic neuropathy	Yes	No	
Yes	12 (20%)	4 (6.7%)	16 (26.7%)
No	10 (16.7%)	34 (56.7%)	44 (73.3%)
Total	22 (36.7%)	38 (63.3%)	60 (100%)
Chi Squaretest =13.57, p=0.0002(Statistically significant)			

In the present study, Diabetic Neuropathy and Prolonged QTc significantly associated as thep-value calculated to be <0.05.20% with Prolonged QTc had Diabetic Neuropathy.

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Graph 13: Diabetic Neuropathy and Prolonged QTc

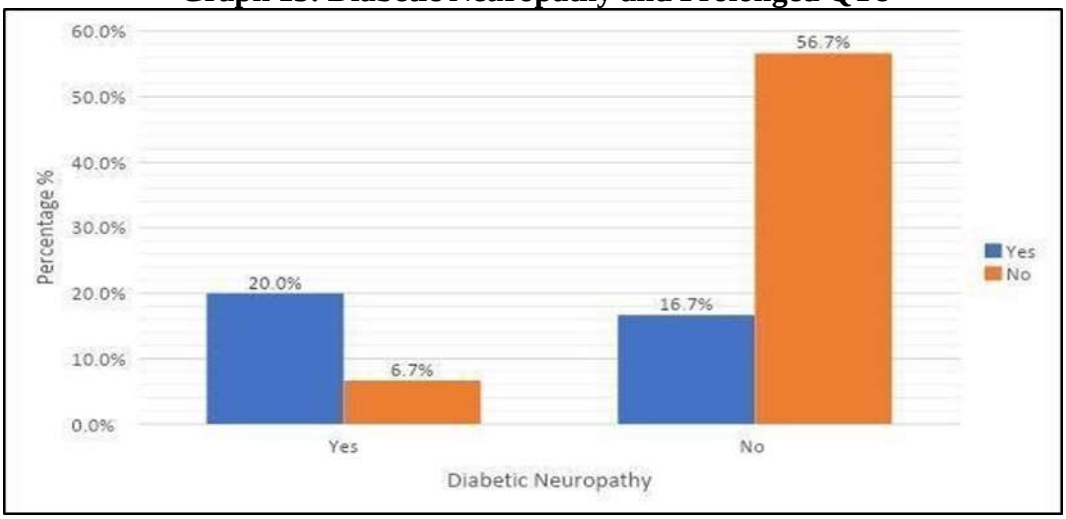

Table 14: Association of Prolonged QTc and Retinopathy

PROLONGED QTc

Retinopathy	Yes	No	
Yes	12 (20%)	3 (5%)	15 (25%)
No	10 (16.7%)	35 (58.3%)	45 (75%)
Total	22 (36.7%)	38 (63.3%)	60 (100%)
Chisquare test= 13.57, p=0.0002(Statistically significant)			

In the present study, Diabetic Retinopathy and Prolonged QTc significantly associated as the p-value calculated to be <0.05.20% with Prolonged QTc had Diabetic Retinopathy.

