"A CROSS SECTIONAL STUDY TO FIND THE ASSOCIATION BETWEEN PROLONGED QT_C INTERVAL AND MICROALBUMINURIA IN PATIENTS OF TYPE 2 DIABETES MELLITUS"

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This is to certify that the dissertation entitled **"A CROSS SECTIONAL STUDY TO FIND THE ASSOCIATION BETWEEN PROLONGED QT_C INTERVAL AND MICROALBUMINURIA IN PATIENTS OF TYPE 2 DIABETES MELLITUS"** is a bonafide research work done by **THE CANDIDATE REG NO. BG0108003** in the Department of General Medicine, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 590 010.

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LIST OF ABBREVIATIONS USED

ACE	-	Angiotensin convertin enzyme
ADA	-	American Diabetic Association
AGES	-	Advanced glycosylation end products
Akt	-	Protein kinase B
ARB	-	Angiotensin receptor blocker
ATP	-	Adenosine triphosphate
BMI	-	Body mass index
CAN	-	Cardiac autonomic neuropathy
CAP/Cb1/Tc10	-	Cbl associated protein
DCCT	-	Diabetes control and complications trial
DF	-	Degree of freedom
dL	-	Deci Litre
DM	-	Diabetes mellitus
DNA	-	De-oxy ribonucleic acid
DPN	-	Diabetic peripheral neuropathy
ECG	-	Electrocardiogram
ERK	-	Extracellular signal regulated kinases
FBS	-	Fasting blood sugar
FPG	-	Fasting plasma glucose
g	-	Gram
GBM	-	Glomerular basement membrane
GDM	-	Gestational diabetes mellitus
GLUT	-	Glucose transporter
GSK 3	-	Glycogen synthase kinase 3

HbA1c	-	Glycated hemoglobin
HGO	-	Hepatic glucose output
HNF	-	Hepatocyte nuclear factor
HTN	-	Hypertension
IDDM	-	Insulin dependent diabetes mellitus
IFG	-	Impaired fasting glucose
IGF	-	Insulin like growth factor
IGT	-	Impaired glucose tolerance
IRS	-	Insulin receptor substrate
L	-	Litre
mg	-	Milligram
mmol	-	Milli moles
MODY	-	Maturity onset diabetes of young
ms	-	Milli seconds
n	-	Number of patients
NGT	-	Normal glucose tolerance
NIDDM	-	Non insulin dependent diabetes mellitus
OGTT	-	Oral gluocse tolerance test
PAI-1	-	Plasminogen activator inhibitor 1
PI3kinase	-	Phophatidyl inositol – 3 kinase.
PKC	-	Protein kinase C
PPARγ	-	Peroxisome proliferators activated receptor γ
PPBS	-	Post prandial blood sugar
PTP 1B	-	Protein tyroine phosphatase 1B
QTc interval	-	Corrected QT interval

RBS	-	Random blood sugar
s	-	Seconds
S.D.	-	Standard deviation
Sr. No.	-	Serial number
TGF	-	Transforming growth factor
UAE	-	Urinary albumin excretion
VEGF A	-	Vascular endothelial growth factor A
µg	-	Micro gram

ABSTRACT

Background and objectives

The link between microalbuminuria and premature death in type 2 diabetes is not completely explained by conventional cardiovascular risk factors. CAN is associated with a high mortality which is attributed not only to sudden death but also to diabetic nephropathy. Prolonged QT_c interval is found to be a specific indicator for CAN. The objective of the present study was to find the association between prolonged QT_c interval and microalbuminuria in type 2 diabetes patients.

Methodology

The present one year cross-sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 86 patients (43 with normoalbuminuria and 43 with microalbuminuria) with type 2 DM during the period of January 2009 to December 2009. Investigations like complete blood count, erythrocyte sedimentation rate, urine routine and microscopy, FBS or PPBS or RBS were done. Urine albumin excretion test and ECG was done. QTc interval was calculated using Bazzet's formula.

Results

In the present study, 60.47% and 69.77% were males in normoalbuminuric and microalbuminuric groups respectively. The mean age in normoalbuminuric group was 54.51±10.15 years and it was 55.93±11.73 years in microalbuminuric group. Most of subjects had duration of diabetes less than 10

years (44.19% in normoalbuminuric and 34.88% in microalbuminuric groups respectively). QTc interval was significantly prolonged in 25.58% of patients in normoalbuminuric and 69.77% in microalbuminuric group (p=0.001). Mean QTc interval was significantly more (454.73±29.33 ms) in microalbuminuric group compared to normoalbuminuric group (418.13±27.44 ms) (p=0.001). Mean duration of diabetes was less (14.93±3.81 years) in microalbuminuric group compared to (16.00±4.87 years) normoalbuminuric group.

Interpretation and conclusion

Prevalence CAN as diagnosed by prolonged QTc interval was more in Type 2 DM patients with microalbuminuria and these patients can develop CAN with short duration of diabetes.

Keywords

Cardiac autonomic neuropathy; Diabetes mellitus; Microalbuminuria; Normoalbuminuria; Prolonged QTc Interval;

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INTRODUCTION

Type 2 diabetes is increasing worldwide in epidemic proportions. It has been estimated that the diabetic population will double from 150 to 300 million in the next 25 years.[1,2] The long term complications associated with diabetes are major causes of morbidity and mortality, imposing a high financial burden on health care systems. Type 2 diabetes will certainly be one of the major diseases of the 21st century.[3,4,5]

Microalbuminuria is an early marker of glomerular disease that has been shown to predict glomerular injury in early diabetic nephropathy.[6] 25% of type 2 diabetic patients have microalbuminuria and it is a strong predictor of premature cardiovascular death in them.[7] Diabetic nephropathy is a leading cause of diabetes related mortality and morbidity.[8]

Cardiac autonomic neuropathy (CAN) can be detected in atleast one third of type 2 diabetes.[9] Cardiac dysfunction due to CAN has been demonstrated in diabetic patients without evidence of ischemic heart disease and this can increase risk of sudden unexpected death.[10] CAN is associated with a high mortality which is attributed not only to sudden death but also to diabetic nephropathy.[9] Prolonged QT_c interval is found to be a specific indicator for CAN.[11-13]

An association between autonomic neuropathy and diabetic nephropathy has been demonstrated in type 1 diabetic patients in many studies and QT interval abnormalities have been shown to be associated with microalbuminuria in type 1 diabetics.[14-17] There are only a few reports in type 2 diabetes.

A study has shown that the presence of proteinuria (microalbuminuria or overt nephropathy) to be significantly associated with the presence of CAN in type 2 diabetic patients.[18]

Another study concluded that prevalence of CAN was two fold higher in type 2 diabetic patients with nephropathy than those without nephropathy.[19]

The QT prolongation is a marker of sudden arrhythmic death in these patients. Opportunities exist for therapeutic intervention since QT prolongation can be reduced through physical training, weight loss, anti hypertensive therapy and beta blockade.[7]

Hence the present study was undertaken to assess if CAN, as predicted by prolonged QT_c interval is associated with microalbuminuric type 2 diabetic patients and correlate it to the severity and duration of diabetes.

OBJECTIVES

The objective of the present study was to find the association between prolonged QT_c interval and microalbuminuria in type 2 diabetes patients.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Diabetes mellitus, is a disease that was recognized in antiquity, but its history has been characterized by numerous cycles of discovery, neglect and rediscovery. Its history, may be divided into four major periods that reflect different phases in the understanding and management of the disease. The 'ancient' period, witnessed the first clinical descriptions of diabetes and complications. The 16th to 18th centuries have been termed the 'diagnostic' period, as DM was then identified as a separate disease entity, while the mid to late 19th century may be regarded, as the first 'experimental' period, during which the glucoregulatory role of the pancreas became clear and the biochemical disturbances of diabetes were initially characterized.[20]

Finally, the 20th century has seen a dramatic increase in knowledge about diabetes. The discovery of insulin in 1921-22 has had profound scientific, clinical and social consequences. Some key developments in scientific and clinical understanding of diabetes may be summarized as follows;[21]

- Polyuric states, clinically resembling DM were described as early as 1550 BC in the ancient Egyptian papyrus discovered by George Ebers.
- The sweet taste of diabetic urine was noted in the fifth and sixth century AD by the Indian physicians (Sushruta and Charaka) and in the 17th century by Thomas Willis. The term 'Diabetes mellitus', an allusion to the honeyed taste of urine, was first used in the late 18th century by John

Rollo and others, to distinguish it from other polyuric states in which urine was tasteless.

- In 1776, Matthew Dobson discovered that diabetic serum as well as urine contained sugar, and concluded that diabetes was a systemic condition rather than a disease of kidneys.
- Claude Bernard, made numerous discoveries in the field of metabolism and diabetes during the mid to late 19th century, describing the storage of glucose in the liver as glycogen and hyperglycemia in experimental animals.
- In 1889, Oskar Minkowski and Josef Von Mering observed that total pancreatectomy produced diabetes in dogs.
- In 1893, Edovard Laguesse named the pancreatic islets after Paul Langerhans, who had described them in 1869, and suggested that they produced a glucose lowering substance. This then hypothetical hormone was named 'insulin' by Jean de Meyer in 1909, over a decade before its discovery.
- Various workers, including George Zuelzer (Germany) and Nicolas Paulesco (Romania), isolated active but impure hypoglycemic extracts from the pancreas during the first two decades of the 20th century; but toxic side effects precluded their formal testing in diabetic patients.
- Insulin, was discovered at the University of Toronto in 1921, through collaboration between Frederick G. Banting, Charles H. Best, James B. Collip and J.J.R. Macleod. Insulin was extracted from chilled pancreas in an acid / ethanol mixture; the extracts were found to lower blood glucose

levels in pancreatectomised dogs and were first tested in a human diabetic (Leonard Thompson) in January, 1922.

- Major advances in the understanding of diabetes and metabolism have included:

  A. The sequencing of insulin in 1955, by Frederick Sanger and elucidation of its three dimensional structure in 1969, by Dorothy Hodgkin.

  B. The measurement of insulin concentration using the first radio immunoassay, by Solomon Berson and Rosalyn Yalow in 1959.

  C. The isolation of proinsulin, in 1967 by Donald Steiner's group.

  D. Identification of specific insulin receptors by Pierre Freychet and colleagues, in 1971.

  E. The sequencing of the insulin receptor, in 1985.

- Mile stones in the management of diabetes have included,

  A. The development of long acting insulin preparations (isophane) in 1936, by Hans Christian Hagedorn and colleagues.

  B. The testing of sulfonylureas by Auguste Loubatieres, in 1944.

  C. First therapeutic use of a biguanide (phenformin) by G. Ungar, in 1957.

  D. Dry reagent test strips suitable for self monitoring of blood glucose, were introduced in the late 1970's.

  E. Definitive proof from the diabetes control and complications trial (DCCT) published in 1993, that strict glycemic control could slow or prevent, the development of diabetic microvascular complications.[22]

EPIDEMIOLOGY

Type 2 DM, is the commonest form of diabetes accounting for 85 to 95% of all cases worldwide with its global prevalence increasing rapidly, as a consequence of westernized lifestyle and is destined to become one of the most costly diseases.[23]

The prevalence is expected to increase by 122% (from 125 to 300 million) between 1995 and 2025. The developing world will suffer the most with a predicted 170% increase in cases that will mainly affect the 45 to 65 group, by contrast the diabetic population in the developed world will increase only by 40%, particularly among those aged more than 65 years.[23]

In the United State of America, 10 to 20% of diabetic children and adolescents now have type 2 DM with ethnic minorities, African Americans, Mexicans and Pima Indians having the highest prevalence. 85% of children with type 2 DM are obese.[24]

Indian scenario

Several epidemiological studies in migrant Indians and India itself show that, the population has a high genetic predisposition for diabetes, which is precipitated by environmental factors such as urbanization.[25] The prevalence of diabetes is four to six fold lower in rural areas, which is probably attributed to a conventional lifestyle which has beneficial effect on glucose tolerance (IGT). National Urban Diabetes Survey done in six cities, found age standardized prevalence rates of 12% for diabetes; with a slight male preponderance and 14%

for impaired glucose tolerance. Subjects under the age of 40 years, had a prevalence of five percent for DM and 13% prevalence of impaired glucose tolerance.

Causes for diabetic pandemic

The type 2 DM epidemic is tightly and consistently linked to that of obesity, both geographically and chronologically. Many factors like, urbanization and mechanization, together with globalized pattern of western pattern of lifestyle, together with poverty, lack of education and low socio-economic status and inner city deprivation are emerging as significant risk factors for DM. Lack of breast feeding, low birth weight is associated with insulin resistance and type 2 DM in adult life (especially in subjects who become obese) due to long term metabolic response during poor fetal nutrition.[26]

Obesity

Prevention of obesity, in women of child bearing age, is another primary goal because exposure to environment of a diabetic pregnancy places the fetus at increased risk for future onset diabetes. About 80% of patients are obviously obese at the time of diagnosis, usually with a central fat distribution in and around the abdominal cavity. In addition, many of those who are not traditionally obese, by weight criteria have increased percentage of fat predominantly distributed in the abdominal region. It is the most obvious target to prevent DM.

