"CORRELATION OF eGFR TO MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES PATIENTS" - A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR.PRABHAKAR KORE HOSPITAL & MRC BELGAUM

By

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Dissertation submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
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M. D. MEDICINE

Under the Guidance of

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KLE UNIVERSITY, BELGAUM,

KARNATAKA

DECLARATION

I hereby declare that this dissertation entitled **"CORRELATION OF eGFR TO MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES PATIENTS" - A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR.PRABHAKAR KORE HOSPITAL & MRC BELGAUM"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. PRAKASH BABALICHE** $_{MD}$ Associate Professor, Department of Medicine, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 10.

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CERTIFICATE

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LIST OF ABBREVIATIONS USED

ADA	American Diabetes Association
AGEs	Advanced glycosylation end products
BMI	Body Mass Index
CDC	Centre for Disease control and prevention
CURES	Chennai urban Rural Epidemiology Study
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FPG	Fasting Plasma Glucose
GDM	Gestational diabetes mellitus
HbA1C	Glycated Hemoglobin
HHS	Hyperglycemic hyperosmolar state
ICMR	Indian council of Medical Research
IFG	Impaired fasting glucose
IGT	Impaired Glucose Tolerance
MDRD Equation	Modification of Diet in Renal Disease Equation
MODY	Maturity onset diabetes of the young
NPDR	Non Proliferative Diabetic Retinopathy
PAI-1	Plasminogen activator inhibitor-1
PKC	Protein kinase C

TGF-B	Transforming growth factor B
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary Tract Infection
VEGF-A	Vascular endothelial growth factor A
WHO	World Health Organization

ABSTRACT

Background and objectives

Diabetes mellitus (DM) is chronic disease which is reaching an epidemic proportion in many parts of the world. Estimated glomerular filtration rate (eGFR) estimation is probably the most rational noninvasive mode of assessing the renal status and the various Microvascular complications in Type 2 DM patients. The objective of the present study was to evaluate the correlation of estimated glomerular filtration rate (eGFR) to microvascular complications in type 2 diabetes mellitus patients.

Methods

The present prospective cross sectional study, was conducted in the Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2008 to December 2008. The study was approved by the Ethical and Research Committee of J. N. Medical College, Belgaum. Fifty (50) Type 2 DM patients with duration of more than five years who fulfilled selection criteria were enrolled in the study and eGFR was measured.

Results

Results showed no significant difference in sex distribution among the study participants (p=0.4876). Subjects with declining eGFR had increased risk of microvascular complications like diabetic retinopathy, diabetic neuropathy and diabetic nephropathy (p=0.0301). Reduced eGFR was associated with hypertension in maximum number of cases (p=0.0401).

Conclusion

Reduced eGFR (Glomerular Filtration Rate) was significantly associated with various microvascular complications.

Key words: eGFR; Diabetes Mellitus; Microvascular Complications;

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

Diabetes is chronic disease which is reaching an epidemic proportion in many parts of the world. Type 2 diabetes mellitus (DM) accounts for more than 90% of the diabetic population world wide.[1,2,3]

Both genetic and environmental factors are important in the development of the disease. The International Diabetes Federation estimates showed that 194 million people had diabetes in 2003 and it is expected to reach 333 million by the year of 2025.[1,3]

Thirty years ago, the prevalence of diabetes in India based on the Indian Council of Medical Research (ICMR) multicentric survey was around two percent in urban India and one percent in rural India. In just three decades, these prevalence rates have shot up to 12 to 16% in urban India and three to eight percent in rural India, in adults over 20 years of age. These represents a 600 to 800% increase in prevalence rates of diabetes something which is unparallel in any Western nation. Indeed, India is now referred to as the “Diabetic Capital” of the world.[1]

The paramount importance of DM is because of its disastrous complications, acute types in the pre-insulin and chronic vascular and neurological problems in the post-insulin era. The latter appear to be so inevitable as to be reckoned as congeners or concomitants.[1]

The disease burden of DM is primarily due to the burden of its many complications. Diabetes exposure, which results from the level as well as

duration of hyperglycemia, represents a metabolic state that favours the development of several long term complications of eye, kidney and heart.[4,5,6]

Diabetes is associated with numerous vascular complications which include cardiovascular disease (CVD), peripheral vascular disease, stroke, retinopathy, neuropathy and diabetic kidney disease (DKD) are responsible for most of the morbidity and mortality attributable to diabetes. The frequency of disability in people with diabetes offers an indirect means of assessing the morbidity associated with various vascular complications.[5,7,8]

Peripheral neuropathy often leads to greater limitations in performing the personal care activities of daily living, but has less impact on mobility. Diabetes is the leading cause of visual deficits in developed countries among people younger than 60 years and visual impairment or blindness can lead to disability affecting both mobility and daily living activities.[3]

The rate of glomerular filtration rate (GFR) decrease in patients with type 2 diabetes, microalbuminuria, and proteinuria is greatest in those with typical diabetic glomerular lesions. The concomitant presence of retinopathy is only partly helpful in discriminating kidney pathology in patients with type 2 diabetes.[8,9]

In those with macroalbuminuria, the positive predictive value (PPV) of retinopathy for typical diabetic glomerulopathy ranges from 67% to 100%. However, the negative predictive value (NPV) had a broader range of 20% to 84%. These figures give sensitivities between 26% and 85% and specificities of 13% to 100%. For microalbuminuria, positive predictive values (PPV) were

lower at around 45%, but negative predictive values (NPV) were close to 100%, giving sensitivities of 100% and specificities of 46% to 62%. Thus, the presence of retinopathy in patients with type 2 DM and macroalbuminuria is strongly suggestive of DKD and its absence in microalbuminuria suggests non DKDs.[8]

Vascular complications are one of the most serious consequences of diabetes and are responsible for most of the excess mortality observed in diabetic patients. It is likely that all blood vessels both small and large are abnormal in diabetic patients with long standing disease. Although there is generalized microangiopathy but microvascular blood vessel in retina, renal glomeruli and microvessels of large nerves seem to have significant pathology.[4,9]

There are no perfect ways to predict which patients with diabetes will develop microvascular complications, nor the severity and at what stage will microvascular complications shall manifest.

Infact, many studies have established beyond doubt that about 20% patients do have atleast one or more microvascular and macrovascular complications at the time of diagnosis of type 2 diabetes.[10]

Diabetes mellitus is a leading cause of end stage renal disease all over the world. Recent study demonstrated a higher incidence of diabetes nephropathy in type 2 DM than type 1 DM.[2,11]

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people, and more than one million of them are receiving kidney replacement therapy.[2]

As the population of patients with diabetes of long duration grows, reports of a dramatically increasing burden of DKD are appearing from developed countries, as well as from Africa, India, the Pacific Islands, and Asia, where infectious disease previously posed the greatest threat. Increased risk and more rapid progression of DKD also have been reported in immigrants from developing to developed countries.[2]

However, to date there is very little published data on whether the development of one diabetic microvascular complication influences the risk of developing a second complication. This study explores the same concept further and identifies the interrelationships of the three diabetic microvascular complications with various stages of kidney disease, a topic that is poorly reported in the literature to date.

OBJECTIVES

The objective of the present study was to evaluate the correlation of estimated glomerular filtration rate (eGFR) to microvascular complications in type 2 diabetes mellitus patients.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Diabetes is perhaps as old as mankind. Cognizance of symptoms related to diabetes and recognition of the disorder was confined to a few geographic and cultural locations in the Ancient Era (upto 600 AD).

The knowledge acquired during this period was lost sight of and progress was tardy and indiscrete during the medieval period (600 to 1500 AD).

With the advent of modern age (1500 to 1758 AD) and its progression to renaissance and industrial revolution (1750 to 1850 AD), certain key features of diabetes were rediscovered and some new information was generated which stand out as landmarks in characterizing diabetes.

During the later decades of the 19th and first half of the 20th century, all round progress was achieved in the knowledge of pathology, predisposing factors, management, course and complications of diabetes mellitus. Growth of knowledge has been very fast in course of the second half of the last century (contemporary period) involving epidemiology, genetics, immunology and molecular biology which has led to accumulation of voluminous information on various aspects of this versatile disorder.[1,7]

Some key developments in scientific and clinical understanding of diabetes may be summarized as follows:

The earliest mention of diabetes like illness characterized by polyuria can be traced to Eqyptian Papyrus dating back to around 1550 B.C.[7]

- The sweet taste of diabetic urine was noted in the 5th and 6th century AD by the Indian physicians 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.[7]

- 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.[7]

- 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.[7]

- In 1889, Oskar Minkowski and Josef Von Mering observed that total pancreatectomy produced diabetes in dogs.[7]

- In 1893, Edovard Laguesse named that 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.[7]

- Various workers, including George Zueler (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.[7]

- 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 pancreatectomized dogs and were first tested in a human diabetic in January 1922.[7]

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

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

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

    - The isolation of proinsulin in 1967 by Donal Steiner's group.

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

    - The sequencing of the insulin receptor in 1985.

Table No. 1: Landmarks in insulin discovery and development[1]

Year	Contribution	Discovery, development
1869	Paul Langerhans	Identified Islet cells
1889	Joseph Von Mehring and Oskar Minkowski	Identified pancreas as the origin of fatal diabetes mellitus
1908	George Ludwig Zeuler	Injected 'acomatrol' pancreatic extract into dying patient
1921	Paulesco	Pancreatin (Insulin)
1921	Banting and Best	Work started at the University of Toronto in the month of April
1922	Banting and Best	Insulin Isolation
1923	Nordisk Insulin Laboratory	Started production of Insulin
1926	Abel	Prepared the first crystalline insulin
1934	Svedberg	Molecular weight of insulin was determined
1936	Hagedorn (Novo Nordisk)	Development of the first protamine Insulin (PZI)
1946	Hagedorn (Novo Nordisk)	Development of the first prolonged acting Insulin-Neutral Protamine Hagedorn (NPH) or Isophane insulin

Year	Contribution	Discovery, development
1952	Hallas-Moller and Schlichtkrull	Development of the Lente series of Insulin
1955	Frederik Sanger	Elucidation on the structure of insulin and awarded with Nobel prize
1964	Novo Nordisk	Premixed insulin preparation were made available
1981	Jan Markussen and associates	First commercially available human insulin preparation using DNA technology
1996	Eli Lilly and company	First commercially introduced insulin analog, Lispro
2000	Novo Nordisk	Rapid- acting insulin analog- insulin aspart made available
2000	Aventis Pharmaceuticals	Marketing of long-lasting form of insulin – insulin Glargine
2003	Novo Nordisk	Detemir another long-acting insulin analogue introduced

Diabetes mellitus refer to a group of common metabolic disorder that shares the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia

include reduce insulin secretion, decreased glucose utilization, and increased glucose production.[3,6]

The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease (ESRD), non traumatic lower extremity amputations, and adult blindness. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be leading cause of morbidity and mortality for the foreseeable future.[1,3,6,12,13]

CLASSIFICATION OF DIABETES

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. The two broad categories of DM are designated type 1 and type 2. Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progresses. Type 1 diabetes is the result of complete or near total insulin deficiency. Type 2 DM is a heterogenous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 DM is preceded by a period of abnormal

glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).[6,7]