Graph 14: Prolonged QTc and Retinopathy

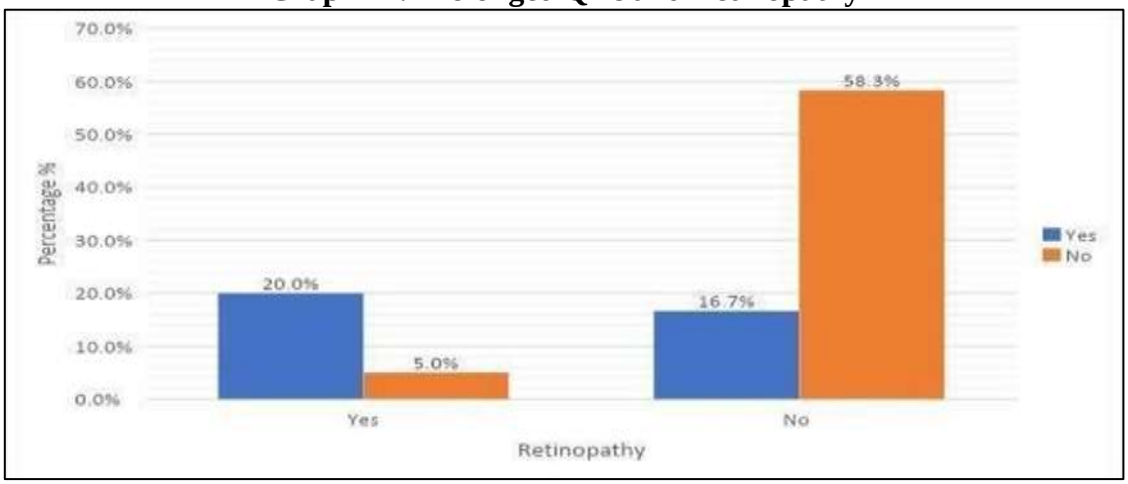

Table 15: Association of Prolonged QTc and Microalbuminuria

Microalbuminuria	Prolonged QTc		Total
	Yes	No	
None	6 (10%)	27 (45%)	33 (55%)
1 +	2 (3.3%)	6 (10%)	8 (13.3%)
2+	7 (11.7%)	5 (8.3%)	12 (20%)

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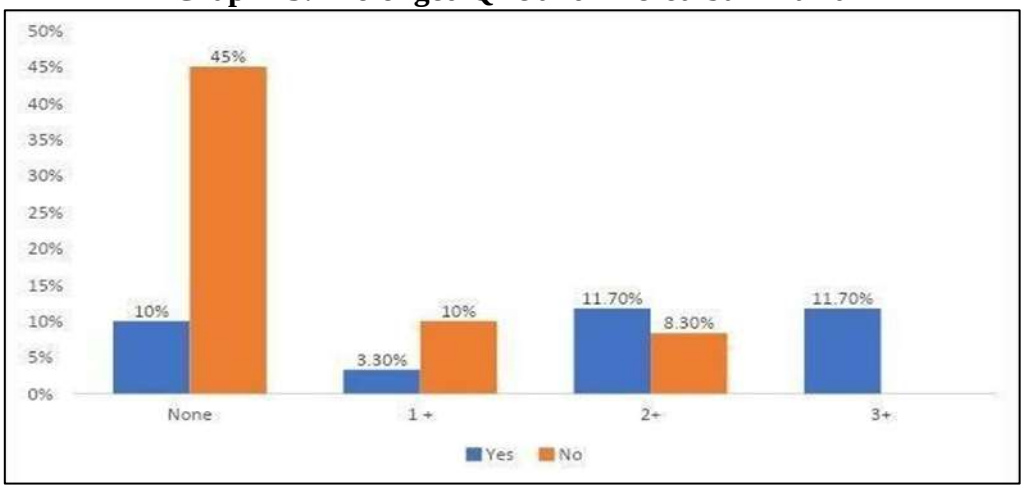
3+	7 (11.7%)	0 (0%)	7 (11.7%)
Total	22 (36.7%)	38 (63.3%)	60 (100%)
Chisquare test= 19.84,p=0.0002(Statistically significant)			

A significant positive correlation, as observed between Microalbuminuria and Prolonged QTc as the p- value calculated to be <0.05. 11.7% had Prolonged QTc with 3+ and 2+ Microalbuminuria.

Graph 15: Prolonged QTc and Microalbuminuria



DISCUSSION

Diabetes mellitus is a disease of ancient times known to humankind since 2000 years. Ancient Indian Scholars like Charaka and Shushmtha knew about it. It is a big concern because of the devastating effect of its chronic complications.

In particular, the triad of neuropathy, retinopathy and nephropathy has been alluded to as primary consequences because of the close and relatively specific relationship between the genesis of Tripathy and the metabolic aberrations characteristic of diabetes.

In our count", non-insulin-dependent diabetes mellitus compared to insulin- dependent diabetes mellitus afflicts a vast population.

By general consequences, neuropathy is the most common among the complications of diabetes. Yet, it remains the least investigated, and its pathogenesis is most poorly understood.

In early diabetic nephropathy, Microalbuminuria is an early marker of glomerular disease that shown to predict injury.