Body mass index (BMI)

Three key anthropometric measurements are important to evaluate the degree of obesity – weight, height and waist circumference. The BMI, calculated as weight (kg)/height $(m)^2$, or as weight (lbs)/height$(inches)^2$ x 703, is used to classify weight status and risk of disease. Body mass index, is used since it provides an estimate of body fat and is related to risk of disease. Lower BMI thresholds for overweight and obesity have been proposed for the Asia-Pacific region since this population appears to be at risk at lower body weights for glucose and lipid abnormalities.[8]

Table No. 1: Classification of weight status and risk of disease[27]

	BMI (Kg/m^2)	Obesity Class	Risk of Disease
Underweight	<18.5		
Healthy weight	18.5 – 24.9		
Overweight	25.0 – 29.9		Increased
Obesity	30.0 – 34.9	I	High
Obesity	35.0 – 39.9	II	High
Extreme Obesity	≥ 40	III	Extremely high

Classification of diabetes and other categories of glucose regulation

Diabetes mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy.[8]

Table No. 2: Spectrum of glucose homeostasis and diabetes mellitus[8]

Type of diabetes	Normal glucose tolerance (NGT)	Impaired fasting glucose or impaired glucose tolerance	Hyperglycemia		
			Diabetes mellitus		
			Not insulin required	Insulin required for control	Insulin required for survival
Type 1	←	———	———	———	——→
Type 2	←	———	———	——→	
Other Specific types	←	———	———	——→	- - - - ▸
Gestational diabetes	←	———	——→		
Time (years)	←	———	———	———	——→
FPG (mg/dl)	< 100	100-125		≥ 126	
2-h plasma glucose (mg/dl)	< 140	140 – 199		≥ 200	

Etiologic classification of diabetes mellitus[8]

I. Type 1 diabetes (-cell destruction, usually leading to absolute insulin deficiency)

A. Immune-mediated

B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes

A. Genetic defects of β-cell function characterized by mutations in :

1. Hepatocyte nuclear transcription factor (HNF) 4α maturity onset diabetes of young (MODY) 1
2. Glucokinase (MODY 2)
3. HNF – 1α (MODY 3)
4. Insulin promoter factor (IPF) 1 (MODY 4)
5. HNF – 1β (MODY 5)
6. Neuro D1 (MODY 6)
7. Mitochondrial deoxyribo nucleic acid (DNA)
8. Sub units of adenosine triphosphate (ATP) – sensitive potassium channel.
9. Proinsulin or insulin conversion

B. Genetic defects in insulin action.

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipodystrophy syndromes.

C. Diseases of the exocrine pancreas – pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy.

D. Endocrinopathies – acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma

E. Drug or chemical induced – Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, beta-adrenergic agonists, thiazides, phenytoin, α– interferon, protease inhibitors, clozapine, beta blockers.

F. Infections – congenital rubella, cytomegalovirus, coxsackie.

G. Uncommon forms of immune-mediated diabetes – "stiff-man" syndrome, anti-insulin receptor antibodies.

H. Other genetic syndromes sometimes associated with diabetes – Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome.

IV. Gestational diabetes mellitus (GDM)[8]

Type 2 DM

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Although the primary defect is controversial, most studies support the view that, insulin resistance precedes an insulin secretory defect and diabetes develops only when insulin secretion becomes inadequate.

Genetic Considerations

Type 2 DM has a strong genetic component. The concordance of type 2 DM in identical twins is between 70 and 90%. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk

approaches 40%. Insulin resistance as demonstrated by reduced glucose utilization in skeletal muscle is present in many nondiabetic, first degree relatives of individuals with type 2 DM. The disease is polygenic and multifactoral since in addition to genetic susceptibility, environmental factors (such as obesity, nutrition and physical activity) modulate the phenotype. The genes that predispose to type 2 DM are incompletely identified but recent genome-wide association studies have identified several genes that convey a relatively small risk for type 2 DM (relative risk of 1.1 to 1.5). Most prominent is a variant of the transcription factor 7-like 2 gene that has been associated with type 2 diabetes in several populations and with IGT in one population at high risk for diabetes. Genetic polymorphisms associated with type 2 diabetes have also been found in the genes encoding the peroxisome proliferators-activated receptor γ (PPAR-γ), inward rectifying potassium channel expressed in beta cells, zinc transporter expressed in beta cells, insulin receptor substrate (IRS) and calpain 10. The mechanisms by which these genetic alterations increase the susceptibility to type 2 diabetes are not clear, but several are predicted to alter insulin secretion, investigation using genome-wide scanning for polymorphisms associated with type 2 DM is ongoing.

Pathophysiology

Type 2 DM, is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production and abnormal fat metabolism. Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM. In the early stages of the disorder, glucose tolerance remains near normal, despite insulin resistance, because the pancreatic beta cells

compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. Impaired glucose tolerance, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure may ensue.[8]

Early onset type 2 diabetes was defined as type 2 DM with age at diagnosis between 25 to 39 years, history of late onset type 2 DM in both parents; history of several paternal and maternal uncles and aunts with DM; history of early onset type 2 diabetes in first sibling and progressive clinical severity towards insulin requirement and micro vascular complication over the course of treatment.[28,29,30]

INSULIN RESISTANCE

Normal physiology of glucose homeostatis

Maintenance of normal glucose levels depends upon, a closed feedback loop between the circulating glucose level and the pancreatic hormones, insulin and glucagons. In the fasting state, glucose is largely produced by the liver via glycogen breakdown and gluconeogenesis. Approximately 70% to 80% of the glucose produced by the liver is used by the brain (independent of insulin) and by other insulin-insensitive tissues, such as the gastrointestinal tract and erythrocytes. The insulin-sensitive tissues, principally muscle and fat, use only small quantities of glucose in the absence of increased insulin levels. Hepatic glucose output (HGO) in the short term (that is minutes to hours) is modulated by

insulin, glucagons, catecholamines and the glucose level itself. Growth hormone, thyroid hormone and cortisol (glucocorticoids) serve as longer-term modulators (that is hours to days) of hepatic glucose production.

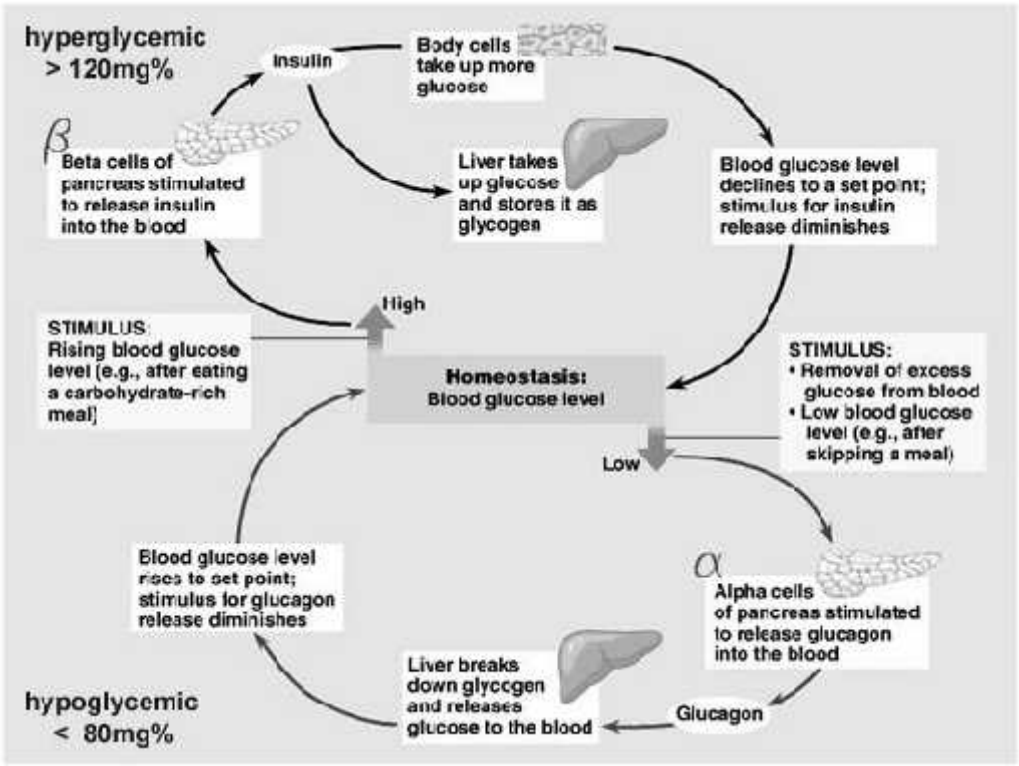


Figure 1. Normal physiology of glucose homeostatis

Insulin (from the pancreatic beta cell) exerts an inhibitory effect on hepatic glucose production. In contrast, glucagons (from the pancreatic alpha cell) stimulates hepatic glucose production. Thus, a reduction in insulin results in a slow rise in HGO. If the feedback loop is intact, as the serum glucose level rises, pancreatic insulin secretion would increase, and glucagons would decrease in order to maintain homeostasis. If peripheral insulin sensitivity changes, this would result in a change in serum glucose, which in turn would result in modulation of insulin and glucagons in order to maintain glucose levels.

Complete adaptation actually does not occur and thus, a new higher steady-state glucose level is reached. One must account for each variable that contributes to this regulatory system - HGO, pancreatic endocrine function and peripheral tissue glucose uptake - in order to appropriately evaluate abnormalities in glucose homeostasis.

At the cellular level, the mechanism of insulin action, involves a cascade of biochemical interactions. The initial event begins with insulin binding to a cell surface receptor, which activates the receptor's intrinsic tyrosine kinase activity. Tyrosine kinases phosphorylate intracellular substrates, including themselves (autophosphorylation). The phosphorylation triggers a molecular phosphorylation /dephosphorylation signaling cascade. Proteins such as IRS-1 and IRS-2 are phosphorylated and ultimately result in the activation of three major pathways: the phosphatidylinositol-3 (PI3) kinase pathway, the Cb1 activated protein/Cbl/Tc10 pathway and the extracellular signal regulated kinase (ERK) pathway.[31] Many researchers studied enzymes such as protein tyrosine phosphatase (PTP) 1B, PI-3 kinase, protein kinase B (Akt) and glycogen synthase kinase 3 (GSK3), among others, in order to understand the nature of the post-receptor defects seen in type 2 diabetes.[31] The ultimate result of the signaling cascade is the recruitment and translocation of the glucose transporter 4 (GLUT4) protein from an intracellular pool to the cell membrane, which facilitates the influx of glucose into the cell for subsequent metabolism.[32]

Diagnosis of diabetes[8]

Criteria for the Diagnosis of Diabetes Mellitus[8]

- Symptoms of diabetes plus random blood glucose concentration more than or equal to 11.1 mmol/L (200 mg/dL)[a] *or*
- Fasting plasma glucose more than or equal to 7.0 mmol/L (126 mg/dL)[b] *or*
- Two-hour plasma glucose more than or equal to 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

[a]Random is defined as without regard to time since the last meal.
[b]Fasting is defined as no caloric intake for at least 8 h.
[c]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.
Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Glucose tolerance is classified into three categories based on the FPG:

1. FPG less than 5.6 mmol/L (100 mg/dL) is considered normal;
2. FPG equal to 5.6–6.9 mmol/L (100–125 mg/dL) is defined as IFG; and
3. FPG more than or equal to 7.0 mmol/L (126 mg/dL) warrants the diagnosis of DM.[8]

Oral glucose tolerance test

The test uses the following procedures.

- It first employs an FPG test.
- A blood test is then taken two hours after drinking a 75 g anhydrous glucose solution.

Based on the OGTT, IGT is defined as plasma glucose levels between 7.8 and 11.1 mmol/L (140 and 199 mg/dL). Diabetes is defined when plasma glucose is more than 11.1 mmol/L (200 mg/dL), 2 h after a 75 g oral glucose load.[8]

The current criteria, for the diagnosis of DM emphasize that the FPG is the most reliable and convenient test for identifying DM, in asymptomatic individuals. A random plasma glucose concentration more than or equal to 11.1 mmol/L (200 mg/dL) accompanied by classic symptoms of DM (polyuria, polydipsia, weight loss) is sufficient for the diagnosis of DM.[8]

Complications of T2DM[8]

Acute

- Diabetic Ketoacidosis
- Hyperglycemic Hyperosmolar State

Chronic

- Microvascular
    - Eye disease
        - Retinopathy (nonproliferative/proliferative)
        - Macular edema
    - Neuropathy
        - Sensory and motor (mono- and polyneuropathy)
        - Autonomic
    - Nephropathy
- Macrovascular
    - Coronary artery disease
    - Peripheral vascular disease
    - Cerebrovascular disease
- Other
    - Gastrointestinal
    - Genitourinary
    - Dermatologic
    - Cataracts
    - Glaucoma
    - Infectious
    - Periodontal disease

Chronic complications of T2DM

The risk of chronic complications increases as a function of the duration of hyperglycemia; they usually become apparent in the second decade of hyperglycemia. Since type 2 DM often has a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis.

The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Large, randomized clinical trials of individuals with type 1 or type 2 DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy, and nephropathy. Other incompletely defined factors may modulate the development of complications.

Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive. However, coronary heart disease events and mortality are two to four times greater in patients with type 2 DM. These events correlate with fasting and postprandial plasma glucose levels as well as with the A1C. Other factors like dyslipidemia and hypertension also play important roles in macrovascular complications.[8]

Mechanisms of Complications

Four prominent theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia might lead to the chronic complications of DM.