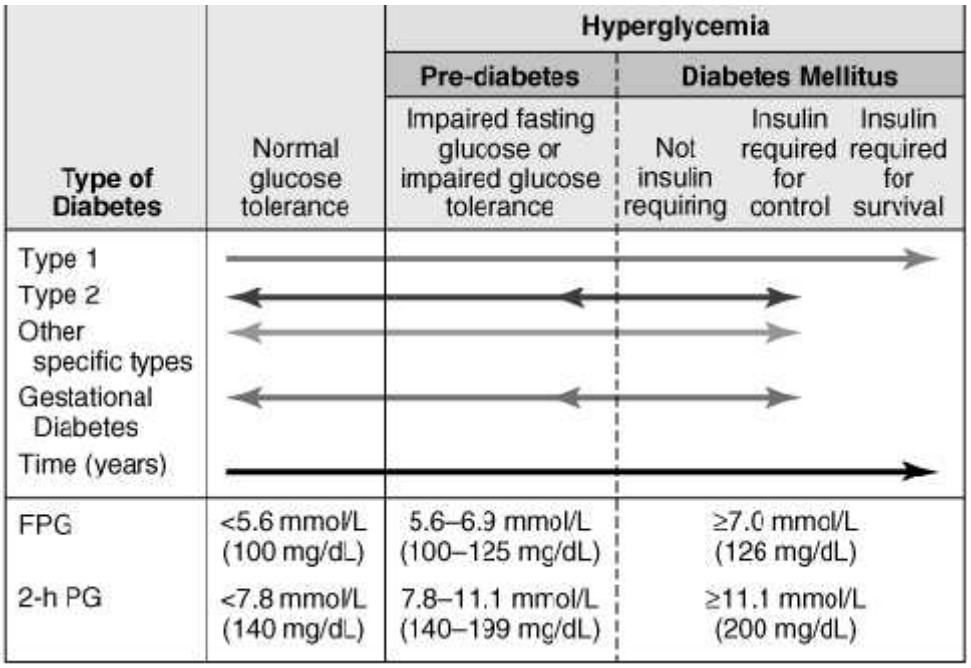


Figure No. 1: Spectrum of glucose homeostasis and diabetes mellitus

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS[6]

I. Type 1 diabetes (B-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 B cell function characterized by mutations in:

i. Hepatocyte nuclear transcription factor (HNF) 4a Maturity onset diabetes of young (MODY 1)
ii. Glucokinase (MODY 2)
iii. HNF-1a (MODY 3)
iv. Insulin promoter factor-1 (IPF-1; MODY 4)
v. HNF-1b (MODY 5)
vi. NeuroD1 (MODY 6)
vii. Mitochondrial DNA
viii. Subunits of ATP-sensitive potassium channel
ix. Proinsulin or insulin conversion

b. Genetic defects in insulin action
    i. Type A insulin resistance
    ii. Leprechaunism
    iii. Rabson-Mendenhall syndrome
    iv. Lipodystrophy syndromes
c. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase.
d. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.
e. Drug- or chemical-induced—Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, B-adrenergic

agonists, thiazides, phenytoin, a-interferon, protease inhibitors, clozapine

f. Infections—congenital rubella, cytomegalovirus, coxsackie

g. Uncommon forms of immune-mediated diabetes—"stiff-person" 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)

EPIDEMIOLOGY

The world wide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, more than 360 million individuals will have diabetes by the year 2030. Although the prevalence of both type 1 and type 2 DM is increasing world wide, the prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized. This is true in most countries, and 6 of the top 10 countries with the highest rates are in Asia. In the United States, the centre for Disease control and prevention (CDC) estimated that 20.8 million persons, or seven percent of the population, had diabetes in 2005 (-30% of individuals with diabetes were undiagnosed).[1,6]

The prevalence is similar in men and women throughout most age ranges but is slightly greater in men more than 60 years. World wide estimates project that in 2030 the greatest number of individuals with diabetes will be 45 to 64 years of age.[6]

INDIAN PROBLEM

India is in the midst of an ever-increasing epidemic of diabetes mellitus. Data on type 1 diabetes mellitus from our country is scant. Clinic based data from the mid sixties to the eighties reported the prevalence of childhood diabetes with onset below 15 years of age as being one to four percent of all the diabetic subjects attending clinics in different parts of the country.[1,3]

According to recent study also, almost 95% of childhood diabetes reportedly belongs to Type 1 DM. Early onset type 2 diabetes, MODY, fibrocalculous pancreatic diabetes and diabetes associated with genetic syndromes accounted for the remaining cases.[1]

Type 2 DM accounts for more than 90% of all patients with diabetes in India. According to WHO there were an estimated 19.4 million diabetes individuals in 1995, and this number is projected to increase in 80 million by 2030. The ICMR study (1972 to 1975) was the first systematic nationwide collaborative study on the prevalence of diabetes mellitus.[1,3]

The prevalence of diabetes was found to be 2.8% in rural and five percent in the urban population above the age of 40 years. The prevalence of Diabetes in India Study (PODIS) carried out in 77 centres recently reported a standardized

prevalence rate for DM, in the total urban and rural population of 4.3, 5.9 and 2.7% respectively.[1]

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS[3,7]

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

Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

[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.

SCREENING[6]

Widespread use of the fasting plasma glucose (FPG) as a screening test for type 2 DM is recommended because:

1. A large number of individuals who meet the current criteria for DM are asymptomatic and unaware that they have the disorder.

2. Epidemiologic studies suggest that type 2 DM may be present for up to a decade before diagnosis.

3. As many as 50% of individuals with type 2 DM have one or more diabetes-specific complications at the time of their diagnosis.

4. Treatment of type 2 DM may favorably alter the natural history of DM. The ADA recommends screening all individuals more than 45 years every three years and screening individuals at an earlier age if they are overweight [body mass index (BMI) more than 25 kg/m^2] and have one additional risk factor for diabetes. In contrast to type 2 DM, a long asymptomatic period of hyperglycemia is rare prior to the diagnosis of type 1 DM.[1,6]

PATHOGENESIS

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 but that 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 multifactorial 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 impaired glucose tolerance 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-r, inward rectifying potassium channel expressed in beta cells, zinc transporter expressed in beta cells, 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.[6]

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. IGT, 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.[6]

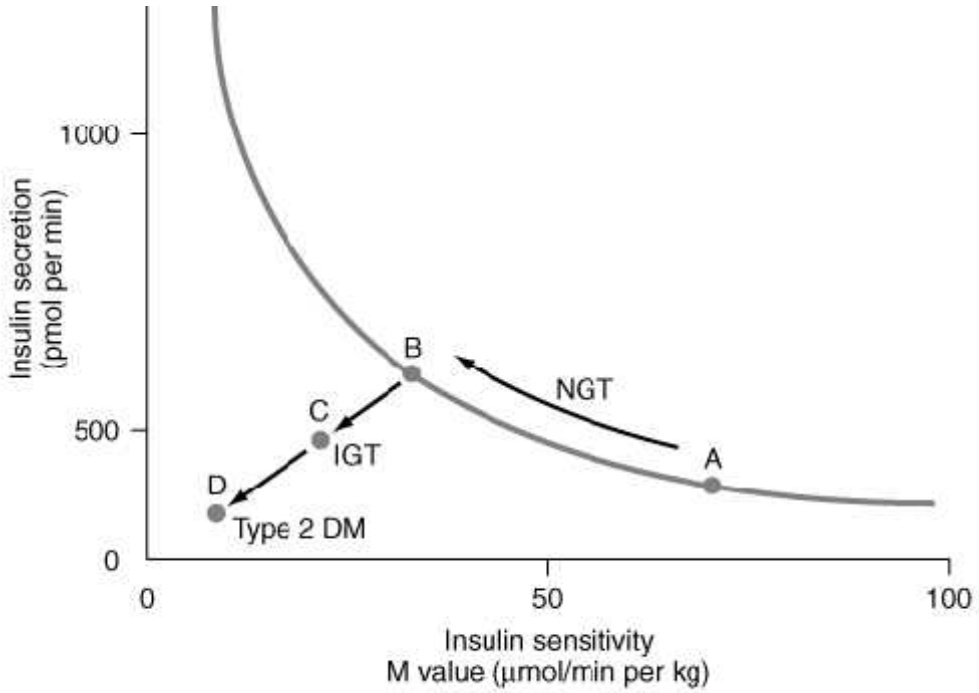


Figure No. 2: Metabolic changes during the development of type 2 diabetes mellitus

COMPLICATIONS OF DIABETES MELLITUS[3,6]

Acute Complications of DM

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes. DKA was formerly considered a hallmark of type 1 DM, but it also occurs in individuals who lack immunologic features of type 1 DM and who can subsequently be treated with oral glucose-lowering agents (these obese individuals with type 2 DM are often of Hispanic or African-American descent). HHS is primarily seen in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid-base abnormalities. DKA and HHS exist along a continuum of hyperglycemia, with or without ketosis. Both disorders are associated with potentially serious complications if not promptly diagnosed and treated.[3,6]

Chronic Complications of DM

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications [coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease]. Nonvascular complications include problems such as gastroparesis, infections, and skin changes. Long-standing diabetes may be

associated with hearing loss. Whether type 2 DM in elderly individuals is associated with impaired mental function is not clear.[6]

Chronic complications of diabetes mellitus

1. Microvascular
    a. Eye disease
        i. Retinopathy (nonproliferative/proliferative)
        ii. Macular edema
    b. Neuropathy
        i. Sensory and motor (mono- and polyneuropathy)
        ii. Autonomic
    c. Nephropathy
2. Macrovascular
    a. Coronary artery disease
    b. Peripheral arterial disease
    c. Cerebrovascular disease
3. Other
    a. Gastrointestinal (gastroparesis, diarrhea)
    b. Genitourinary (uropathy/sexual dysfunction)
    c. Dermatologic
    d. Infectious
    e. Cataracts
    f. Glaucoma
    g. Periodontal disease

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.[14]

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.[8,15]

Mechanisms of Complications

Although chronic hyperglycemia is an important etiologic factor leading to complications of DM, the mechanism(s) by which it leads to such diverse cellular and organ dysfunction is unknown.[16]

Four prominent theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia might lead to the chronic complications of DM.[6,8,17]

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. However, testing of this theory in humans, using aldose reductase inhibitors, has not demonstrated significant beneficial effects on clinical endpoints of retinopathy, neuropathy, or nephropathy.

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. Inhibitors of PKC are being studied in clinical trials.