There is Microalbuminuria in 25 per cent of type 2 diabetic patients, and it is a good indicator of premature cardiovascular death in them. Diabetic nephropathy is a leading cause of mortality and morbidity associated with diabetes.

It is possible to detect cardiac autonomic neuropathy (CAN). Cardiac instability due to CAN has shown without evidence of ischemic heat* disease in diabetic patients, raising the risk of sudden unexpected death.

High mortality is due not only to sudden death but also to diabetic nephropathy associated

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with May
. A particular indicator for CAN found to be prolonged QTc. The independent predictor of all causes and cardiovascular mortality in type 2 found to be QTc-max.

In several studies, a correlation between autonomic neuropathy and diabetic nephropathy has shown in I diabetic patients. QT interval disorders in type I diabetics are consistent with Microalbuminuria. Just a few studies are available on type 2 diabetes.

A predictor of sudden arrhythmic death in these patients is QT prolongation. Therapeutic intervention opportunities exist as QT prolongation decreased by physical activity, weight loss, anti-hypertensive and beta-blockade.
The present study conducted to determine the association between Microalbuminuria and prolonged QT interval in type 2 diabetes mellitus among the patients admitted, and those attending an outpatient unit in Government General Hospital, Guntur.

Age

In this study, the mean age of the study participants was 63.83 ± 8.48. The majority in the present study belonged to 61 - 70 years age group, i.e. 43.3%, 40% belonged to 50- 60 years age group, 10% in 71 - 80 years age group, 6.7% in 81 - 90 years age group.

Present study	63.83 ± 8.48.
XiangLiet al[4]	54.9 ± 10.8 years
Beyzaetal[5]	57.52 ± 10.47
Royetal[6]	53.78± 11.98
Yasaretal[7]	56.45 ±9.95
Kanwaretal[8]	Out of 50 patients, majority of the patients belonged to age group 41–50years
Sayushetal[9]	53.61 + 8.75 years
Pillaietal[10]	55.2±8.2 years.

Association of Prolonged QTc and Age

The majority in 50 - 60 years age group, i.e., 18.3% followed by 13.3% in 61- 70 years age group. There was no significant difference between the Age and Prolonged QTc as the p-value calculated to be >0.05.
Analysis by NHANES showed a significant association between QTc and age in both sexes. The impact of age was evident, regardless of whether one considered a linear or non-linear relationship between QTc and age. Indeed, the complexity-adjusted goodness-of-fit analysis found a relatively strong association between age and QTc. [11]
Ageing processes may affect the QT interval's molecular determinants or alter the myocardium with increased myocardial fibrosis. Ageing is also associated with alterations in the amount of sympathetic and parasympathetic tone which can alter myocardial repolarization and duration of the QTc. [12]

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The increase in QTc with age means that drugs which induce QT prolongation may more readily reach potentially 'dangerous' QTc durations in an older compared to a younger person.[13] An FDA statement is relevant precisely "While the degree of QT prolongation recognized as an imperfect biomarker for pro- arrhythmic risk, in general. The importance of QT and age underscored by the finding that there is over a threefold increase in cardiovascular events in older men with a QTc greaterthan 420 ms. [14]

Gender

60% were male, and 40% were female in the present study.

Present study	60% were maleand 40% werefemale
XiangLietal[4]	3156patientswithtype2 diabetesincluded 1425 (45. 2%) females and1731(54.8%) males.
Jayeshetal[15]	Male to femaleratio is 1.15:1.
Royetal[6]	48.5% were maleand 51.5%were female
Yasaretal[7]	103/172
Sayush et al[9]	Out of the 120 diabetic cases, majority 69 (57.5%) were males, and 51 (42.5%) were females
Khoharo et al[16]	535 were male and 47% were female

Association of Prolonged QTc and Gender

30% with Prolonged QTc were male, and 6.7% were female. A statistically significant difference observed between the Gender and Prolonged QTc as the p-value calculated to be <0.05.

Using multiple linear stepwise regression analysis using QTc intervals as a dependent variable, female gender predicted a longer QTc interval. Females had a 13.02 ms (95% CI, 7.10 to 18.83) increase in their estimated intervals than males.