One theory is that increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via the nonenzymatic glycosylation of intra- and extracellular proteins. Nonenzymatic glycosylation results from the interaction of glucose with amino groups on proteins. AGEs have been shown to cross-link proteins (for example, collagen, extracellular matrix proteins), accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, induce endothelial dysfunction, and alter extracellular matrix composition and structure. The serum level of AGEs correlates with the level of glycemia, and these products accumulate as glomerular filtration rate declines.

A second theory is based on the observation that hyperglycemia increases glucose metabolism via the sorbitol pathway. Intracellular glucose is predominantly metabolized by phosphorylation and subsequent glycolysis, but when increased, some glucose is converted to sorbitol by the enzyme aldose reductase. Increased sorbitol concentration alters redox potential, increases cellular osmolality, generates reactive oxygen species, and likely leads to other types of cellular dysfunction.[8]

A third hypothesis proposes that hyperglycemia increases the formation of diacylglycerol leading to activation of protein kinase C (PKC). Among other actions, PKC alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons.[8]

A fourth theory proposes that hyperglycemia increases the flux through the hexosamine pathway, which generates fructose-6-phosphate, a substrate for

O-linked glycosylation and proteoglycan production. The hexosamine pathway may alter function by glycosylation of proteins such as endothelial nitric oxide synthase or by changes in gene expression of transforming growth factor (TGF-) or plasminogen activator inhibitor-1 (PAI-1).

Growth factors appear to play an important role in DM-related complications and their production is increased by most of these proposed pathways. Vascular endothelial growth factor A (VEGF-A) is increased locally in diabetic proliferative retinopathy and decreases after laser photocoagulation. TGF- is increased in diabetic nephropathy and stimulates basement membrane production of collagen and fibronectin by mesangial cells. Other growth factors, such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor I, growth hormone, basic fibroblast growth factor, and even insulin, have been suggested to play a role in DM-related complications. A possible unifying mechanism is that hyperglycemia leads to increased production of reactive oxygen species or superoxide in the mitochondria; these compounds may activate all four of the pathways described above.[8]

Diabetic Nephropathy

Diabetic nephropathy is the single most common cause of chronic renal failure, accounting for 45% of patients receiving renal replacement therapy, and is a rapidly growing problem worldwide. The dramatic increase in the number of patients with diabetic nephropathy reflects the epidemic increase in obesity, metabolic syndrome, and Type 2 diabetes mellitus. Approximately 40% of patients with Types 1 or 2 diabetes develop nephropathy, but due to the higher

prevalence of Type 2 diabetes (90%) compared to Type 1 (10%), the majority of patients with diabetic nephropathy have Type 2 disease. Risk factors for the development of diabetic nephropathy include hyperglycemia, hypertension, dyslipidemia, smoking, a family history of diabetic nephropathy, and gene polymorphisms affecting the activity of the renin-angiotensin-aldosterone axis.

Within one to two years after the onset of clinical diabetes, morphologic changes appear in the kidney. Thickening of the GBM is a sensitive indicator for the presence of diabetes but correlates poorly with the presence or absence of clinically significant nephropathy. The composition of the GBM is altered notably with a loss of heparan sulfate moieties that form the negatively charged filtration barrier. This change results in increased filtration of serum proteins into the urine, predominately negatively charged albumin. The expansion of the mesangium due to the accumulation of extracellular matrix correlates with the clinical manifestations of diabetic nephropathy. This expansion in mesangial matrix can be associated with the development of *mesangial sclerosis.* Some patients also develop eosinophilic, PAS^{+} nodules called *nodular glomerulosclerosis* or *Kimmelstiel-Wilson nodules*. Immunofluorescence microscopy often reveals the nonspecific deposition of IgG (at times in a linear pattern) or complement staining without immune deposits on electron microscopy. Prominent vascular changes are frequently seen with hyaline and hypertensive arteriosclerosis. This is associated with varying degrees of chronic glomerulosclerosis and tubulointerstitial changes.[8]

These pathologic changes are the result of a number of postulated factors. Multiple lines of evidence support an important role for increases in glomerular

capillary pressure (intraglomerular hypertension) in alterations in renal structure and function. Direct effects of hyperglycemia on the actin cytoskeleton of renal mesangial and vascular smooth-muscle cells as well as diabetes-associated changes in circulating factors such as atrial naturetic factor, angiotensin II, and insulin-like growth factor (IGF) may account for this. Sustained glomerular hypertension increases matrix production, alterations in the GBM with disruption in the filtration barrier (and hence proteinuria) and glomerulosclerosis. A number of factors have also been identified which alter matrix production, including the accumulation of advanced glycosylation end products, circulating factors including growth hormone, IGF-I, angiotensin II, connective tissues growth factor, TGF-β and dyslipidemia.[8]

The natural history of diabetic nephropathy in patients with Types 1 and 2 diabetes is similar. However, since the onset of Type 1 diabetes is readily identifiable and the onset of Type 2 diabetes is not, a patient newly diagnosed with Type 2 diabetes may have renal disease for many years before nephropathy is discovered and presents as *advanced diabetic nephropathy.* At the onset of diabetes, renal hypertrophy and glomerular hyperfiltration are present. The degree of glomerular hyperfiltration correlates with the subsequent risk of clinically significant nephropathy. In the approximately 40% of patients with diabetes who develop diabetic nephropathy, the earliest manifestation is an increase in albuminuria detected by sensitive radioimmunoassay. Microalbuminuria is defined as 30–300 mg/d in a 24-h collection or 30–300 μg/mg creatinine in a spot collection (preferred method). In patients with Types 1 or 2 diabetes, microalbuminuria appears 5–10 years after the onset of diabetes. It

is currently recommended to test patients with Type 1 disease for microalbuminuria 5 years after diagnosis of diabetes and yearly thereafter, and, because the time of onset of Type 2 diabetes is often unknown, to test Type 2 patients at the time of diagnosis of diabetes and yearly thereafter.[8]

Patients with small rises in albuminuria increase their levels of urinary albumin excretion, typically reaching dipstick positive levels of proteinuria (>300 mg albuminuria) 5–10 years after the onset of early albuminuria. Microalbuminuria is a potent risk factor for cardiovascular events and death in patients with Type 2 diabetes. Many patients with Type 2 diabetes and microalbuminuria succumb to cardiovascular events before they progress to proteinuria or renal failure. Proteinuria in frank diabetic nephropathy can be variable, ranging from 500 mg to 25 g/24 h, and is often associated with nephrotic syndrome. Fever and congestive heart failure can cause transient proteinuria. ACE inhibitors and ARBs decrease proteinuria. More than 90% of patients with Type 1 diabetes and nephropathy have diabetic retinopathy, so the absence of retinopathy in Type 1 patients with proteinuria should prompt consideration of a diagnosis other than diabetic nephropathy; only 60% of patients with Type 2 diabetes with nephropathy have diabetic retinopathy.[8]

There is a highly significant correlation between the presence of retinopathy and the presence of Kimmelstiel-Wilson nodules. Also, characteristically, patients with advanced diabetic nephropathy have normal to enlarged kidneys, in contrast to other glomerular diseases where kidney size is usually decreased. Using the above epidemiologic and clinical data, and in the absence of other clinical or serologic data suggesting another disease, diabetic

nephropathy is usually diagnosed without a renal biopsy. After the onset of proteinuria >500 mg/24 h, renal function inexorably declines, with 50% of patients reaching renal failure in 5–10 years; thus, from the earliest stages of microalbuminuria, it usually takes 10–20 years to reach end-stage renal disease. Hypertension may predict which patients develop diabetic nephropathy, as the presence of hypertension accelerates the rate of decline in renal function. Once renal failure appears, however, survival on dialysis is far shorter for patients with diabetes compared to other dialysis patients; some diabetics do better clinically if they are started on dialysis before they reach advanced renal failure.[8]

Diabetic neuropathy

Diabetic neuropathy occurs in ~50% of individuals with long-standing type 1 and type 2 DM. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Additional risk factors are BMI (the greater the BMI, the greater the risk of neuropathy) and smoking. The presence of cardiovascular disease, elevated triglycerides, and hypertension is also associated with diabetic peripheral neuropathy. Both myelinated and unmyelinated nerve fibers are lost. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy should be made only after other possible etiologies are excluded . The ADA recommends screening for distal symmetric neuropathy beginning with the initial diagnosis of diabetes and screening for autonomic neuropathy 5 years after diagnosis of type 1 DM and at the time of

diagnosis of type 2 DM. All individuals with diabetes should then be screened annually for both forms of neuropathy.[8]

Polyneuropathy/Mononeuropathy

The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss, but up to 50% of patients do not have symptoms of neuropathy. Hyperesthesia, paresthesia, and dysesthesia also may occur. Any combination of these symptoms may develop as neuropathy progresses. Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting <12 months) and a chronic form of painful diabetic neuropathy have been described. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit in the lower extremities persists. Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense.

Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain over the thorax or abdomen. Involvement of the lumbar plexus or femoral nerve may cause severe pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Fortunately,

diabetic polyradiculopathies are usually self-limited and resolve over 6–12 months.[8]

Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve. A vascular etiology has been suggested, but the pathogenesis is unknown. Involvement of the third cranial nerve is most common and is heralded by diplopia. Physical examination reveals ptosis and ophthalmoplegia with normal pupillary constriction to light. Sometimes other cranial nerves IV, VI, or VII (Bell's palsy) are affected. Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.[8]

Autonomic Neuropathy Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P) systems.[8] Autonomic neuropathy is associated with a high mortality which is attributed not only to sudden death but also to diabetic nephropathy.[9] DM-related autonomic neuropathy can involve multiple systems, including the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause resting tachycardia and orthostatic hypotension. Reports of sudden death have also been attributed to autonomic neuropathy. Gastroparesis and bladder-emptying abnormalities are often caused by the autonomic neuropathy seen in DM. Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction. Anhidrosis of

the feet can promote dry skin with cracking, which increases the risk of foot ulcers. Autonomic neuropathy may reduce counter regulatory hormone release, leading to an inability to sense hypoglycemia appropriately (hypoglycemia unawareness), thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.[8]

Cardiac autonomic neuropathy

The CAN is a common form of diabetic autonomic neuropathy and causes abnormalities in heart rate control as well as central and peripheral vascular dynamics, the clinical manifestations of which include exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension and painless myocardial ischaemia, and contributes to morbidity, mortality, and reduced quality of life for persons with diabetes mellitus.[33] The incidence of silent myocardial ischaemia in diabetics is very high and CAN seems to be the most probable reason for the absence of pain.[34] The risk of sudden death is also high in patients with CAN.[11,35]

The CAN is a complication that develops slowly over the years. The prevalence of CAN has been reported to be high.[36] Higher age, longer duration of diabetes mellitus and coexistent peripheral neuropathy are associated with higher prevalence of CAN in diabetics Several non-invasive tests, such as cardiac autonomic function tests by Eving's methodology,[37] downward tilting baroreflex sensitivity test,[38] analyses of spontaneous beat-to-beat blood pressure and heart rate variabilities,[39] time domain heart rate variability and heart rate turbulence parameters assessed on 24 h digital Holter recordings,[40] and a new indicator test

based on the measurement of sweat production after exposure to dermal foot perspiration,[41] can be used for the diagnosis of CAN. These tests, although sensitive and reproducible, are laborious and time consuming, and therefore are not practical screening methods for the large number of patients with diabetes mellitus. The following are five tests for detecting cardiac autonomic neuropathy;[37]

1. Resting heart rate (heart rate > 100 beats/min was taken as abnormal);

2. Blood pressure for postural or orthostatic hypotension (blood pressure was recorded in the supine posture and again just after 2 min of standing; a fall in the systolic blood pressure of > 20 mm Hg and/or diastolic blood pressure of > 10 mm Hg were considered abnormal);

3. Heart rate response to Valsalva manoeuvre (ECG was continuously monitored during the procedure and the ratio of the longest RR interval during the release phase to the shortest RR interval during the straining phase was calculated and a value < 1.2 was considered abnormal);

4. Heart rate response to deep breathing (ECG was recorded continuously while the patient was taking breath at a regular rate of 6–12 breaths/min and a difference in heart rate < 15 beats/min between expiration and inspiration was considered abnormal); and

5. Diastolic blood pressure response to an isometric exercise (the patient was asked to squeeze a small ball in his/her left hand for about 5 min and an

increase in diastolic blood pressure < 15 mm Hg was considered. abnormal).

Prolongation of the corrected QT interval (QTc) in the electrocardiogram (ECG) is found to be a specific indicator of CAN in most studies.[11,12,13] The QT interval includes both ventricular depolarization and repolarization times and varies inversely with the heart rate. Severe hypocalcemia can cause prolongation of QT interval.[8] A rate-related ("corrected") QT interval, QT_c, can be calculated as $QT/\sqrt{RR}$ and normally is ≤0.44 s.[8] The prolongation of the QTc interval in the ECG has reasonable sensitivity, specificity and positive predictive value for the detection of CAN in both types of diabetes.[42] The severity of CAN has a correlation with the degree of QTc interval prolongation. QTc interval prolongation, being a high risk factor for major vascular events in patients with diabetes mellitus, should be assessed periodically by 12 lead ECG in patients with type 1 and type 2 diabetes mellitus.[42]

In a cross sectional case control study[18] comparing Type 2 diabetic patients with and without CAN, found the presence of proteinuria (microalbuminuria or overt nephropathy) to be significantly associated with the presence of CAN.