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 B (TGF-B) 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-B 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. Although hyperglycemia serves as the initial trigger for complications of diabetes, it is still unknown whether the same pathophysiologic processes are operative in all complications or whether some pathways predominate in certain organs.[1]

Glycemic Control and Complications

The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM. This large multicenter clinical trial randomized over 1400 individuals with type 1 DM to either intensive or conventional diabetes management, and prospectively evaluated the development

of retinopathy, nephropathy, and neuropathy. Individuals in the intensive diabetes management group received multiple administrations of insulin each day along with extensive educational, psychological, and medical support.[18]

Individuals in the conventional diabetes management group received twice-daily insulin injections and quarterly nutritional, educational, and clinical evaluation. The goal in the former group was normoglycemia; the goal in the latter group was prevention of symptoms of diabetes. Individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (7.3%) than individuals in the conventional diabetes management group (9.1%).[18]

The DCCT demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications. There was a nonsignificant trend in reduction of macrovascular events during the trial (most individuals were young and had a low risk of cardiovascular disease). The results of the DCCT predicted that individuals in the intensive diabetes management group would gain 7.7 additional years of vision, 5.8 additional years free from ESRD, and 5.6 years free from lower extremity amputations. If all complications of DM were combined, individuals in the intensive diabetes management group would experience 15.3 more years of life without significant microvascular or neurologic complications of DM, compared to individuals who received standard therapy. This translates into an additional 5.1 years of life expectancy for individuals in the intensive diabetes management group.[18]

The benefit of the improved glycemic control during the DCCT persisted even after the study concluded and glycemic control worsened. For example, individuals in the intensive diabetes management group for a mean of 6.5 years had a 42–57% reduction in cardiovascular events [nonfatal myocardial infarction (MI), stroke, or death from a cardiovascular event] at a mean follow-up of 17 years, even though their subsequent glycemic control was the same as those in the conventional diabetes management group.[18]

The benefits of an improvement in glycemic control occurred over the entire range of A1C values, suggesting that at any A1C level, an improvement in glycemic control is beneficial. The goal of therapy is to achieve an A1C level as close to normal as possible, without subjecting the patient to excessive risk of hypoglycemia.[18]

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that each percentage point reduction in A1C was associated with a 35% reduction in microvascular complications. As in the DCCT, there was a continuous relationship between glycemic control and development of complications. Improved glycemic control did not conclusively reduce (nor worsen) cardiovascular mortality but was associated with improvement with lipoprotein risk profiles, such as reduced triglycerides and increased HDL.[10]

One of the major findings of the UKPDS was that strict blood pressure control significantly reduced both macro- and microvascular complications. In fact, the beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control. Lowering blood pressure to moderate goals

(144/82 mmHg) reduced the risk of DM-related death, stroke, microvascular end points, retinopathy, and heart failure (risk reductions between 32 and 56%).[10]

Similar reductions in the risks of retinopathy and nephropathy were also seen in a small trial of lean Japanese individuals with type 2 DM randomized to either intensive glycemic control or standard therapy with insulin (Kumamoto study). These results demonstrate the effectiveness of improved glycemic control in individuals of different ethnicity and presumably, a different etiology of DM (that is phenotypically different from those in the DCCT and UKPDS).[10]

The findings of the DCCT, UKPDS, and Kumamoto study support the idea that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic microvascular complications. These landmark studies prove the value of metabolic control and emphasize the importance of (1) intensive glycemic control in all forms of DM, and (2) early diagnosis and strict blood pressure control in type 2 DM.[10]

Ophthalmologic complications of diabetes mellitus

Despite the introduction of various treatment strategies, diabetes remains a major cause of new-onset blindness. Diabetic retinopathy (DR) is a leading cause of new-onset blindness in many industrialized countries. A population based survey done in the city of Chennai (Chennai urban Rural Epidemiology Study) CURES estimated the overall prevalence of DR as 17.6%. If this is applied to all the diabetics in India, this would translate to more than 5.6 million subjects with DR. Furthermore, the number of diabetic subjects is expected to increase to 79.4 million by 2030, which could translate into a heavy economic

burden. According to the available epidemiological data from WHO (2004), approximately 64 million persons are suffering from diabetes, of them, one third were from India. It is estimated that this figure will go upto 300 millions of world population by the year 2030, of them >79 million will be in India.[1,19]

Although there is an explosion of diabetes in India, the prevalence of DR in India is lower compared to the other populations. The prevalence of Diabetic Retinopathy in a cohort of 6792 Type 2 Diabetic patients attending a diabetes centre at Chennai in South India (1996) screened using a combination of retinal photography and clinical examination by retinal specialists was 34.1%. This included 30.8% with NPDR, 3.4% with PDR and 6.4% had maculopathy. As DR may be present even at the time of diagnosis of Type 2 Diabetes due to the insidious onset of this disease, a study of consecutive 448 newly diagnosed type 2 south Indian diabetic population reported that 7.3% already had diabetic retinopathy. The finding from the studies in India shows that the prevalence of DR in Indian is lower when compared to the Europeans. However, given the large number of diabetic subjects in India (31.7 million), even with the lower prevalence rates (17.6%), this would translate to over 5.6 million subjects with DR, causing an heavy economic burden.[1]

Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of the disease and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton wool spots. Mild nonproliferative retinopathy progresses to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and

more numerous microaneurysms and hemorrhages. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which lead to retinal ischemia.[1,19]

The appearance of neovascularization in response to retinal hypoxia is the hallmark of proliferative diabetic retinopathy. These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ultimately retinal detachment. Not all individuals with nonproliferative retinopathy develop proliferative retinopathy, but the more severe the nonproliferative disease, the greater the chance of evolution to proliferative retinopathy within five years.[1,19,20]

This creates an important opportunity for early detection and treatment of diabetic retinopathy. Clinically significant macular edema can occur when only nonproliferative retinopathy is present. Fluorescein angiography is useful to detect macular edema, which is associated with a 25% chance of moderate visual loss over the next three years.[21]

Duration of DM and degree of glycemic control are the best predictors of the development of retinopathy; hypertension is also a risk factor. Nonproliferative retinopathy is found in almost all individuals who have had DM for more than 20 years (25% incidence with five years, and 80% incidence with 15 years of type 1 DM). Although there is genetic susceptibility for retinopathy, it

confers less influence than either the duration of DM or the degree of glycemic control.

Cross sectional and longitudinal studies showed a relationship between proteinuria or microalbuminuria and retinopathy. Patients with progressive renal dysfunction need to be monitored closely for rapidly worsening retinopathy. Conversely, rapidly progressive retinopathy especially in a patient with long history of diabetes and where retinopathy has been previously stable, should suggest the need for renal evaluation.[1,9,22,23,24]

Diabetic retinopathy screening

American Diabetes Association recommends that Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination shortly after the diagnosis of diabetes and subsequently every one year. Level of frequent examination may be considered in the setting of a normal eye exam and more frequent exam will be required if retinopathy is progressing.[4]

However, women who are planning preqnancy or who have become pregnant should have a comprehensive eye examination during 1st trimester with close follow up during pregnancy and should be counseled on the risk of development or progression of diabetic retinopathy.[4]

Renal complications of diabetes mellitus

Diabetic nephropathy, a relatively common microvascular complication of both type 1 and type 2 DM contributes maximally to the pool of patients with chronic renal failure. It is defined clinically as the presence of persistent

proteinuria in a diabetic patient usually with retinopathy, elevated blood pressure and declining glomerular function, in the absence of UTI, other renal disease and/or heart failure.[17,25]

Figures from the U.S. renal data system, over the last three decades has shown a continual increase in the incidence of renal failure among patients with diabetes, predominantly with type 2 DM. This trend has been observed both in developed and developing countries. It is commoner to see more patients with type 2 DM with nephropathy, than those with type 1 DM (9:1) even though the incidence of nephropathy is higher in patients with type 2 DM. Recent data suggest that the incidence of end stage renal disease (ESRD) in patients with type 2 DM has increased dramatically and the reason for this change is due to the availability of better management options for hypertension and coronary artery disease in diabetic patients. As a result, more patients with type 2 DM live long enough for nephropathy and ESRD to develop. ESRD is patients with type 2 DM patients is therefore a disease of medical progress.[1,2,25,26]

Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to ESRD, though incompletely defined, involve the effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through angiotensin II receptors. Smoking accelerates the decline in

renal function. Because only 20–40% of patients with diabetes develop diabetic nephropathy, additional susceptibility factors remain unidentified. One known risk factor is a family history of diabetic nephropathy.[17,25,26]

The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type 1 DM but appears to be similar in type 2 DM. Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the glomerular filtration rate (GFR). During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After five to ten years of type 1 DM, ~40% of individuals begin to excrete small amounts of albumin in the urine.[25,27]

Microalbuminuria is defined as 30–300 mg/d in a 24-h collection or 30 to 300 mg/gm creatinine in a spot collection (preferred method). Although the appearance of microalbuminuria in type 1 DM is an important risk factor for progression to overt proteinuria (>300 mg/d), only ~50% of individuals progress to macroalbuminuria over the next 10 years. In some individuals with type 1 diabetes and microalbuminuria of short duration, the microalbuminuria regresses. Once macroalbuminuria is present, there is a steady decline in GFR, and ~50% of individuals reach ESRD in 7–10 years. Once macroalbuminuria develops, blood pressure rises slightly and the pathologic changes are likely irreversible. Some individuals with type 1 or type 2 DM have a decline in GFR in the absence of micro- or macroalbuminuria and this is the basis for assessing the GFR on an annual basis using serum creatinine.[28,29,30,31]

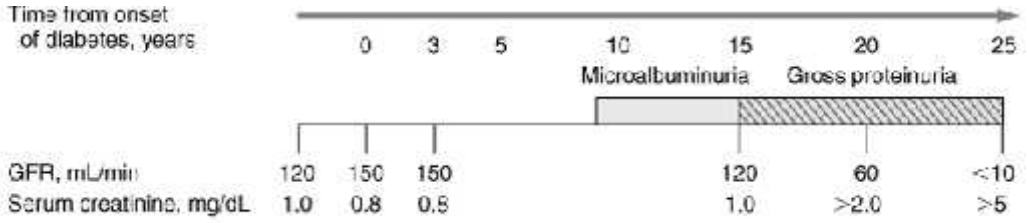


Figure No. 3: Time course of development of diabetic nephropathy

The nephropathy that develops in type 2 DM differs from that of type 1 DM in the following respects: (1) Microalbuminuria or macroalbuminuria may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period; (2) Hypertension more commonly accompanies microalbuminuria or macroalbuminuria in type 2 DM and (3) Microalbuminuria may be less predictive of diabetic nephropathy and progression to macroalbuminuria in type 2 DM. Finally, it should be noted that albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as hypertension, congestive heart failure (CHF), prostate disease, or infection. Diabetic nephropathy and ESRD secondary to DM develop more commonly in African Americans, Native Americans, and Hispanic

individuals than in Caucasians with type 2 DM. Microalbuminuria is associated with other Microvascular complications as well as with cardiovascular disease suggesting some common pathophysiological mechanisms.[28]

In the past three decades, urinary albumin excretion has assumed a central role in the diagnosis and management of kidney disease among people with diabetes, both type 1 and type 2. Microalbuminuria was initially found to predict subsequent over albuminuria (more than 300mg/24h), which in turn predicted loss of GFR. From the strength of these relationships it has frequently been

assumed that microalbuminuria and overt albuminuria are requisite first and second steps along a single pathway that leads to loss of GFR and ESRD. Persistent microalbuminuria was strong risk factor for subsequent loss of GFR, reemphasizing earlier work that established the importance of sustained increases in urine albumin excretion in the pathogenesis and diagnosis of diabetic kidney disease.[2,32]

However, patients who lost GFR at a high rate did not have overt albuminuria, by study design, and some had 'normal' urinary excretion of albumin. This study contributes to a growing literature that suggest that overt albuminuria does not always precede a significant loss of GFR in the setting of diabetes and that measuring albuminuria alone does not fully capture the scope of early diabetic kidney disease. Instead, albuminuria and GFR loss may represent complementary, if overlapping, manifestations of kidney damage.[33,34]

The National Kidney Disease Education Program and the National Kidney Foundation now recommended the use of estimating equations to improve the diagnostic accuracy of serum creatinine. These recommendations constitute a large step forward, with GFR most often estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation.[35]