The differences in QTc between men and women lessen significantly for people over 50. Sex differences in ECG variables recognized and attributed, in part, to differences in sex hormones. In men, QT interval correlates with testosterone levels. [17] Of note, QT interval is longer in castrated men and shorter in women with virilization. [18]

The decline in testosterone levels with age may account for the increase in QTc with age. Hormonal changes, however, are not the entire explanation for the QTc differences between sexes. [19]

Our evaluation found that the correlation between age and QTc was more significant in men than in women. This finding is due to the more considerable prolongation of the QTc observedin Older men compared to younger men. The QTc is more significant in women than men at younger ages, but the difference in QTc between the sexes diminishes at the older age groups, which means the increase in QTc with age is not parallel. Family h/o Diabetes. In the

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present study, 41.7% had a family history of diabetes.

Duration of Diabetes

5 -10 years duration in 53.3%, 11 – 15 years duration in 38.3%, 8.3% had a course of >16 years inthe present study. The mean duration of diabetes in the present study was 10.05 ± 3.03years. The median duration of DM was 3.0 years.

Present study	10.05 ± 3.03 years
Beyzaetal[5]	12.34 ± 7.11 years
Yasaretal[7]	9.76± 7.65
Mahajanetal[20]	12.87±4.42

The duration of diabetes is an independent factor for developing CAN irrespective to diabetes type [21]. CAN detect in 7% of both T1DM and T2DM at the time of initial diagnosis, estimated that risk for developing CAN increase by 6%, 2% in patients T1DM, T2DM respectively. [22]

Treatment

41.7% of the study population were on Oral Hypoglycemics, 36.7% were on Oral Hypoglycemics and Insulin, 21.7% were on insulin in the present study. Yasar et al. [7] in their study reported that Insulin usage was 52.3%, Metformin usage was 92.7%, Sulfonylurea usage was 20%

Hyperglycaemia is a significant risk factor for CAN development and progression. In the DCCT trial, intensive glycaemic management in a group of patients with T1DM reduced the CAN incidence by 50% over 6.5 years follow-up compared with conventional therapy (7% vs 14% respectively).

These beneficial effects persisted 13-14 years after close-out of the trial. Although both formertreatment arms exhibited deterioration in CAN during follow-up after the end of the DCCT, the former intensive treatment group continued to demonstrate a statistically significant slowerdecline in CAN. [23]

PET cardiac imaging with the use of 11C-HED showed similar beneficial effects in a 3- year prospective trial. Reasonable glycaemic control (defined as mean HbA1c < 8%) was associated with a reduction of sympathetic denervation as opposed to the group of poor diabetes control (HbA1c ≥ 8%).

In the SEARCH CVD study, 354 young patients with T1DM were assessed for sub- clinical autonomic dysfunction, as demonstrated by the use of HRV parameters and the presence of parasympathetic loss with sympathetic override.

As defined by HbA1C > 7.5%, poor glycemic control was independently associated with the company of subclinical CAN compared to a frequency-matched control group without DM. [23]

The effects of glycaemic control in T2DM are not similarly encouraging. Data from recent studies have failed to demonstrate differences in CAN-based incidence on the application of intensive therapy in T2DM patients.

The sensitivity of tests utilized for CAN diagnosis in those trials questioned, suggesting that more research is needed to investigate the relationship between metabolic control and CAN in patients with T2DM. [23]

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CONCLUSION

This study is done in 60 patients of type 2 diabetes mellitus. Detailed history related to diabetes and its complications involving neuropathy was asked. Evidence of CAN like QTc interval prolongation and nephropathy in the form of microalbuminuria was looked for. Most patients were in their 6^{th} and 7^{th} decade of life and male preponderance was noted. Higher duration of diabetes, higher age groups have increased risk of cardiacautonomic neuropathy. There is a significant association between QTc interval prolongation and microalbuminuriaas evidenced by, more number of microalbuminuria cases seen with prolongedQTc interval. As duration of diabetes increases prevalence of microalbuminuria increases. 20% of peripheral neuropathy cases are associated with CAN and 20% of retinopathy are associated with CAN.

FUNDING

Nil

CONFLICT OF INTEREST

None

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