A study[19] has showed that, presence of nephropathy was associated with the risk of CAN in Type 2 diabetes. The prevalence was 2-fold higher in Type 2 diabetic patients with nephropathy (80%) than in those without nephropathy (36%). Moreover, they developed CAN with a short duration of diabetes. This

study highlighted a high risk, and a more severe form of CAN in diabetic patients with nephropathy.

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with type 2 DM during the period of January 2009 to December 2009.

Study design

One year cross-sectional study.

Study period

The present study was conducted during January 2009 to December 2009.

Method of collection of data

Source of Data

Type 2 diabetic patients attending KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

A total of 86 type 2 diabetic patients (43 normoalbuminuric and 43 microalbuminuric) were studied.

Sampling procedure

Based on the literature, considering the proportion of patients with prolonged QTc as 67% in microalbuminuric and 38% in normoalbuminuric type

2 diabetics the sample size was calculated using 2 sample proportions, P1 and P2 using the formula given below.

$$n = \frac{(Z\alpha + Z\beta)\, 2\overline{P}\,(1-\overline{P})}{(P1 - P2)^2}$$

Where, P1 = 0.67

P2 = 0.38

$\overline{P} = (P1 + P2) / 2$

Using the above mentioned formula the sample size was calculated as two sample of 43 each that is 43 type 2 diabetic patients with normalbuminuria and 43 type 2 diabetic patients with microalbuminuria.

Selection criteria

Inclusion Criteria

- All type 2 diabetes patients attending KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over a period of one year

Exclusion Criteria

- History of myocardial infarction / angina.
- Clinical evidence of Heart failure.
- Left bundle branch block.
- Atrial fibrillation.
- Uncontrolled hypertension (more than 180/100 mm Hg).
- Febrile illness.
- Urinary tract infection.

- History of drug intake like ACE inhibitors / ARB /NSAID's.
- Acute poor metabolic control.
- Smoking.
- High serum calcium levels.

Procedure

The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum. During the study period, all patients presenting with and fulfilling the selection criteria were included in this study after obtaining informed written consent (Annexure–I).

Detailed relevant history and clinical examination was done according to predesigned and pretested proforma (Annexure-II).

Investigations like complete blood count, erythrocyte sedimentation rate, urine routine and microscopy, fasting blood sugar or post prandial blood sugar or random blood sugar were done.

Urine albumin excretion (UAE) test (Microalbumin to creatinine ratio) was done. Electrocardiogram was done to calculate the QT_c interval. Average of three QT and RR intervals from the leads where QT interval was easily identified was taken. These intervals were substituted in the Bazzet's formula and the QTc interval was calculated.[8]

Bazzet's formula: $QTc = QT / RR^{1/2}$ ms

Statistical methods

The results were tabulated and the data was analysed using rates, ratios and percentages. The data was compared using chi-square (x^2) test and student 't' test.

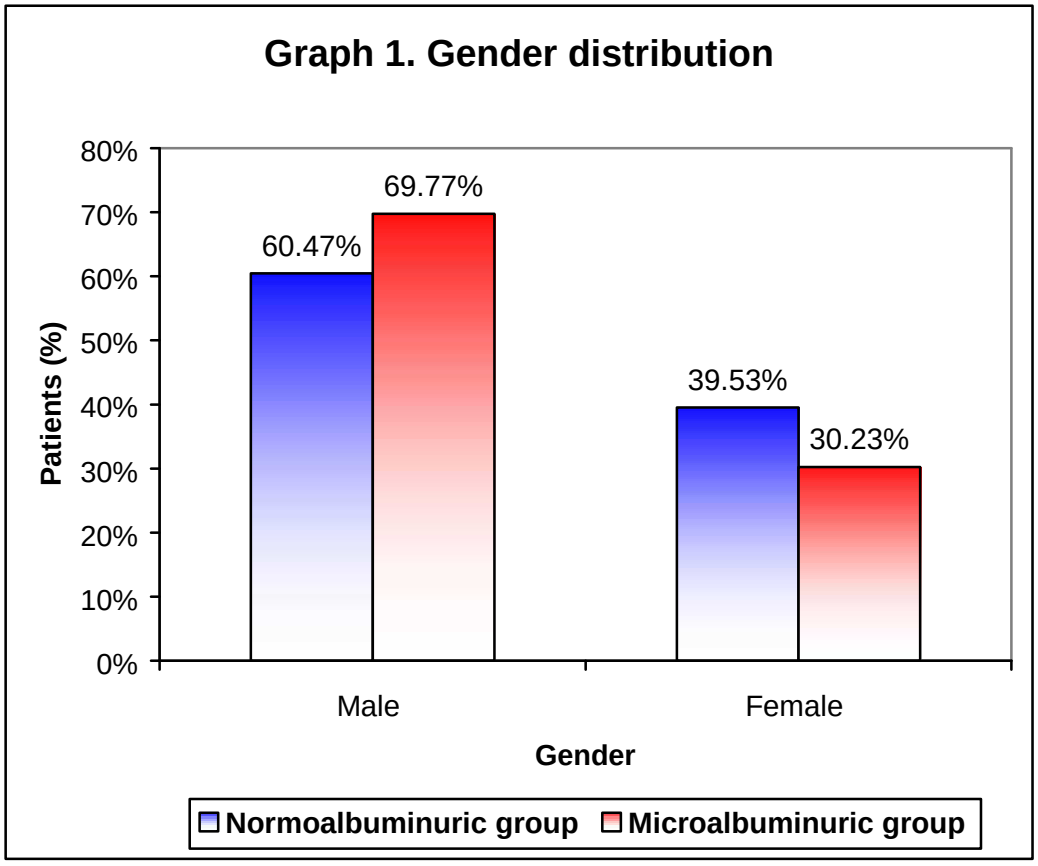
RESULTS

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum in 43 normoalbuminuric and 43 microalbuminuric type 2 diabetic patients. The data obtained was recorded and analysed as follows.

DEMOGRAPHIC CHARACTERISTICS

Table 3. Gender distribution

Gender	Normoalbuminuric group		Microalbuminuric group	
	Number	**Percentage**	**Number**	**Percentage**
Male	26	60.47	30	69.77
Female	17	39.53	13	30.23
Total	**43**	**100.00**	**43**	**100.00**
x^2=0.819		DF=1		p=0.365

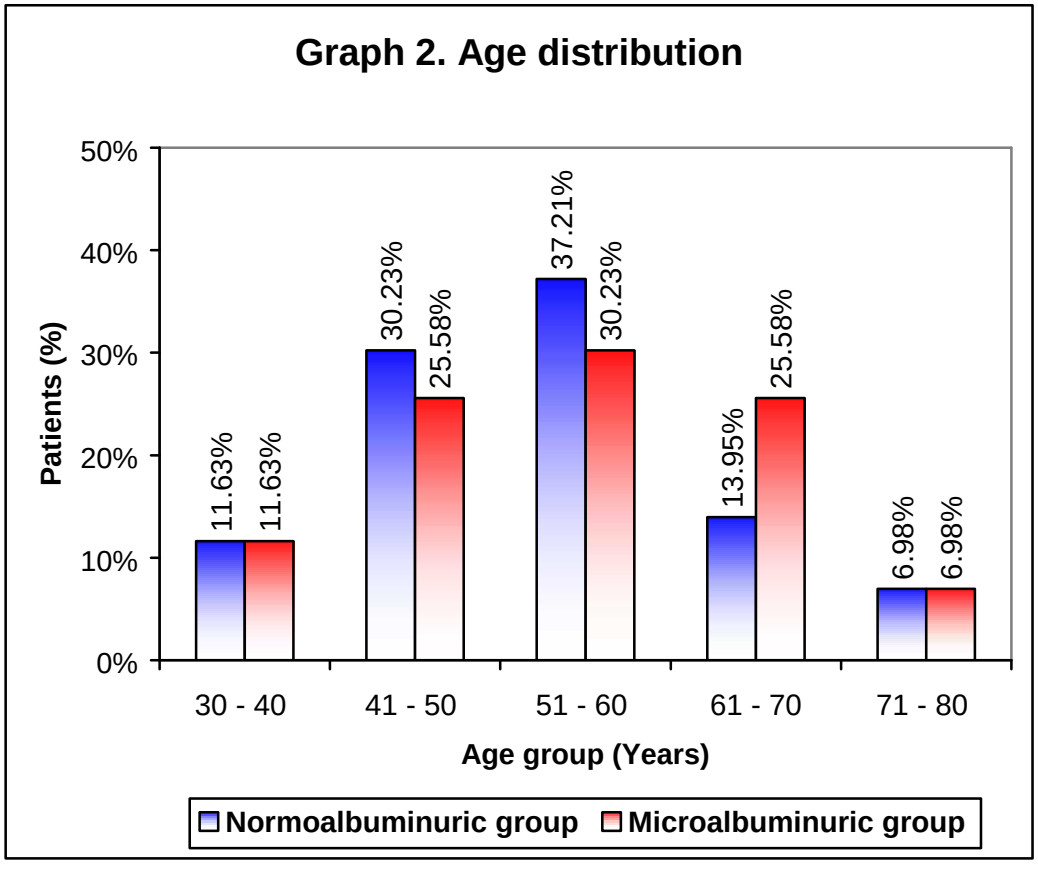


In the present study, 60.47% and 69.77% were males in normoalbuminuric and microalbuminuric groups whereas 39.53% and 30.23% females respectively. The male to female ratio in normoalbuminuric group was 1.52:1 and it was 2.30:1 in microalbuminuric group. The comparison showed equal distribution of gender in both the groups (p=0.365).

Table 4. Age distribution

Age Group (Years)	Normoalbuminuric group		Microalbuminuric group	
	Number	**Percentage**	**Number**	**Percentage**
30 – 40	5	11.63	5	11.63
41 – 50	13	30.23	11	25.58
51 – 60	16	37.21	13	30.23
61 – 70	6	13.95	11	25.58
71 – 80	3	6.98	3	6.98
Total	**43**	**100.00**	**43**	**100.00**

x^2=1.948 DF=4 p=0.745



The above table shows the distribution of subjects according to age. Most of the subjects were in the age group of 51 to 60 years that is 37.21% subjects in normoalbuminuric group and 30.23% in microalbuminuric group and in the age group of 71 to 80 years had least number of subjects that is, 6.98% of subjects each in normoalbuminuric and microalbuminuric group. This difference was statistically not significant (p=0.745).

Table 5. Mean age

	Normoalbuminuric group		**Microalbuminuric group**	
	Mean	**S.D.**	**Mean**	**S.D.**
Mean Age (Years)	54.51	10.15	55.93	11.73
T=0.600	DF=84		p=0.550	

In the present study, the mean age in normoalbuminuric group was 54.51 ± 10.15 years and it was 55.93 ± 11.73 years in microalbuminuric group. This difference was statistically not significant (p=0.550).

Table 6. Duration of diabetes

Duration (Years)	Normoalbuminuric group		Microalbuminuric group	
	Number	**Percentage**	**Number**	**Percentage**
< 10	19	44.19	15	34.88
10 – 15	16	37.21	14	32.56
16 – 20	4	9.30	12	27.91
21 – 25	1	2.33	2	4.65
Newly Detected	3	6.98	0	0.00
Total	**43**	**100.00**	**43**	**100.00**

In the present study most of the subjects had duration of diabetes less than 10 years that is 44.19% in normoalbuminuric group and 34.88% in microalbuminuric group. The least number of subjects that is 2.33% in normoalbuminuric group and 4.65% in microalbuminuric group had duration of diabetes between 21 to 25 years. The newly detected diabetic subjects were 6.98% in normoalbuminuric group and microalbuminuric group had no newly detected diabetic subjects.