A doubling of serum creatinine level indicates a halving of GFR; a threefold increase suggests a 75% loss of kidney function. It is now clear that stage 3 or higher chronic kidney disease occurs in the absence of urine albumin excretion in a substantial proportion of adults with diabetes. Screening this

population for increased urine albumin excretin alone therefore, will miss a considerable number of chronic kidney disease cases.[31,33,36]

GFR estimation is the only renal parameter which can singly provide a picture of the actual renal status of Type 2 DM patients at any duration irrespective of the status of albuminuria, azotemia or renal size and morphology as their variability or progression is non-linear.[32,36]

End stage renal disease as a percentage is still very low, the cause of which is probably increased cardiovascular mortality and not a better management strategy as the prevalence of albuminuria (micro and macro) is still very high in our population. We can expect a higher percentage of ESRD in the coming decade if cardiovascular mortality improves.[12,32]

In overt diabetic nephropathy an overall decrease of glomerular filtration rate is present at the same time with proportional enhancement of albumin filtering. How ever, when progression to the renal failure stage is achieved further huge drop of GFR, but only negligible urine albumin excretion increase is evidenced due to total occlusion of a significant proportion of glomeruli.[17]

Although albuminuria is claimed to be a marker of nephropathy progression, at this stage it fails to reflect appropriately glomerular function and could not be used as its valuable parameter.[31,37]

However, previous studies concluded that higher levels of albumin creatinine ratio even within the normal range was associated with faster decline in eGFR in diabetic patients.[35]

Related to albuminuria, the results of previous study favour that the glomerular filtration rate estimation to define kidney disease stage in diabete mellitus patients.[38]

Diabetic nephropathy screening – As per ADA Clinical practice Recommendations 2006 – perform an annual test for the presence of microalbuminuria in type 1 diabetic patients with diabetes duration of more than five years and in all type 2 diabetic patients, starting at diagnosis and during pregnancy.[4]

Neuropathy and diabetes mellitus

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.[6]

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), smoking, Retinopathy, Microalbuminuria, and Alcoholism. 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.[39]

The ADA recommends screening for distal symmetric neuropathy beginning with the initial diagnosis of diabetes and screening for autonomic neuropathy five 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.[4]

Polyneuropathy/Mononeuropathy[3,6]

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 less than 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 six to 12 months.

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.[6]

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, etc.) systems. DM-related autonomic neuropathy can involve multiple systems, including the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause a 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 counterregulatory hormone release, leading to an inability to sense hypoglycemia appropriately, thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.[6,7]

Diabetic neuropathy screening

Patients with diabetes should be screened for Distal symmetric polyneuropathy at diagnosis using tests such as pin prick sensations, temperature and vibration perception, 10 gm monofilament pressure sensation at the dorsal surface of both great toes, just proximal to the nail bed and ankle reflexes.[4]

Combinations of more than one test have more than 87% sensitivity in detecting DPN. Loss of 10 gm monofilament perception and reduced vibration perception predict foot ulcers.[4]

A minimum of one clinical test should be carried out annually, and the use of two tests will increase diagnostic ability.[4]

Focal and multifocal neuropathy assessment requires clinical examination in the area related to the neurological symptoms.

Diabetes duration and glycemia, blood pressure, and lipid control have consistently been shown to correlate with diabetic retinopathy, neuropathy, and nephropathy, but to date the relationship of one diabetic Microvascular complications to another has not been clearly described. A review of literature has raised the question that apart from other known risk factors, there is a possible relationship among the diabetic Microvascular complications themselves, and this appears to be a much stronger than the sparse published data on it would suggest.

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 50 type 2 diabetic patients during the period of January 2008 to December 2008.

Study design

One year cross-sectional study.

Study period

The present study was conducted during January 2008 to December 2008.

Method of collection of data

Source of Data

Type 2 DM patients admitted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

The study comprised a total of 50 cases of type 2 DM patients.

Sampling procedure

As there was no data available in KLES Dr. Prabhakar Kore Hospital and Medical records section particularly regarding the study subjects, the sample size of 50 cases were randomly selected. This was a cross sectional study.

Selection criteria

Inclusion Criteria

- Type 2 DM patients of more than five years duration.

Exclusion Criteria

- Patients with Type 1 DM.
- Febrile Illness.
- Exercise.
- Urinary tract infection.
- H/o Drug Intake like ACE inhibitors, ARBs, NSAIDS.
- Congestive heart failure.
- Acute poor metabolic control.
- Smoking.

Procedure

The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum. During the study period, all patients fulfilling the inclusion 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). Further the patients underwent the following investigations

Routine investigations

1. Complete blood count

2. Erythrocyte sedimentation rate
3. Urine routine and microscopy
4. Fasting blood sugar levels.
5. Post prandial blood sugar levels.
6. HbA1c

Specific investigations

1. Urine Micro-Albumin Excretion(UAE) Test (Microalbumin to creatinine Ratio)

    a. Urine Micro-Albumin (by immunoturbidometry) and urine creatinine (by Jaeffe's method)

2. Serum Creatinine (to calculate eGFR by MDRD Formula)

    a. Serum creatinine (by Jaeffe's method)

Statistical methods

The data was tabulated and analysis of variance (ANOVA) was used to compare means of variables in more than two groups. A p value of less than 0.05 was considered significant.

RESULTS

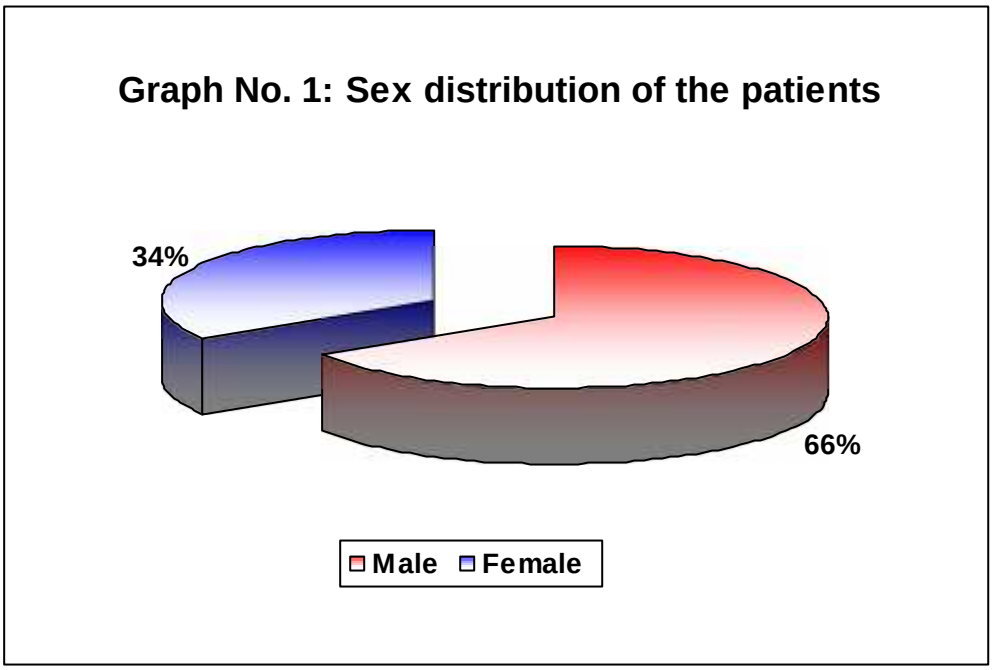
The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 50 type 2 Diabets Mellitus patients. The data obtained was tabulated as below.

The study comprised a total of 50 cases of Type 2 DM patients of more than five years duration. Observations of the study are as follows.

Basic demographic characteristics

Table No. 2: Sex distribution of the patients

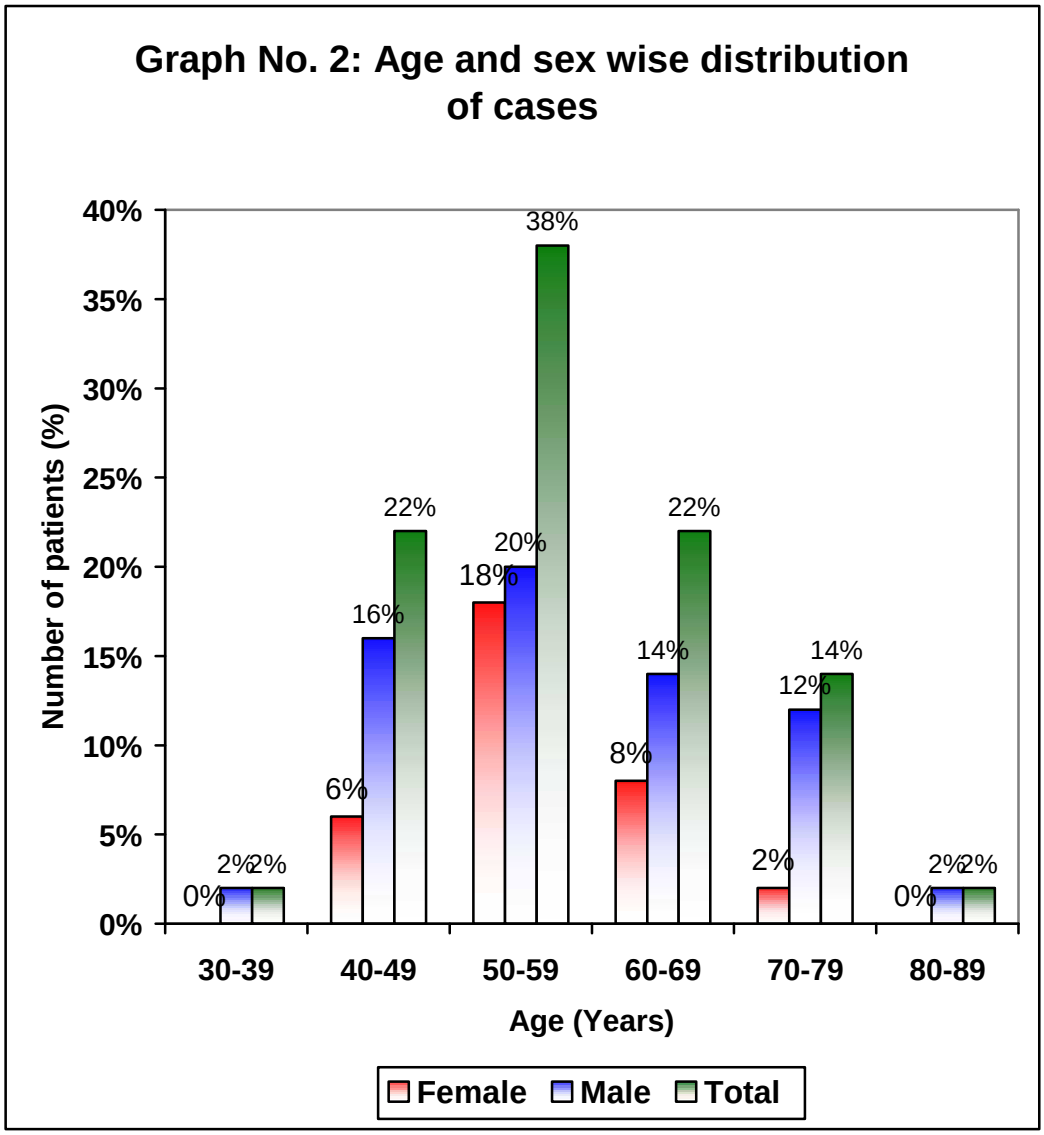
Sex	No. of Cases	Percentage
Male	33	66%
Female	17	34%



In the present study male subjects comprised 33 (66%) and female 17 (34%) of total subjects. There was a male preponderance. However there was no statistical significant difference of sex distribution in various stages of kidney disease (p=0.4876)

Table No. 3: Age and sex wise distribution of cases

Age (Yrs)	Female		Male		Total	
	No	**Percentage**	**No**	**Percentage**	**No**	**Percentage**
30 – 39	00	0%	01	2%	01	2%
40 – 49	03	6%	08	16%	11	22%
50 – 59	09	18%	10	20%	19	38%
60 – 69	04	8%	07	14%	11	22%
70 – 79	01	2%	06	12%	07	14%
80 – 89	00	0%	01	2%	01	2%
Total	17	34%	33	66%	50	100%



The above table and graph shows the distribution of patients according to age and sex. The mean age of the study population was 57.76 ± 10.35 years. Maximum number of patients in various stages of kidney disease was between 50 to 60 years which consisted 38% of sample size.