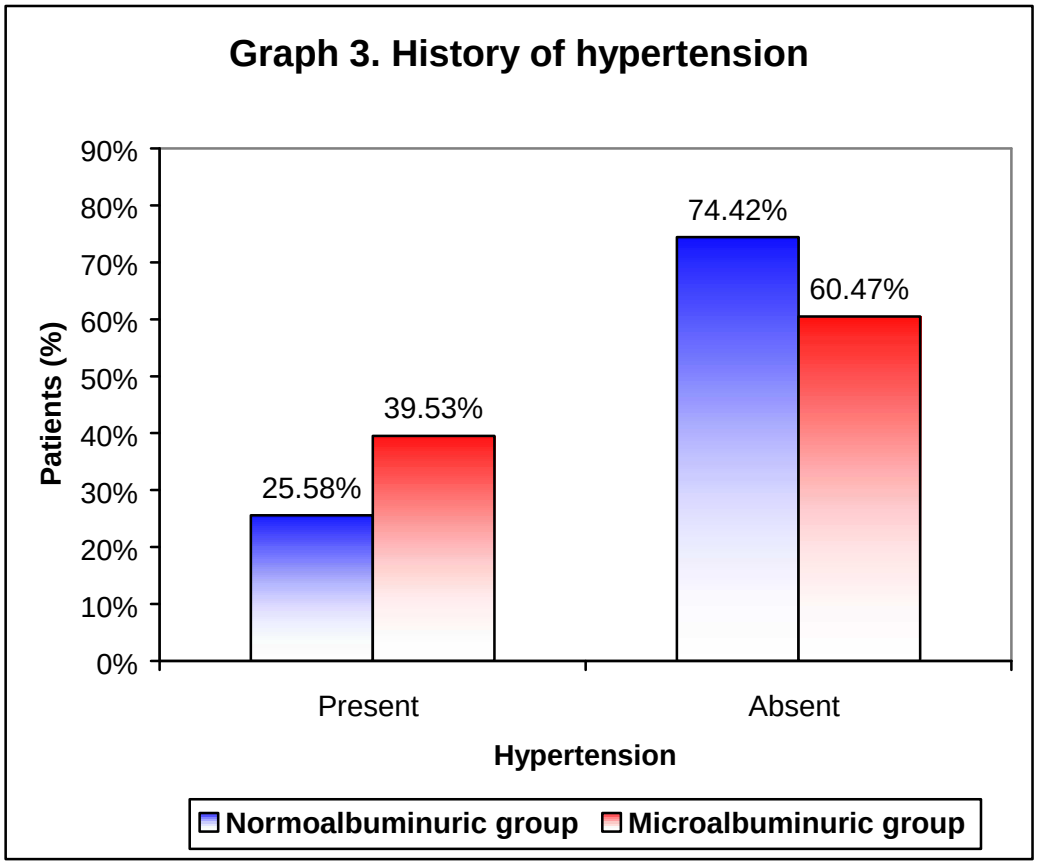
Table 7. Mean duration of diabetes

	Normoalbuminuric group		**Microalbuminuric group**	
	Mean	**S.D.**	**Mean**	**S.D.**
Mean duration of diabetes (Years)	10.90	4.88	12.51	5.04
t=1.505	DF=84		p=0.136	

In the present study, the mean duration of diabetes in normoalbuminuric group was 10.90 ± 4.88 years and it was 12.51 ± 5.04 years in microalbuminuric group. This difference was statistically not significant (p=0.136).

Table 8. History of hypertension

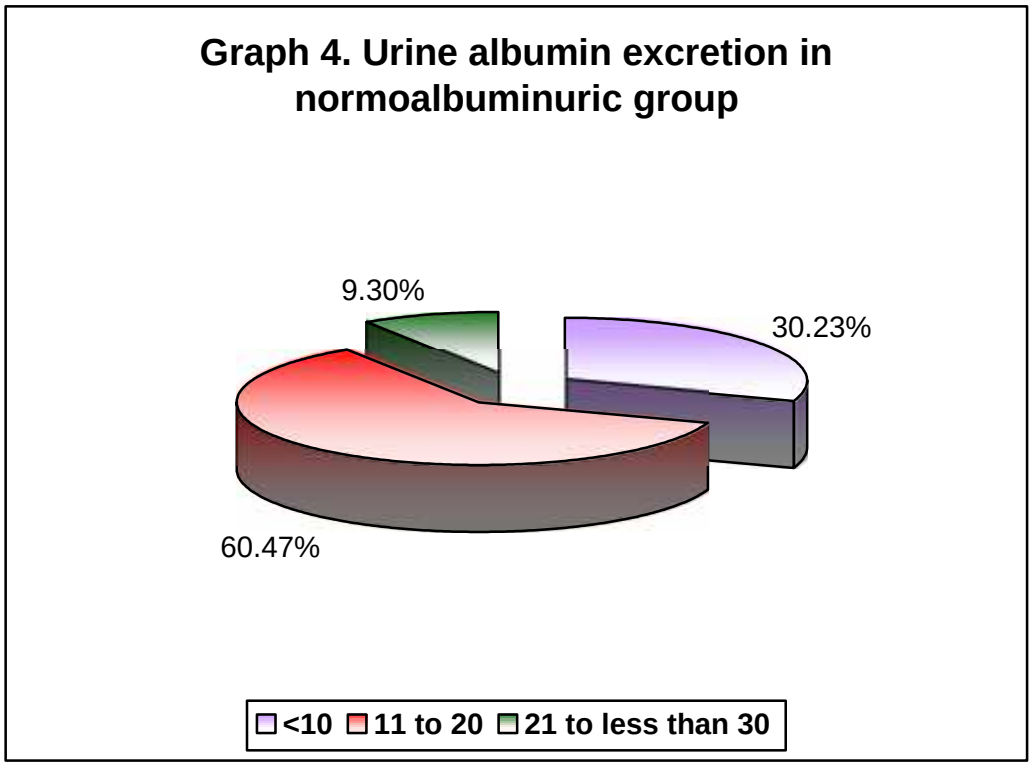
History	Normoalbuminuric group		Microalbuminuric group	
	Number	**Percentage**	**Number**	**Percentage**
Present	11	25.58	17	39.53
Absent	32	74.42	26	60.47
Total	**43**	**100.00**	**43**	**100.00**
x^2 =1.906		DF=1		p=0.167



In the present study, history of hypertension was present in 25.58% in normoalbuminuric group and 39.53% in microalbuminuric group. However this difference was statistically not significant (p=0.167).

Table 9. Urine albumin excretion in normoalbuminuric group

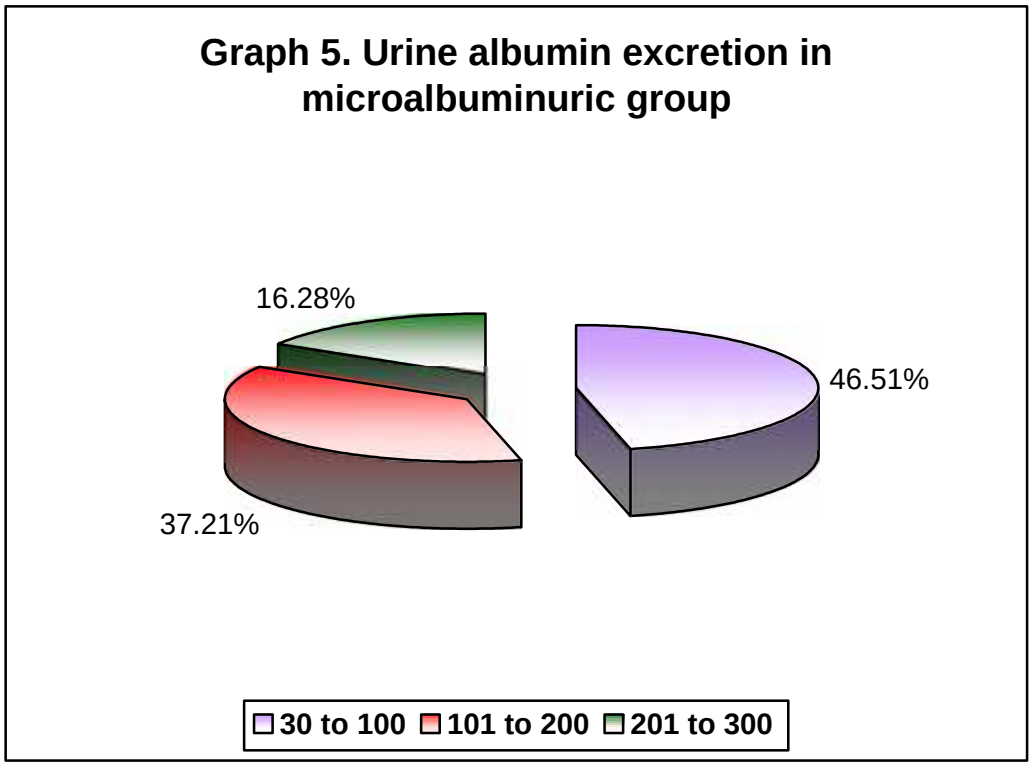
Urine albumin excretion (µg/mg of creatinine)	Normoalbuminuric group	
	Number	**Percentage**
< 10	13	30.23
11 – 20	26	60.47
21 - <30	4	9.30
Total	**43**	**100.00**



In the present study most of the subjects (60.47%) had urine albumin excretion between 11 to 20 µg/mg of creatinine followed by 30.23% with less than 10 µg/mg of creatinine, and 9.30% with 21 to less than 30 µg/mg of creatinine.

Table 10. Urine albumin excretion in microalbuminuric group

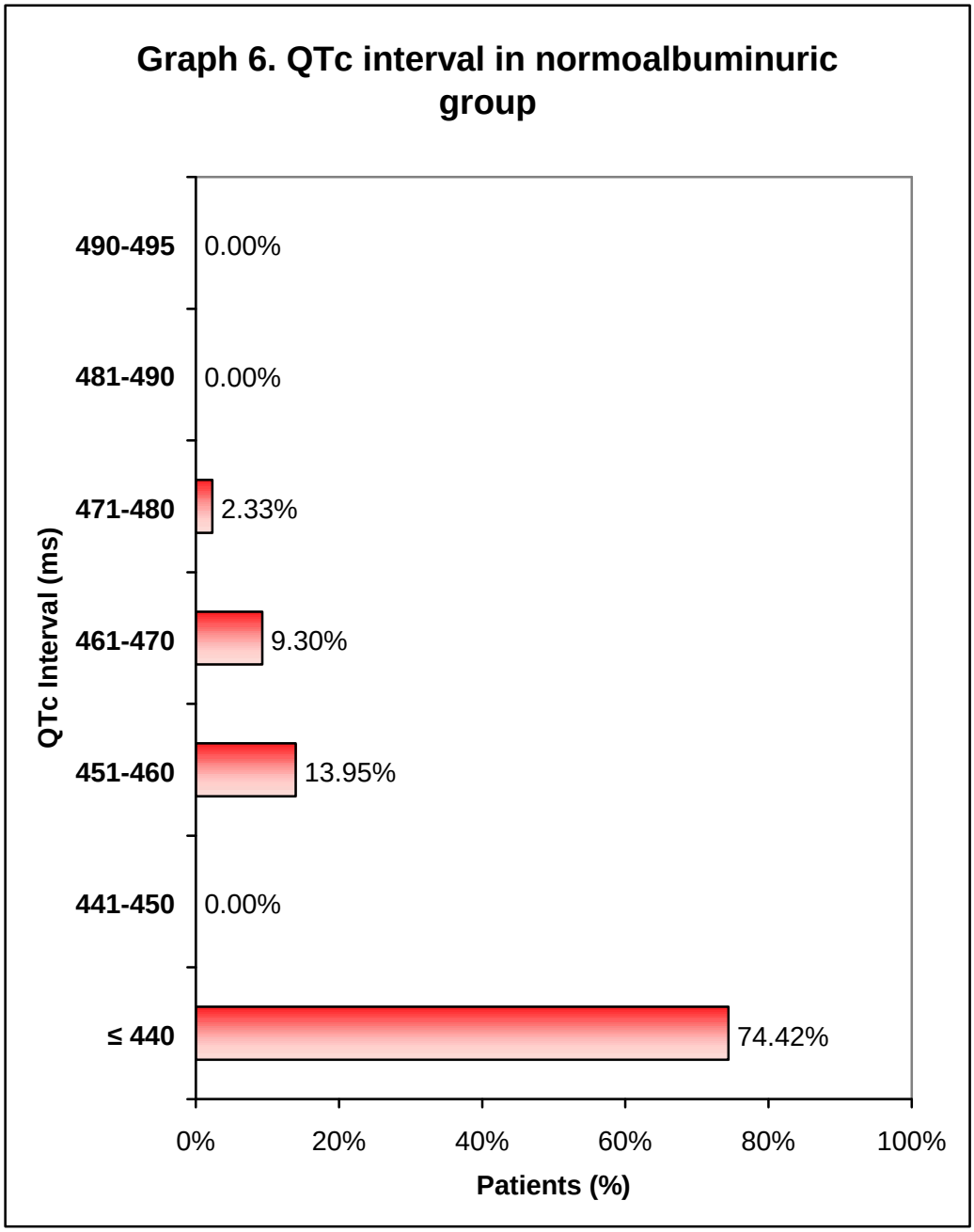
Urine albumin excretion (µg/mg of creatinine)	Microalbuminuric group	
	Number	**Percentage**
30 – 100	20	46.51
101 – 200	16	37.21
201 – 300	7	16.28
Total	**43**	**100.00**



In the present study most of the subjects (46.51%) had urine albumin excretion between 30 to 100 µg/mg of creatinine followed by 37.21% between 101 to 200 µg/mg of creatinine, and 16.28% between 201 to 300 µg/mg of creatinine.

Table 11. QTc interval in normoalbuminuric group

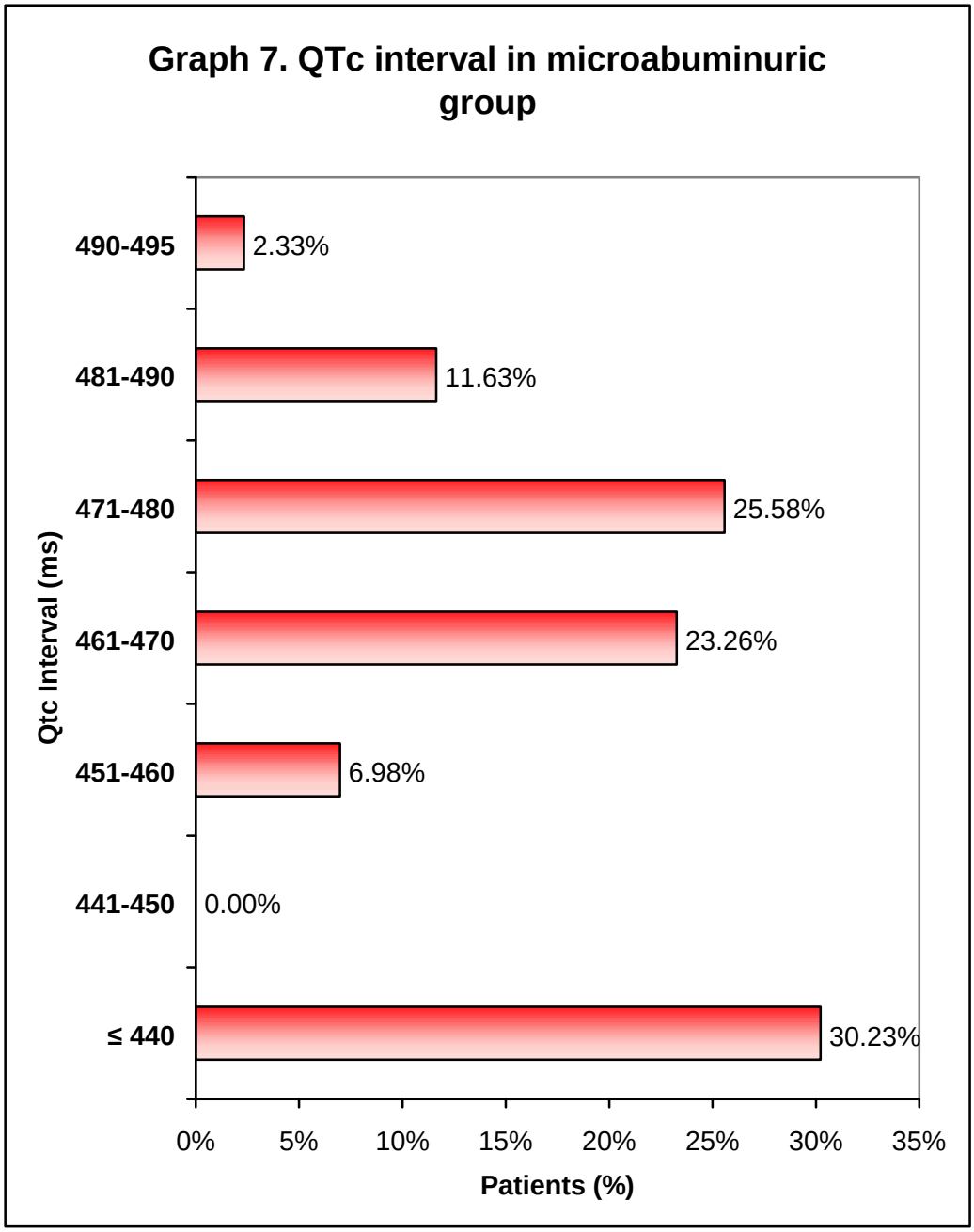
QTc interval (ms)	Normoalbuminuric group	
	Number	**Percentage**
≤ 440	32	74.42
441 – 450	0	0.00
451 – 460	6	13.95
461 – 470	4	9.30
471 – 480	1	2.33
481 – 490	0	0.00
490 – 495	0	0.00
Total	**43**	**100.00**



The above table shows, in normalbuminuric group 74.42% had normal QTc interval whereas 25.58% had prolonged QTc interval of which majority (13.95%) had QTc interval between 451 to 460 ms.

Table 12. QTc interval in microabuminuric group

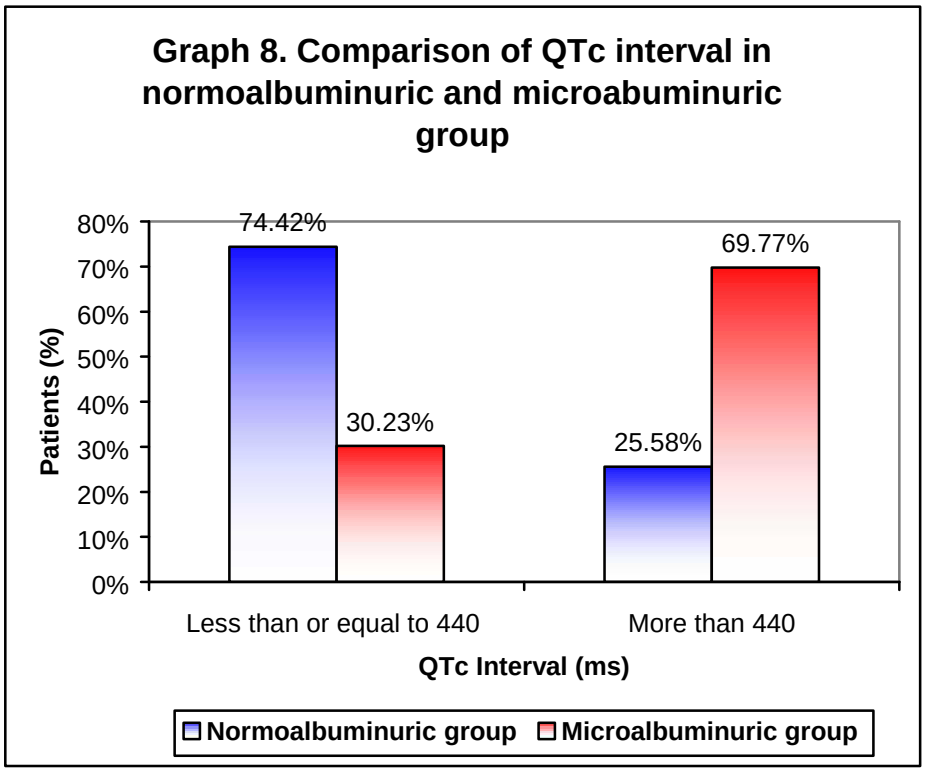
QTc interval (ms)	Microalbuminuric group	
	Number	**Percentage**
≤ 440	13	30.23
441 – 450	0	0.00
451 – 560	3	6.98
461 – 470	10	23.26
471 – 480	11	25.58
481 – 490	5	11.63
490 – 495	1	2.33
Total	**43**	**100.00**



The above table shows, in microalbuminuric group 30.23% had normal QTc interval whereas 69.77% had prolonged QTc interval of which majority (25.58%) had QTc interval between 471 to 480 ms.

Table 13. Comparison of QTc interval in normoalbuminuric and microabuminuric groups

QTc interval (ms)	Normoalbuminuric group		Microalbuminuric group	
	Number	Percentage	Number	Percentage
≤ 440	32	74.42	13	30.23
> 440	11	25.58	30	69.77
Total	**43**	**100.00**	**43**	**100.00**
x^2 =16.827		DF=1		p=0.001



In the present study, QTc interval was prolonged in 25.58% of patients in normoalbuminuric and 69.77% in microalbuminuric group. This difference was statistically significant (p=0.001).

Table 14. Comparison of mean QTc interval in normoalbuminuric and microabuminuric groups

	Normoalbuminuric group		Microalbuminuric group	
	Mean	**SD**	**Mean**	**SD**
QTc interval (ms)	418.13	27.44	454.73	29.33
t=5.975		DF=84		p=0.001

In the present study the mean QTc interval was more (454.73 ± 29.33 ms) in microalbuminuric group compared to normoalbuminuric group (418.13 ± 27.44 ms). This increase in mean QTc interval among microalbuminuric group was statistically significant (p=0.001)

Table 15. Comparison of duration of diabetes to QTc interval in normoalbuminuric group

Duration (Years)	**Normal QTc**		**Prolonged QTc**	
	Number	**Percentage**	**Number**	**Percentage**
< 10	20	62.50	1	9.09
10 – 15	12	37.50	5	45.45
16 – 20	0	0.00	4	36.36
21 – 25	0	0.00	0	0.00
26 – 30	0	0.00	1	9.09
Total	**32**	**100.00**	**11**	**100.00**

In the present study, among patients with normoalbuminuria more number of patients (62.50%) had duration of diabetes was less than 10 years with normal QTc interval whereas in patients with prolonged QTc interval majority (45.45%) had duration between 10 to 15 years.

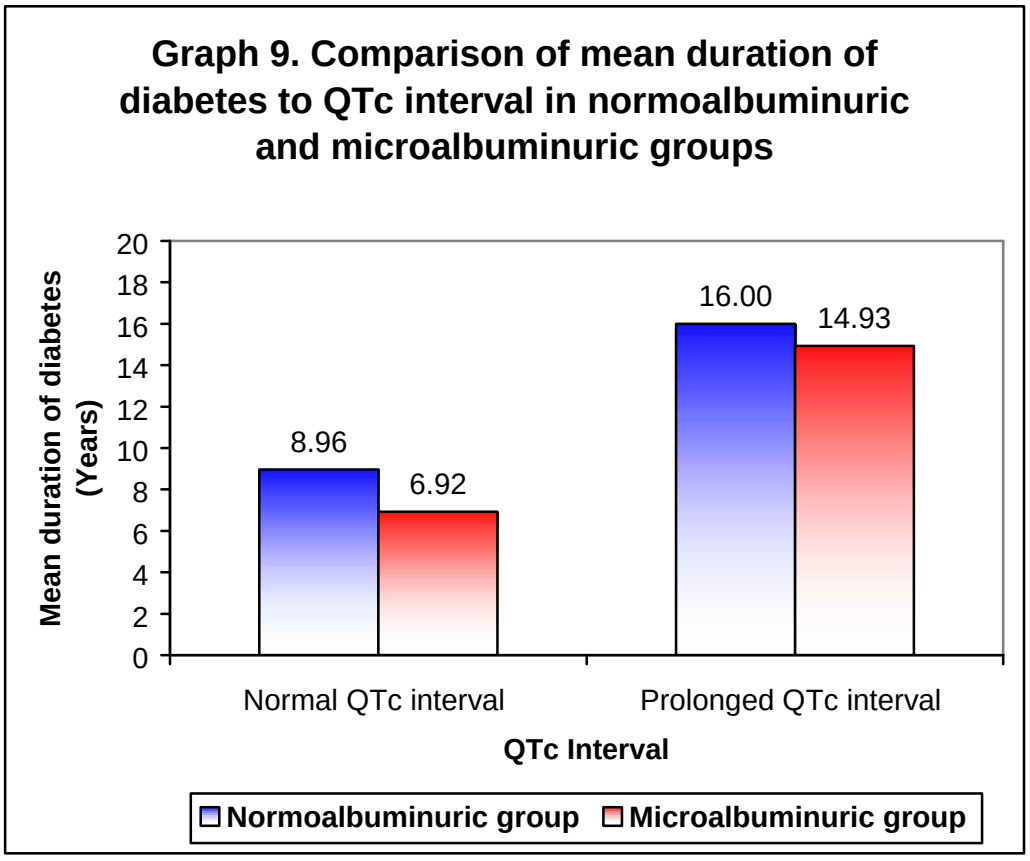
Table 16. Comparison of duration of diabetes to QTc interval in microalbuminuric group

Duration (Years)	Normal QTc		Prolonged QTc	
	Number	**Percentage**	**Number**	**Percentage**
< 10	12	92.31	3	10.00
10 – 15	1	7.69	13	43.33
16 – 20	0	0.00	12	40.00
21 – 25	0	0.00	2	6.67
26 – 30	0	0.00	0	0.00
Total	**13**	**100.00**	**30**	**100.00**

In the present study, among patients with microalbuminuria more number of patients (92.31%) had duration of diabetes was less than 10 years with normal QTc interval whereas in patients with prolonged QTc interval majority (43.33%) had duration between 10 to 15 years.

Table 17. Comparison of mean duration of diabetes to QTc interval in normoalbuminuric and microalbuminuric groups

Groups	Mean duration of diabetes (Years)			
	Normal QTc interval		Prolonged QTc interval	
	Mean	SD	Mean	SD
Normoalbuminuric	8.96	3.25	16.00	4.87
Microalbuminuric	6.92	2.32	14.93	3.81
t	2.054		0.739	
Df	43		39	
p	0.046		0.464	

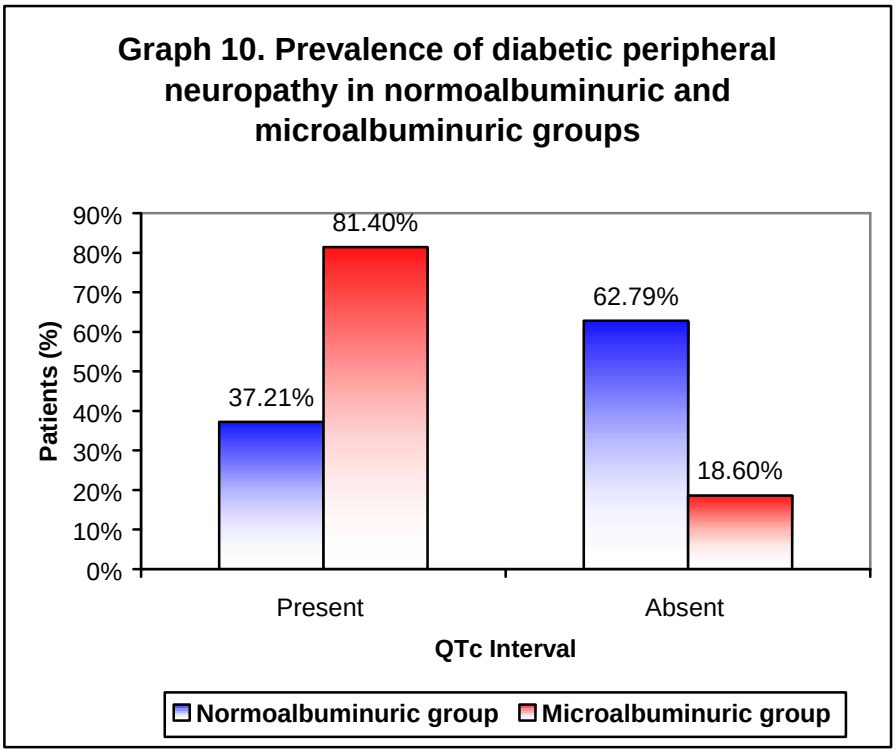


In this study the mean duration of diabetes was significantly high (8.96 ± 3.25 years) among patients with normoalbuminuria and normal QTc interval compared to 6.92 ± 2.32 years in patients with microalbuminuria and normal QTc interval (p=0.046). The mean duration of diabetes was high (16.00 ± 4.87 years) among patients with normoalbuminuria and prolonged QTc interval compared to 14.93 ± 3.81 years in patients with microalbuminuria and prolonged QTc interval. However this difference was statistically not significant (p=0.464).