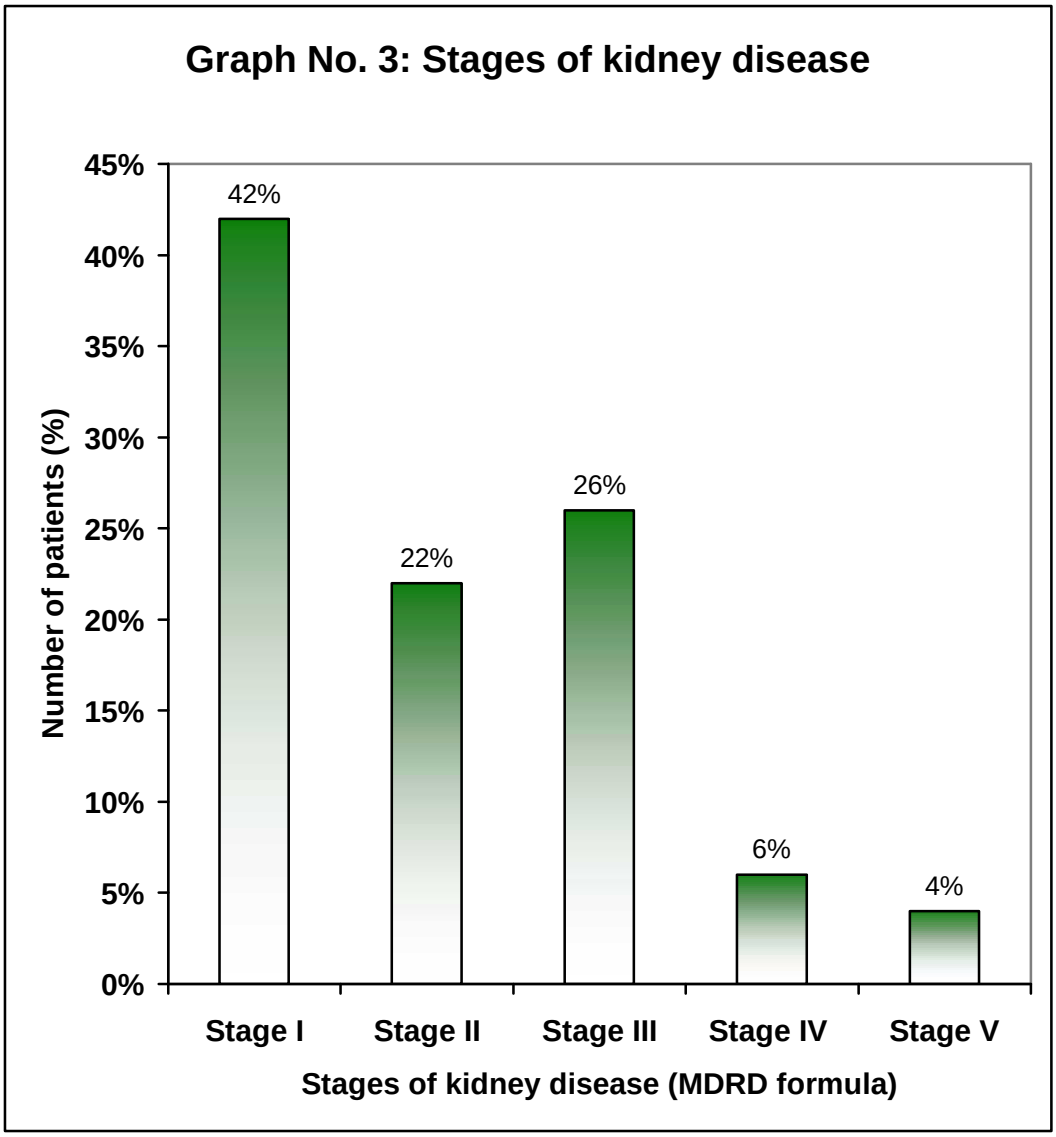
Table No. 4: Clinical and biochemical characteristics

Characteristics	Number	Percentage
Hypertension	29	58%
Nephropathy	33	66%
Retinopathy	22	44%
Neuropathy	32	64%

In present study 58% of sample size that is, 29 patients out of 50 has got history of Hypertension. Various Microvascular complications were assessed like diabetic nephropathy, retinopathy and neuropathy. The presence of various microvascular complications in total sample size was nephropathy 66%, retinopathy 44% and neuropathy 64% respectively.

Table No. 5: Stages of kidney disease

eGFR (MDRD)	Number	Percentage
Stage I	21	42%
Stage II	11	22%
Stage III	13	26%
Stage IV	03	6%
Stage V	2	4%



All Type 2 Diabetes Mellitus patients were divided into various stages of kidney disease by calculating estimated Glomerular Filtration Rate by Modified Diet for Renal Disease formula (MDRD). Among which maximum number of cases were in stage I of kidney disease which constitutes 42% of total sample size.

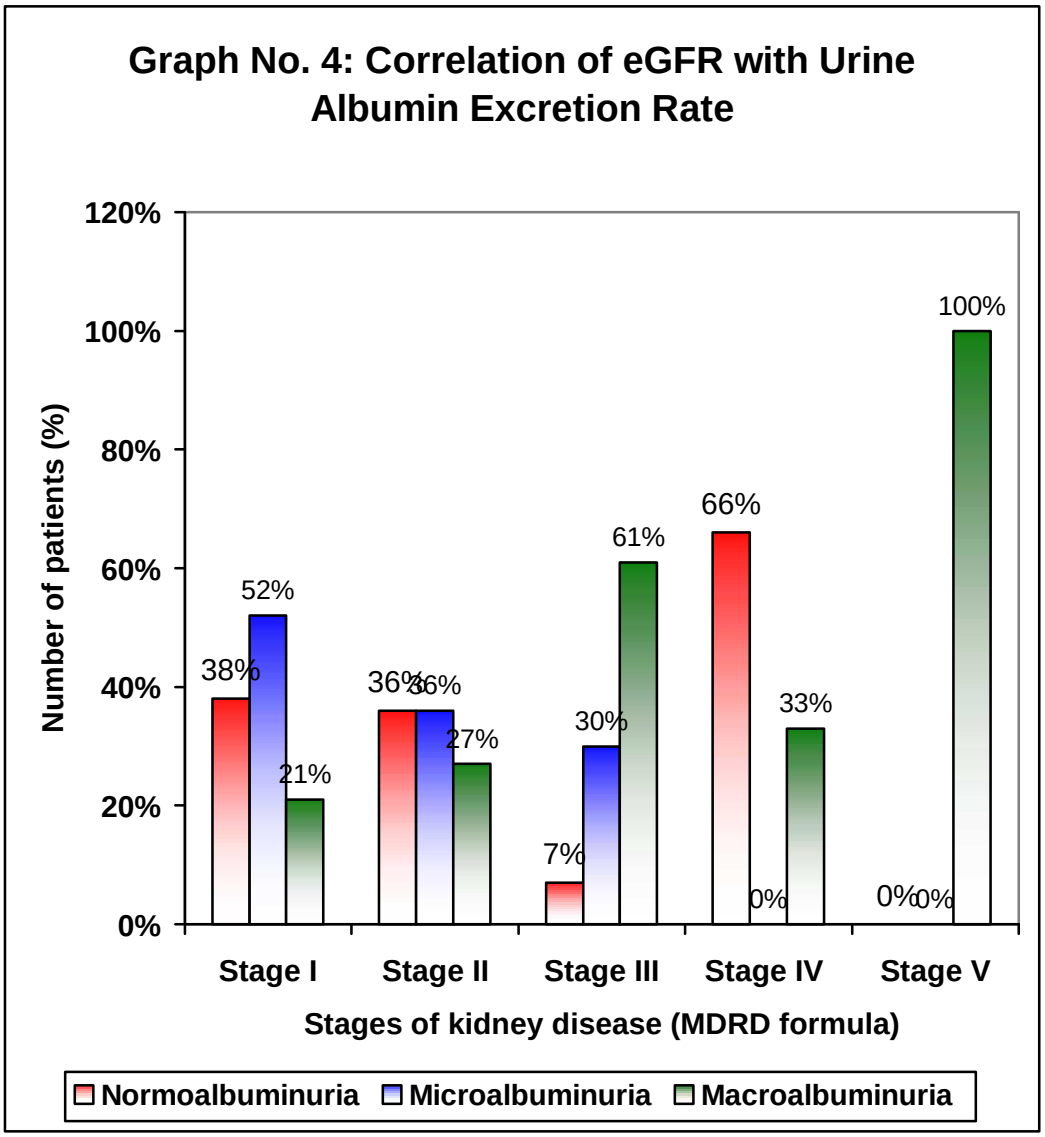
Table No. 6: Duration of diabetes among the study subjects

Duration (Years)	No. of Cases	Percentage
5 – 10	38	76%
11 –15	11	22%
16 – 20	01	2%

Maximum number of the subjects had diabetes from 5 to 10 years duration. They comprised 76% of sample size. There was one case in the present study who was having diabetes for more than 15 years.