Table 18. Prevalence of diabetic peripheral neuropathy in normoalbuminuric and microalbuminuric groups

Prevalence of DPN	Normoalbuminuric group		Microalbuminuric group	
	Number	**Percentage**	**Number**	**Percentage**
Present	16	37.21	35	81.40
Absent	27	62.79	8	18.60
Total	**43**	**100.00**	**43**	**100.00**

x^2 = 17.393 DF = 1 p=0.001



In this study the prevalence of diabetic peripheral neuropathy was high (81.40%) in microalbuminuric group compared to normoalbuminuric group (37.21%). This higher prevalence of diabetic peripheral neuropathy among patients with microalbuminuria was statistically significant (p=0.001).

Table 19. Prevalence of prolonged QTc interval in DPN patients with normoalbuminuria and microalbuminuria

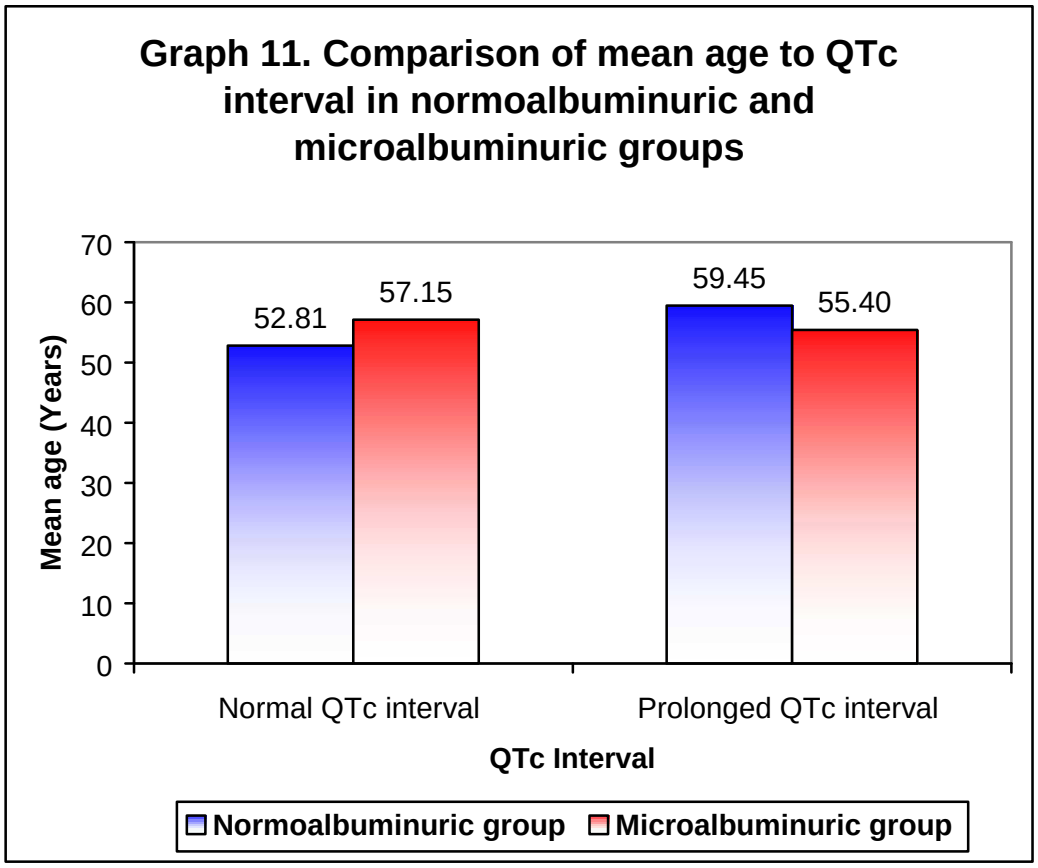
	Normoalbuminuric patients with DPN (n = 16)		Microalbuminuric pateints with DPN (n = 35)	
	Number	**Percentage**	**Number**	**Percentage**
Prevalence of prolonged QTc	11	68.75	30	85.71

$x^{2} =$ 2.005 DF = 1 p=0.157

In this study the prevalence of prolonged QTc interval was high (85.71%) in microalbuminuric patients with diabetic peripheral neuropathy compared to normoalbuminuric patients with diabetic peripheral neuropathy (68.75%). However this higher prevalence of prolonged QTc interval among patients with microalbuminuria and diabetic peripheral neuropathy was statistically not significant (p=0.157).

Table 20. Comparison of mean age to QTc interval in normoalbuminuric and microalbuminuric groups

Groups	Mean age (Years)			
	Normal QTc interval		Prolonged QTc interval	
	Mean	SD	Mean	SD
Normoalbuminuric	52.81	9.81	59.45	9.88
Microalbuminuric	57.15	13.40	55.40	11.14
t	1.207		1.061	
Df	43		39	
p	0.234		0.295	



In this study, the mean age was high (57.15 ± 13.40 years) among patients with microalbuminuria and normal QTc interval compared to patients with normoalbuminuria and normal QTc interval (52.81 ± 9.81 years). However this difference was statistically not significant (p=0.295).

The mean age was less (55.40 ± 11.14 years) among patients with microalbuminuria and prolonged QTc interval compared to normoalbuminuria and prolonged QTc interval (59.45 ± 9.88 years). However this difference was statistically not significant (p=0.295).

DISCUSSION

Type 2 diabetes is a common condition with a greatly increased risk of premature cardiovascular death compared to the general population.[7]

The presence of microalbuminuria is associated with a further doubling of the risk of early death, mostly from cardiovascular disease. The increased risk is not fully explained by standard cardiovascular risk factors.[7]

Microalbuminuria (increased urinary albumin excretion) is present in 25% of subjects with type 2 diabetes and is a strong and independent predictor of premature cardiovascular death.[7]

Cardiac dysfunction due to CAN has been demonstrated in diabetic patients without evidence of ischemic heart disease and this can increase the risk of sudden unexpected death.[10] CAN can be detected in atleast one third of type 2 diabetic patients.[9]

An association between autonomic neuropathy and diabetic nephropathy has been demonstrated in type 1 diabetic patients.[14-17] There are not many studies conducted on type 2 diabetic patients with nephropathy.

The total subjects in the present study were 86. Of them 43 were type 2 diabetic patients with normoalbuminuria and the other 43 were type 2 diabetic patients with microalbuminuria. Out of the 86 patients 56 were male and 30 were female. Male patients were 26 and 30 in number and female patients were 17 and 13 in number in normoalbuminuric and microalbuminuric groups respectively.

This was in accordance with a study done in 2002, on asymptomatic patients with type 2 diabetes with no clinical evidence of coronary disease (43 patients with normoalbuminuria matched with 43 microalbuminuric patients).[7]

Most of the subjects in the present study, were between 51 to 60 years of age, who comprised 37.21% of sample size in normoalbuminuric group and 30.23% of sample size in microalbuminuric group.

The mean age of the subjects in the present study was 54.51 ± 10.15 years and 55.93 ± 11.73 years in normoalbuminuric and microalbuminuric groups respectively.

Hence, both the groups were sex and age matched.

The history of HTN was present in 25.58% in normoalbuminuric group and 39.53% in microalbuminuric group. This was not statistically significant (p=0.167) even though more number of patients had history of HTN in the microalbuminuric group.

A cross sectional study was done in Kottayam medical College during 2008 in central Kerala to study the prevalence and risk factors for cardiac autonomic neuropathy (CAN) and the utility to prolongation of corrected QT interval (QTc) in the ECG to diagnose CAN in 100 patients with type 1 and type 2 diabetes mellitus. This study concluded that, QTc interval in the ECG can be used to diagnose CAN with reasonable sensitivity, specificity and positive predictive value.[42]

A study[13] was done in Athens, Greece during 1997 to investigate, to what extent the existence of objective signs of diabetic autonomic neuropathy affects the QTc interval in 105 type 1 and type 2 diabetic subjects. This study confirmed the well known relation between autonomic neuropathy and QTc interval and showed that QTc prolongation is associated with major degrees of autonomic neuropathy.

The present study calculated QTc interval in normoalbuminuric group and microalbuminuric group subjects to diagnose cardiac autonomic neuropathy.

A study[7] conducted in UK during 2002 to determine if QT prolongation and/or dispersion are linked to microalbuminuria in patients with type 2 diabetes, showed that the rate corrected maximum QTc interval was greater in the microalbuminuric group and rate corrected QT dispersion was similar in the two groups.

A study[43] done in UK during 1998 showed that the presence of microalbuminuria is linked to autonomic neuropathy and reduced heart rate variability in type 2 diabetes patients.

A study[19] conducted in Madras during 2000 showed that the presence of nephropathy was associated with the risk of cardiac autonomic neuropathy in type 2 diabetic patients. A study[36] done in Jaipur during 2002 showed a positive correlation of CAN to microalbumiuria in NIDDM patients.

The present study showed that, prevalence of prolonged QTc interval was higher in microalbuminuric group compared to normoalbuminuric group i.e.

(69.77% vs 25.58% respectively). This was statistically significant (p=0.001). This shows that presence of microalbuminuria is associated with the risk of CAN in type 2 diabetes.

The mean QTc interval was also higher in microalbuminuric group compared to normoalbuminuric group (454.73 ± 29.33 ms vs 418. 13 ± 27.44 ms respectively). This was statistically significant. (p=0.001).

A study[19] done in Madras during 2000 showed that type 2 diabetes mellitus patients developed cardiac autonomic neuropathy with a short duration of diabetes.

In the present study, the mean duration of diabetes in prolonged QTc interval patients was lesser in microalbuminuric group (14.93 ± 3.81 years) than in normalbuminuric group (16 ± 4.87 years) that is, type 2 diabetic patients with microalbuminuria developed CAN with short duration of diabetes. But statistical significance was not obtained due to less number of patients in each group.

A study[19] done in Madras during 2000 showed that peripheral neuropathy was significantly higher in the nephropathic group than in the non nephropathic group, in type 2 diabetic patients.

In the present study, the prevalence of diabetic peripheral neuropathy was higher in microalbuminuric group (81.40%) than in normalbuminuric group (37.21%). This was statistically significant (P = 0.001).

A study[44] conducted in 2000 showed that QTc interval, but not QT-dispersion is an independent predictor of all cause and cardiovascular mortality in NIDDM patients.

The MONICA/KORA Augsburg Cohort study[45] showed that prolonged QTc interval, but not QT dispersion, is an independent predictor of a two fold and three fold increased risk of mortality in the nondiabetic and type 2 diabetic elderly general populations respectively.

A study[9] done in Edinburgh in 1980, on 72 diabetic who complained of symptoms suggestive of autonomic neuropathy. These patients were followed prospectively for up to five years and showed a calculated mortality rate of 44% after two and half years and 56% after five years. Half of the deaths in the study were from renal failure. The study showed that autonomic neuropathy was associated with a high mortality which is attributed not only to sudden death, but also to diabetic nephropathy.

Observations from the present study highlight the necessity for larger studies to show that presence of microalbuminuria is associated with the risk of cardiac autonomic neuropathy in type 2 diabetes.

CONCLUSION

- The prevalence of CAN as diagnosed by prolonged QTc interval was more in Type 2 DM patients with microalbuminuria.

- Type 2 diabetic patients with microalbuminuria can develop CAN with short duration of diabetes.

- Prevalence of diabetic peripheral neuropathy was more in type 2 diabetic patients with microalbuminuria.

- In asymptomatic type 2 diabetic patients with no clinical evidence of heart disease the presence of microalbuminuria is associated with the risk of CAN.

SUMMARY

The link between microalbuminuria and premature death in type 2 diabetes is not completely explained by conventional cardiovascular risk factors. Cardiac autonomic neuropathy can be detected in atleast one third of type 2 diabetic patients. CAN is associated with a high mortality which is attributed not only to sudden death but also to diabetic nephropathy. Prolonged QT_c interval is found to be a specific indicator for CAN. The present study was undertaken to find the association between prolonged QT_c interval and microalbuminuria in type 2 diabetes patients.

The present one year cross-sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 86 (43 with normoalbuminuria and 43 with microalbuminuria) patients with type 2 DM during the period of January 2009 to December 2009. Investigations like complete blood count, erythrocyte sedimentation rate, urine routine and microscopy, fasting blood sugar or post prandial blood sugar or random blood sugar were done. Urine albumin excretion test (Microalbumin to creatinine ratio) was done. Electrocardiogram was done to calculate the QT_c interval. QTc interval was calculated using Bazzet's formula.

In the present study, 60.47% and 69.77% were males in normoalbuminuric and microalbuminuric groups respectively. The mean age in normoalbuminuric group was 54.51±10.15 years and it was 55.93±11.73 years in microalbuminuric group. Most of subjects had duration of diabetes less than 10 years (44.19% in normoalbuminuric and 34.88% in microalbuminuric groups

respectively). QTc interval was significantly prolonged in 25.58% of patients in normoalbuminuric and 69.77% in microalbuminuric group (p=0.001). Mean QTc interval was significantly more (454.73±29.33 ms) in microalbuminuric group compared to normoalbuminuric group (418.13±27.44 ms) (p=0.001). Mean duration of diabetes was less (14.93±3.81 years) in microalbuminuric group compared to (16.00±4.87 years) normoalbuminuric group.

The study showed that, prevalence of CAN as diagnosed by prolonged QTc interval was more in Type 2 DM patients with microalbuminuria and type 2 diabetic patients with microalbuminuria can develop CAN with short duration of diabetes.

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ANNEXURE I - CONSENT FORM

"A CROSS SECTIONAL STUDY TO FIND THE ASSOCIATION BETWEEN PROLONGED QT_C INTERVAL AND MICROALBUMINURIA IN PATIENTS OF TYPE 2 DIABETES MELLITUS"

Objective and purpose of the study

This research is intended to find the association between prolonged QTc interval and microalbuminuria in type 2 diabetes mellitus patients. The principal investigator of the study is Dr. ***** *******. under the guidance of Dr. ***** ******.

Procedure

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about my rights as a participant you may call Principal and Chairman, J.N.M.C Ethical Committee for Human Research.

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant:_____ Signature / Thumb print _____

In case of queries during study or in future you may contact following person

Principal investigator : Dr. ***** *******

Guide : Dr. ****** ******

Name of the Witness _____ Signature _____

Investigator Name_____ Signature _____

Date: Place:

ANNEXURE II – PROFOMA

Name S. No.

Age Case/Control

Sex OPD / IPD No:

Address

Occupation

Date of enrollment

HISTORY

Presenting Complaints

History of presenting illness

Significant Past History

Diabetic history

Duration of Diabetes

Age at onset of Diabetes

Family history of diabetes

Treatment History of diabetes:

Drug Name/Dosage/Frequency/Duration of treatment

Other Drugs (If any)

Significant personal history:

Significant Family history:

GENERAL PHYSICAL EXAMINATION

VITAL SIGNS

Pulse: Respiratory rate:

Blood Pressure Temperature:

- In Sitting position
- In Standing position

Examination of peripheral pulses

Any significant findings (Pallor, Icterus Etc)

SYSTEMIC EXAMINATION

Respiratory system

Cardio-vascular system

Per-Abdominal examination

Central nervous examination

EVALUATION OF DIABETIC COMPLICATIONS

VASCULAR COMPLICATIONS

1. MICRO VASCULAR COMPLICATIONS

DIABETIC NEUROPATHY

Symptoms –

Tingling/Numbness/Burning

Neuropathic pain

Diabetic polyradicular pain

Mononeuropathy – Cranial-

Peripheral

Examination –

Primary sensations:

Pain:

Temperature:

Touch:

Vibration:

Position sense:

Loss of ankle reflex

DIABETIC RETINOPATHY

Fundus examination

DIABETIC NEPHROPATHY

Microalbuminuria

2. MACRO VASCULAR COMPLICATIONS

History suggestive of:

Coronary artery disease

Cerebro vascular disease

Peripheral vascular disease

NON VASCULAR COMPLIACTIONS

Gastrointestinal Manifestations

Anorexia/Nausea/Vomiting/Bloating/ Nocturnal Diarrhea

Genitourinary Complications

History suggestive of Diabetic vesicopathy

History of Erectile dysfunction/retrograde ejaculation

Dermatological manifestations

Diabetic dermopathy

Sclererderma

Lipoatrophy/hypertrophy

Xerosis/Pruritis

INVESTIGATIONS

ROUTINE INVESTIGATIONS

COMPLETE BLOOD COUNT-

1. Hemoglobin
2. Total leukocyte count
3. Differential leukocyte count

URINE ROUTINE -

MICROALBUMINURIA

SERUM CALCIUM

BLOOD UREA (Whenever possible)-

SERUM CREATININE (Whenever possible)-

SPECIFIC INVESTIGATIONS

FASTING BLOOD SUGAR/

POST PRANDIAL BLOOD SUGAR /

RANDOM BLOOD SUGAR –

ECG –

QT interval:

RR interval:

QTc interval:

GLYCATED HAEMOGLOBIN (Whenever possible)–

FUNDUS EXAMINATION (Whenever possible) –

_____

SIGNATURE OF THE GUIDE

ANNEXURE III - MASTER CHART – NORMOALBUMINURIC GROUP

Sr. No.	IP. No. / OP. No.	Gender	Age (Years)	Duration of DM	HTN	FBS/RBS (mg/dL)	UAE Test	Heart rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	QTc Interval (ms)	DPN
1	593025	M	50	7	AB	138	16.0	74	112	76	404	AB
2	1277670	M	45	8	AB	117	12.6	80	128	76	416	AB
3	813993	F	40	6	AB	R170	8.0	86	122	78	421	AB
4	1369124	F	60	10	AB	105	20.0	74	114	72	395	AB
5	1352912	M	50	9	AB	R174	14.0	76	108	70	392	AB
6	1364311	M	65	12	AB	128	7.0	104	110	72	453	PR
7	1323457	M	65	14	PR	115	6.0	96	140	90	455	PR
8	1341512	M	72	11	AB	R126	12.4	80	112	74	411	AB
9	1351925	M	53	6	AB	139	5.1	78	110	70	388	AB
10	1186443	M	58	11	PR	110	16.0	80	138	86	397	AB
11	665971	F	47	7	AB	R160	14.2	82	114	70	407	AB
12	1170772	M	65	10	AB	114	10.0	84	116	74	431	AB
13	1370975	F	48	5	PR	139	9.0	70	136	84	389	AB
14	1333938	F	50	4	AB	124	12.0	72	108	72	399	AB
15	666759	M	52	9	AB	96	15.0	82	110	70	402	AB
16	1361062	F	60	15	AB	126	20.0	86	122	78	417	PR
17	1356521	F	60	8	AB	136	8.0	72	128	78	381	AB
18	1351930	M	70	14	PR	128	18.0	84	136	88	421	PR
19	1162149	M	55	15	AB	R142	22	98	110	74	460	PR
20	641776	M	50	10	AB	88	12.2	78	114	78	411	PR
21	1120204	M	35	5	AB	R180	14.8	72	106	70	399	AB
22	1352912	M	45	N.D	AB	100	11	74	112	72	395	AB
23	593856	F	66	18	PR	R92	19.6	86	142	94	460	PR
24	375095	M	77	14	AB	R169	20	80	116	74	402	PR
25	655373	M	49	18	AB	99	26.8	100	102	70	465	PR
26	1085455	M	45	14	AB	134	28.0	94	100	68	456	PR
27	1262488	F	54	9	AB	132	9.0	72	110	70	386	AB
28	1315912	F	51	12	AB	R152	18.0	88	112	74	465	PR
29	1154362	F	55	20	PR	102	19.0	84	144	98	464	PR
30	1355327	F	38	N.D	AB	114	10.0	88	128	70	412	AB
31	1304194	M	50	9	PR	116	8.0	70	140	92	385	AB
32	1363394	F	52	5	AB	132	14.0	74	110	68	400	AB
33	855473	M	59	19	AB	R178	28.0	100	108	78	465	PR
34	1349037	F	50	6	AB	84	14.0	72	114	72	399	AB
35	1168862	F	39	7	AB	R178	6.0	74	110	78	400	AB
36	370977	M	80	8	PR	118	18.0	82	150	100	458	PR
37	1354539	M	58	12	PR	127	5.0	76	146	92	405	AB
38	1351591	M	59	14	AB	R176	9.1	78	112	74	415	PR
39	1354965	F	40	N.D	AB	106	8.0	78	116	78	406	AB
40	1359898	M	64	26	PR	138	15.2	94	144	98	471	PR
41	1362329	F	49	9	AB	R142	10.0	82	110	70	407	AB
42	10312000	M	59	15	PR	96	16.4	80	142	72	407	AB
43	374067	M	55	5	AB	R98	6.0	84	120	76	412	AB

MICROALBUMINURIC GROUP

Sr. No.	IP. No. / OP. No.	Gender	Age (Years)	Duration of DM	HTN	FBS/RBS (mg/dL)	UAE Test	Heart rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	QTc Interval (ms)	DPN
1	134539	M	58	14	PR	110	121.0	100	156	102	465	PR
2	1368180	F	60	14	PR	92	216.0	102	144	98	475	PR
3	1369119	M	68	8	AB	R146	94.6	74	110	72	404	AB
4	1351459	M	59	15	PR	124	82.9	106	140	90	473	PR
5	856202	M	37	6	AB	140	55.0	92	112	78	458	PR
6	618570	F	34	4	AB	92	122.0	74	110	76	391	AB
7	1186260	M	65	15	PR	R176	48.5	100	146	94	470	PR
8	581444	F	52	21	AB	122	196.0	105	114	74	482	PR
9	1320161	M	61	8	AB	110	66.0	84	118	78	426	PR
10	917070	F	43	8	AB	98	43.0	98	120	76	455	PR
11	1342931	M	82	7	PR	R146	135.0	78	146	100	415	AB
12	1364691	M	58	8	AB	128	244.0	70	120	80	389	PR
13	1228490	M	48	18	AB	139	59.0	104	116	76	474	PR
14	1022647	M	52	16	AB	R140	101.0	97	112	70	473	PR
15	1361621	M	75	14	AB	116	115.7	88	110	78	470	PR
16	1360349	F	45	18	PR	96	86.0	94	140	96	486	PR
17	1270646	F	57	16	AB	147	76.5	107	112	74	475	PR
18	976353	M	80	17	PR	R182	281.0	94	132	70	458	PR
19	603325	F	47	19	AB	R176	185.7	102	106	70	475	PR
20	1363243	M	36	4	AB	R112	94.45	80	116	78	420	AB
21	597271	M	56	15	PR	129	141.0	99	140	84	478	PR
22	1276178	M	38	10	AB	132	83.0	102	110	70	475	PR
23	1216452	M	38	8	AB	R156	38.0	88	116	78	465	PR
24	902412	M	55	7	PR	86	135.7	84	130	90	431	AB
25	599122	F	59	9	AB	99	223.0	88	118	78	431	PR
26	1137791	M	50	20	PR	138	279.0	112	120	82	492	PR
27	10328283	M	50	17	AB	126	52.7	98	110	70	481	PR
28	591546	F	65	13	PR	100	168.0	108	128	86	467	PR
29	585036	M	58	12	AB	R148	117.0	94	114	78	461	PR
30	1321246	M	65	16	PR	128	286.0	98	132	76	475	PR
31	736775	M	70	6	AB	112	111.0	88	116	80	426	AB
32	1320411	M	59	22	PR	136	48.0	108	120	82	483	PR
33	1346018	M	49	8	AB	R190	93.7	72	114	74	390	PR
34	1351162	M	63	4	AB	98	55.9	92	110	74	436	AB
35	375017	F	69	13	PR	139	150.0	86	116	70	469	PR
36	1355079	M	68	10	AB	127	69.0	104	120	80	463	PR
37	374357	M	49	16	AB	116	156.0	110	110	70	482	PR
38	371893	F	45	19	AB	136	101.0	96	110	76	476	PR
39	1349593	M	70	15	PR	R168	90.0	100	142	90	465	PR
40	1358858	F	62	12	PR	R182	74.0	92	148	96	436	PR
41	680709	M	60	15	PR	92	283.0	98	150	98	465	PR
42	661862	F	44	16	AB	114	58.6	104	116	80	479	PR
43	1358862	M	46	5	AB	R172	151.0	76	110	74	396	AB

KEY TO MASTER CHART

AB	-	Absent
BP	-	Blood pressure
dL	-	Deci Litre
DM	-	Diabetes mellitus
DPN	-	Diabetic peripheral neuropathy
F	-	Female
FBS	-	Fasting blood sugar
HTN	-	Hypertension
IP. No.	-	In patient number
M	-	Male
mg	-	Milligram
Min	-	Minute
mm Hg	-	Millimeter of mercury
N.D.	-	Newly detected
OP. No.	-	Out patient number
PR	-	Present
QTc interval	-	Corrected QT interval
R	-	Random
RBS	-	Random blood sugar
Sr. No.	-	Serial Number
UAE Test	-	Urine albumin excretion test