Table No. 7: Correlation of eGFR with Urine Albumin Excretion Rate

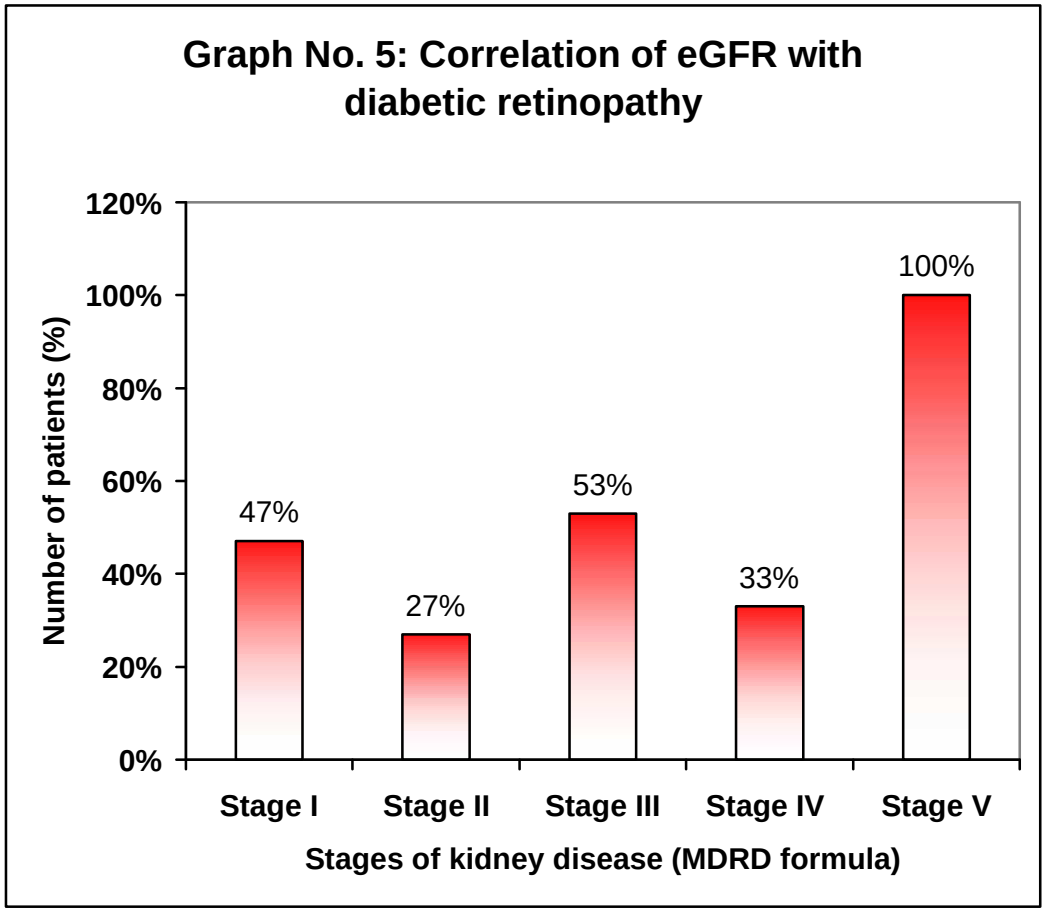
eGFR (MDRD)	Normoalbuminuria		Microalbuminuria		Macroalbuminuria	
	No	Percentage	No	Percentage	No	Percentage
Stage I	09	38%	11	52%	01	21%
Stage II	04	36%	04	36%	03	27%
Stage III	01	7%	04	30%	08	61%
Stage IV	02	66%	00	00%	01	33%
Stage V	00	00%	00	00%	02	100%



On correlation of various stages of kidney disease with urine Albumin Excreation Rate (measured by Micro Albumin Creatinine Ratio) it was found that at the End stage of kidney disease there is increase in urine albumin excretion Rate (Macroalbuminuria).

Table No. 8: Correlation of eGFR with diabetic retinopathy

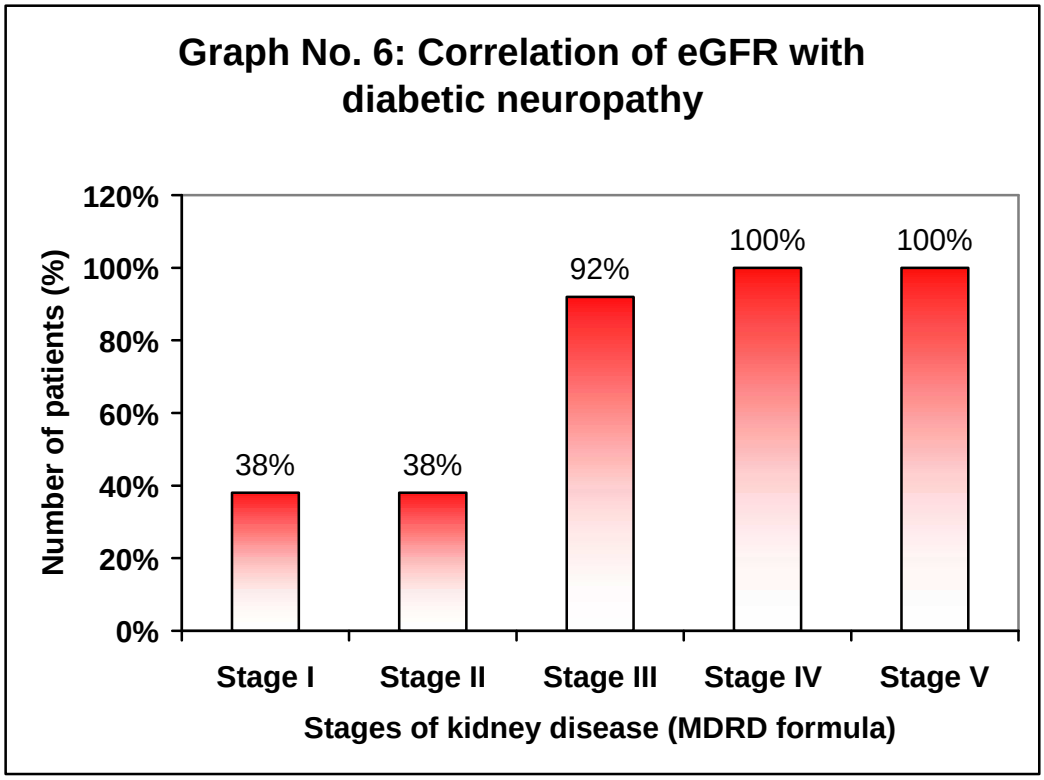
eGFR (MDRD formula)	Patients with diabetic retinopathy	
	Number	**Percentage**
Stage I (n=21)	10	47%
Stage II (n=11)	3	27%
Stage III (n=13)	7	53%
Stage IV (n=3)	1	33%
Stage V (n=2)	2	100%



On correlation of various stages of kidney disease with Diabetic Retinopathy it was found that there is significant association of Diabetic Retinopathy at the End Stage kidney disease i.e 100%.

Table No 9: Correlation of eGFR with Diabetic Neuropathy

eGFR (MDRD)	Patients with diabetic neuropathy	
	No. of Cases	Percentage
Stage I (n=21)	8	38%
Stage II (n=11)	8	38%
Stage III (n=13)	12	92%
Stage IV (n=3)	3	100%
Stage V (n=2)	2	100%



Correlating various stages of kidney disease with Diabetic Neuropathy

showed a significant correlation between the progression of kidney disease with the diabetic neuropathy that is, 100% at the later stage of kidney disease.

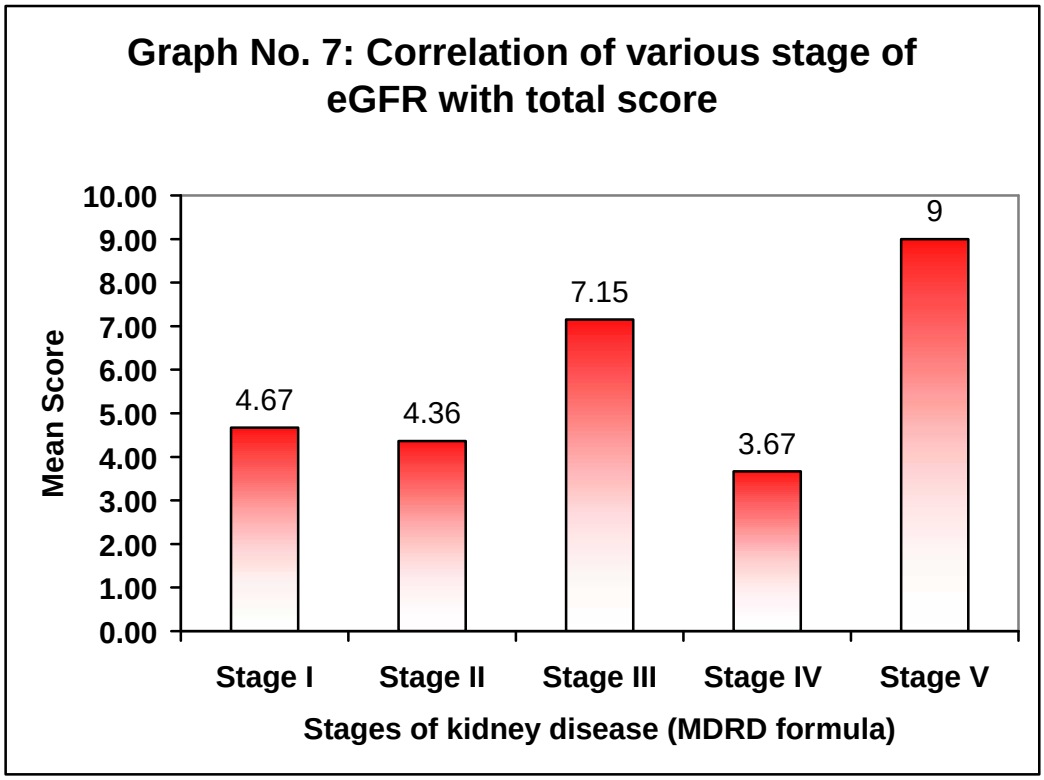
Table No. 10: Scoring of each Microvascular complications

Diabetic Nephropathy	Diabetic Retinopathy	Diabetic Neuropathy
5	3	1

Random Scoring was given to each Microvascular complications of Type 2 Diabetes for Correlation of eGFR with the microvascular complications (diabetic nephropathy, diabetic retinopathy and diabetic neuropathy) and its statistical significance.

Table No. 11. Correlation of various stage of eGFR with total score

eGFR (MDRD formula)	Mean	S.D.
Stage I	4.67	3.48
Stage II	4.36	3.87
Stage III	7.15	1.72
Stage IV	3.67	2.52
Stage V	9.00	0.00



Mean of Total Score in various stages of Kidney Disease were calculated which showed significant difference in stage III , IV and V with a mean of 7.15 , 3.67 and 9.00 respectively.

Table No 12: One Way Analysis of Variance For Total Scores (ANOVA)

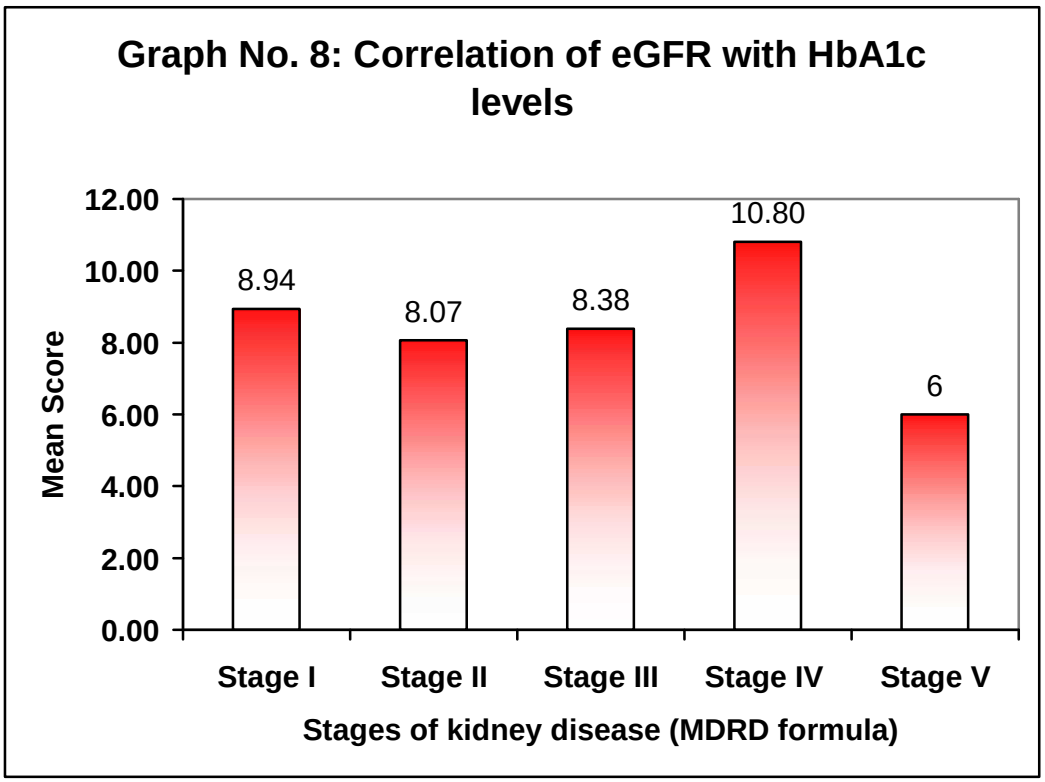
Score	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	97.95	4	24.49	2.95	0.0301
Within Groups	373.57	45	8.30		
Total	471.52	49			

p=0.0301

One way analysis indicate that there is significance difference between groups 3 and 4 for "Total Score" with a (p=0.0301). But the number of cases in group IV and V were just three and two generalisation is not justified.

Table No 13. Correlation of eGFR with HbA1c levels

eGFR (MDRD Formula)	Mean	S.D.
Stage I	8.94	2.19
Stage II	8.07	1.47
Stage III	8.38	1.16
Stage IV	10.80	2.12
Stage V	6.00	0.99



The mean HbA1c levels in total population was 8.598 ± 1.88.On correlation of eGFR with the mean of HbA1c levels it was found that the there was significant differences at the later stages of kidney disease with the mean of 10.80 and 6.00 in Stage IV and V respectively.

Table No 14: One way analysis of variance for HbA1c counts (ANOVA)

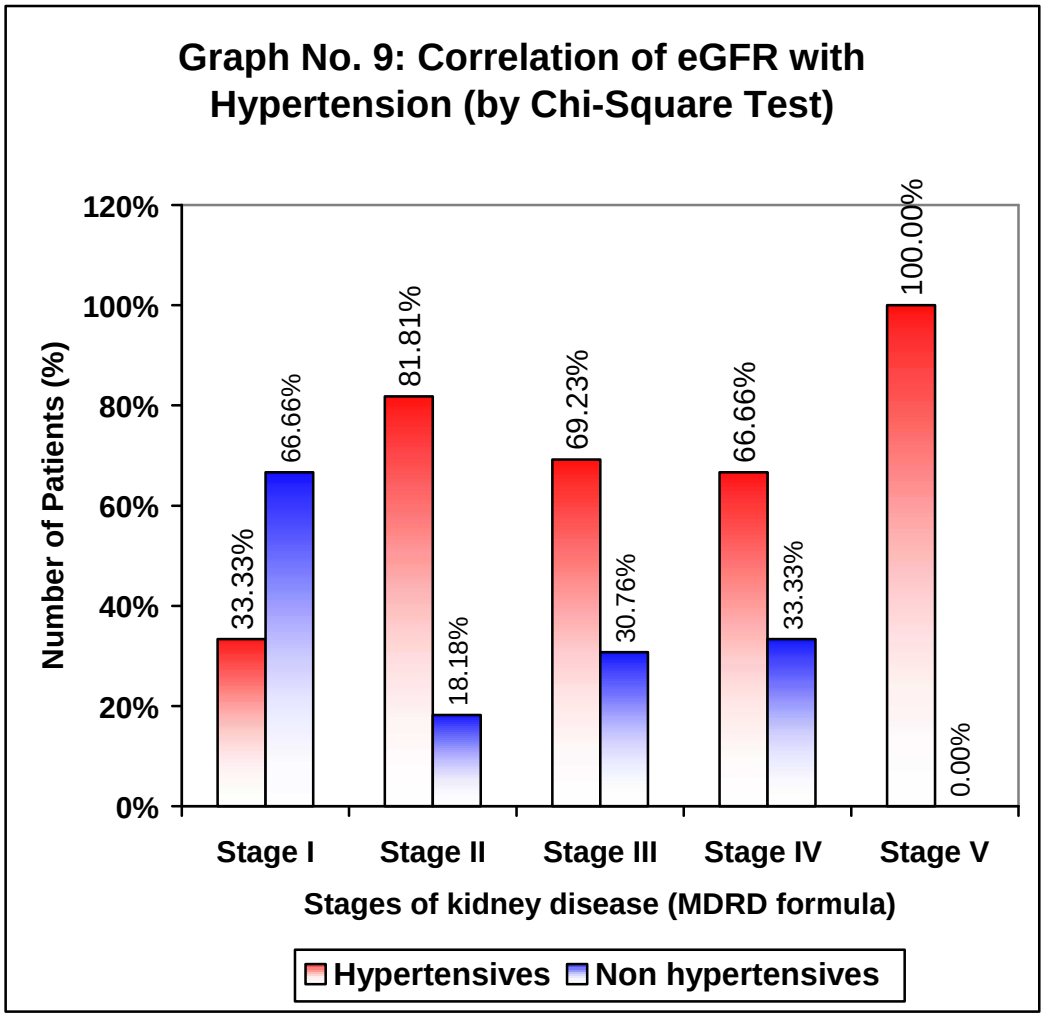
HbA1c	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	34.10	4	8.53	2.66	0.0446
Within Groups	144.13	45	3.20		
Total	178.2298	49			

One way analysis indicate that there is significance difference between the groups 4 and 5 for "HbA1C" counts. (p=0.0446). This signifies that as the Kidney disease progresses there was decrease in HbA1c levels at later stages.

Table No 15: Correlation of eGFR with Hypertension (by Chi-Square Test)

eGFR (MDRD)	Hypertension present		Hypertension absent	
	No	Percentage	No	Percentage
Stage I	7	33.33%	14	66.66%
Stage II	9	81.81%	2	18.18%
Stage III	9	69.23%	4	30.76%
Stage IV	2	66.66%	1	33.33%
Stage V	2	100%	0	0.00%
Total	29	58%	21	42%

p=0.0401



Various stages of kidney disease was found to be invariably associated with hypertension with statistical significance (p Value= 0.0401) by chi-square test. It consisted of 58% of sample size.

DISCUSSION

The present study aims to assess correlation between eGFR and various microvascular complications in type 2 DM patients.

This study was performed in 50 patients with type 2 DM of more than five years duration admitted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

The mean age of 50 patients in this study was 57.76 ± 10.35 with 33 males and 17 females.

50 Type 2 DM patients were divided according to various stages of kidney diseases by calculating eGFR by MDRD Formula (Modified Diet for the Renal Disease) among which maximum number of patients were there in Stage I (n=22) 42%. In other stages of kidney diseases number of patients were Stage II - (n=11) 22%, Stage III (n=13) 26%, Stage IV (n=3) six percent and Stage V (n=2) four percent respectively.

Less number of patients in the Stage IV and Stage V is supported by a study done in 2004 which concluded that as the End Stage renal disease as a percentage is still very low, the cause of which is probably increased cardiovascular mortality and not a better management strategy as the prevalence of albuminuria (micro and macro) is still very high in our population.[32,40]

Each of this microvascular complication of Type 2 DM patients was correlated with the various stages of kidney diseases by calculating eGFR with MDRD Formula.

A previous study in 2002 concluded that diabetic retinopathy, nephropathy and neuropathy account for almost 50% of the total costs of complications resulting from type 2 diabetes.[8]

Microvascular complications were assessed as follows

Diabetic nephropathy

Patients with urine microalbuminuria or macroalbuminuria were considered to have nephropathy. MicroAlbumin creatinine ratio was done by morning urine sample collections.[28] Diabetic Nephropathy was graded as;

- Micro Albumin creatinine ratio less than 30 mg/gm - Normoalbuminuric.
- Micro Albumin creatinine ratio 30 to 300 mg/gm - Microalbuminuric and
- Micro Albumin creatinine ratio more than 300 mg/gm - Macroalbuminuric.[28]

35 out of 50 Type 2 DM patients were found to have Diabetic nephropathy. Correlating eGFR with Urine Albumin excretion rate found that as the kidney diseases progresses to ESRD, Urine Albumin Excretion rate increases (Microalbuminuria/Macroalbuminuria). This was supported by the previous studies done in 1990 which found that microalbuminuria is an established surrogate marker of subsequent overt nephropathy and it is also found in other

studies done in 1991 that it is one of the most serious complications of diabetes and is the most frequent cause of ESRD in Western countries.[8]

The principle new finding of the previous study done in 2002 was baseline urine albumin creatinine ratio is the most powerful independent predictor of ESRD in type 2 diabetes mellitus patients with nephropathy. This relationship was applicable to both genders and all ethnic groups. These findings regarding the predictive power of proteinuria confirm and expand on observational studies in Pima Indians and other populations. In these studies proteinuria was also a powerful predictor of ESRD.[13]

Diabetic retinopathy

Patients with diabetic retinopathy were assessed by fundoscopy which was confirmed by an opthalmologist after mydriasis. The findings were graded as:

1. No signs of diabetic retinopathy.
2. Non-proliferative diabetic retinopathy (NPDR); and
3. proliferative diabetic retinopathy (PDR).

Individuals were classified as having PDR if they had new vessels, vitreous haemorrhage, vitreoretinal traction, or retinal detachment believed to be attributable to diabetic neovascularisation. NPDR and PDR were taken together as retinopathy for this study.[21]

Twenty three (23) out of 50 Type 2 DM patients were found to have Diabetic Retinopathy. In present study there was a positive correlation between

eGFR and diabetic retinopathy. As the Kidney disease progresses, presence of diabetic retinopathy is more significant. It was supported by the study done by in 2002 and 1999 concluding that the presence of diabetic retinopathy itself may reveal patients at risk of diabetic nephropathy. A study done in 2002, enrolled 648 patients with type 1 and type 2 diabetes in a cross-sectional study to determine the predictive value of diabetic retinopathy. Univariate analysis indicated that patients with diabetic retinopathy were 5.68, 13.39 and 3.51 times as likely to have diabetic nephropathy when compared with those without diabetic retinopathy in the whole study population and in patients with type 1 and type 2 diabetes respectively. In the above study, the prevalence of diabetic nephropathy was found to rise with increasing severity of diabetic retinopathy.[8,41]

A study done in 1999 enrolled 340 patients with type 1 DM and 258 patients with type 2 DM demonstrated that diabetic retinopathy was one of the most important risk factors responsible for the development of incipient nephropathy in normoalbuminuric, normotensive patients with either type 1 or type 2 diabetes.[21]

Further evidence that diabetic retinopathy may predict the development of microalbuminuria comes from a study done in 2002 on 537 non albuminuric adult patients.

It has also been shown in previous study conducted on 772 patients in 1993 over a period of one year that the prevalence of proteinuria increases in relation to the severity of diabetic retinopathy.[8]

In previous study done in 2004 concluded that Diabetic retinopathy is one of the most common Microvascular complications and the most frequent cause of new cases of blindness among adults ages 20 to 74 years.[8]

Diabetic neuropathy

Neuropathy was considered if patient had;

- Complaints suggestive of peripheral neuropathy.
- Decreased vibration sense or signs of sensory disturbances without complaints.
- Sensory complaints and reduced vibration sense or sensory defects.[39,42]

33 out of 50 patients had diabetic neuropathy. It was found that there was a positive correlation between eGFR and diabetic neuropathy. As the stages of kidney disease progresses risk of associated diabetic neuropathy increases.

It was supported by previous study conducted in the year 1996 showed that there was significant trend in the increase in the relative risk for the presence of diabetic neuropathy with an increase in the progression of kidney disease.[8]

An earlier epidemiological study done in 1989 also reported a univariate association of diabetic neuropathy with diabetic nephropathy.

The Appropriate Blood Pressure control in Diabetes study (1998) found that both diabetic retinopathy and diabetic nephropathy were significantly associated with diabetic neuropathy in patients with type 2 diabetes.[8]

On correlation of sex distribution in various stages of kidney disease there was no significanct difference (p=0.4876).

Correlation between the presence of Hypertension and various stages of Kidney Disease was also done which showed there was statistically significant association of hypertension with various stages of Kidney disease in total sample size (p=0.0401).

In the present study random score was given to each of the microvascular complications of type 2 DM to detect the statistical significance. Scoring to each microvascular complications was as follows.

Diabetic nephropathy	**Diabetic retinopathy**	**Diabetic neuropathy**
5	3	1

On correlating the total score with the various stages of kidney disease it was found that there was significant correlation of total score with the progression of kidney disease (p=0.0301). As the kidney disease progressed total score was increased. However, there were less number of patients in later stages of kidney disease (Stage IV and V), further studies are required with equal or more number of cases in each stage of kidney disease for better statistical significance. To our knowledge similar reports have not been published so far from Indian population.

CONCLUSION

From the present study we conclude that;

1. eGFR is probably the most rational non-invasive mode of assessing the renal status in patients with Type 2 DM.

2. Decline in eGFR is associated with the various microvascular complications like diabetic nephropathy, diabetic retinopathy and diabetic neuropathy.

3. The association between the various stages of kidney diseases and the microvascular complications seems to be much stronger as per above data and previous studies.

4. The above Data suggest that the presence of a preexisting complication (diabetic retinopathy, diabetic nephropathy or diabetic neuropathy) contributes to the development of another.

5. There was significant association of hypertension with various stages of kidney disease.

SUMMARY

In the present study we assessed the correlation between eGFR and Microvascular complications of type 2 DM. This was a cross sectional study conducted in KLES Dr.Prabhakar Kore Hospital and MRC, Belgaum between January 2008 to December 2008.

1. Among the 50 patients in our study, 33 were males and 17 were females.

2. The mean age of patients in the present study was 57.76 ± 10.35 years. Most of the subjects in the present study were between 50-59 yrs of the age and comprised 32% of sample size.

3. The duration of diabetes in the present study was more than five years. There was one case in the present study having diabetes more than 15 years.

4. All 50 type 2 DM patients were divided in to various stages of kidney disease by calculating their eGFR by MDRD Formula. Among which maximum number of patients were in Stage I of kidney disease (n=21) which comprise about 42% of sample size.

5. Each Microvascular complications were correlated with the eGFR and it was found that the decline in eGFR was associated with the Microvascular complications.

6. There was no statistically significant difference observed in this study in respect to sex distribution.

7. On correlation of eGFR with hypertension it was found that there was significant difference (p=0.0401) i.e Hypertension was present in majority of patients of the total sample size.

8. It was also found in this study that HbA1c level has reduced gradually as there was decline in eGFR.

eGFR is probably the most rational non-invasive mode of assessing the renal status in patients with Type 2 DM. And its decline is found to be associated with the various Microvascular complications (Diabetic Nephropathy, Diabetic Retinopathy and Diabetic Neuropathy).

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ANNEXURE I - CONSENT FORM

Objective and Purpose of the study

This study is a **Correlation of eGFR to microvascular complications in type 2 diabetes mellitus patients**. The principal investigator of the study are Dr. Prakash Babaliche and Dr. Rishit A. Nadpara. This research is intended to study the Correlation of eGFR to Microvascular complications in Type 2 Diabetes patients and my co-operation will be of great help to the patients of diabetes infuture.

Procedure

If I agree to be a part of the study I will be asked the relevant history and will be subjected to relevant clinical and Laboratory examination and I will also have to give Blood Sample for CBC, ESR, FBS, PPBS, HbA1c, Serum Creatinine and Urine sample for Urine Albumin excretion test (MicroAlbumin to Creatinine Ratio) and Urine Routine and Microscopy.

Risk and Benefit

The only risk and possible discomfort I might get is while taking blood from my arm for assessment of CBC, ESR, FBS, PPBS, HbA1c and Serum Creatinine. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is withdrawn.

Alternatives

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

Privacy and Confidentiality

All information collected about me during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify me in this research record.

Institutional / Sponsors Policy

Does not apply to this research.

Financial Incentives for Participation

I will not be charged any amount for the investigations subjected to me. I will not receive compensation or reimbursement for taking part in this study.

Authorization to Publish Results

Information from this study may be published but my identity will be confidential in any publication.

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 any 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 Study Participant or legally authorised representative

Signature / Thumb Print

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

Principal investigator: Dr. Prakash Babaliche Phone: 0831-2473787

Dr. Rishit A. Nadpara Phone: 97423 50735

Name of Witness : Signature :

Investigator Name : Signature :

Date : Place :

ANNEXURE II - PROFORMA

Title: "Correlation of eGFR to microvascular complications in type 2 diabetes patients" A one year cross sectional study at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Name: I.P. No.:-

Age (In Years): Sex:

Date: Occupation:

HISTORY:

Present history:

Fever	Present/Absent
Chest pain	Present/Absent
Oedema	Present/Absent
Oliguria/polyuria	Present/Absent
Blurring of vision	Present/Absent
Tingling/numbness/pain in extremities	Present/Absent
Leg ulcers/wounds	Present/Absent

Past History: Laser therapy for retinopathy, LL amputation/ulcers, dialysis

Family history: DM, diabetic nephropathy

General Physical Examination:-

Build and nourishment:

Pulse: /min

Peripheral pulses: Present/Absent/Weak

Blood Pressure: mmHg

Systemic Examination:-

C.V.S:

R.S:

Per Abdomen:

C.N.S:

1. Higher Function:
2. Cranial Nerves:
3. Motor System:
    a) Nutrition:
    b) Tone:
    c) Power:
    d) Co-ordination:
    e) Abnormal movements:

4. Reflexes: Superficial:

    Deep:

5. Sensory System:
6. Cerebellar Signs:
7. Miscellaneous: a) Signs of meningeal irritation:

    b) Carotid artery pulsations:

    c) Skull and Spine

Investigations

<u>Urine Albumin Excretion Test (MicroAlbumin to Creatinine Ratio):</u>

NormoAlbuminuria – 0 - 30 mg/gm creatinine

MicroAlbuminuria - 30 – 300 mg/gm creatinine

MacroAlbuminuria - >300 mg/gm creatinine

eGFR:- mL/min/1.73m^2

MDRD Formula:- eGFR = 175 x [(Serum Creatinine x 0.0113) $^{-1.154}$] x (age $^{-0.203}$) x F

Where F = 1 if male, and 0.742 if female

Stage -1 eGFR =**90+** Normal kidney function

Stage -2 eGFR =**60-89** Mildly reduced kidney function,

Stage -3 eGFR =**30-59** Moderately reduced kidney function

Stage-**4** eGFR =**15-29** Severely reduced kidney function

Stage -5 eGFR =**<15** Very severe, or **endstage** kidney failure

Fasting Plasma Glucose:- mg/dl

Post Prandial Plasma Glucose:- mg/dl

HbA1c:-

CBC : -

ESR :-

Urine Routine and Microscopy :-

Fundoscopy :-

Inférence:-

MASTER CHART

S.I No.	I. P. No.	AGE	SEX	DURATION OF DIABETES IN YEARS	HYPERTENSION	STAGES OF KIDNEY DISEASE (eGFR) MDRD FORMULA	Diabetic Nephropathy	Diabetic Retinopathy	Diabetic Neuropathy	TOTAL SCORE	HbA1C
1	292050	55	Male	10	Present	stage 1	Absent	Absent	Absent	0	8.8
2	291503	62	Male	10	Present	stage 1	Absent	Absent	Absent	0	6.4
3	291597	48	Female	5	Absent	stage 1	Absent	Absent	Absent	0	10.1
4	291505	50	Male	5	Absent	stage 1	Absent	Absent	Present	1	11
5	281410	55	Female	5	Absent	stage 1	Present	Present	Absent	8	8.6
6	290793	58	Male	5.5	Present	stage 1	Present	Absent	Absent	5	6.7
7	269602	50	Male	7	Absent	stage 1	Present	Present	Absent	8	8.3
8	272745	57	Female	10	Absent	stage 1	Present	Present	Present	9	7
9	268474	70	Male	10	Present	stage 1	Present	Absent	Absent	5	8.4
10	266775	48	Male	6	Absent	stage 1	Present	Absent	Absent	5	5.6
11	273487	48	Female	6	Absent	stage 1	Present	Present	Present	9	9.5
12	269366	35	Male	5	Absent	stage 1	Present	Absent	Absent	5	9.3
13	271612	46	Male	10	Absent	stage 1	Absent	Present	Absent	3	8.4
14	274627	53	Male	10	Absent	stage 1	Absent	Present	Present	4	6.2
15	275772	43	Male	7	Absent	stage 1	Present	Absent	Absent	5	7.8
16	271359	52	Male	7	Absent	stage 1	Present	Present	Present	9	14
17	300007	62	Female	12	Present	stage 1	Absent	Absent	Absent	0	7.2
18	309849	45	Male	5	Present	stage 1	Absent	Present	Present	4	10.4
19	309378	49	Male	15	Absent	stage 1	Present	Present	Present	9	10.6
20	299180	42	Male	6	Absent	stage 1	Absent	Absent	Absent	0	10.1
21	301913	55	Female	10	Present	stage 1	Present	Present	Present	9	13.3
22	292089	67	Female	12	Present	stage 2	Absent	Absent	Present	1	8.2
23	281297	48	Male	8	Absent	stage 2	Present	Present	Present	9	10.7
24	290594	65	Male	5	Present	stage 2	Present	Absent	Absent	5	8.1
25	289687	65	Female	5	Present	stage 2	Present	Absent	Present	6	6.5

S.I No.	I. P. No.	AGE	SEX	DURATION OF DIABETES IN YEARS	HYPERTENSION	STAGES OF KIDNEY DISEASE (eGFR) MDRD FORMULA	Diabetic Nephropathy	Diabetic Retinopathy	Diabetic Neuropathy	TOTAL SCORE	HbA1C
26	275473	63	Male	5	Absent	stage 2	Absent	Absent	Absent	0	6.3
27	275462	76	Male	5	Present	stage 2	Absent	Absent	Absent	0	9.2
28	269493	53	Male	6	Present	stage 2	Present	Absent	Absent	5	9.1
29	309594	62	Female	5	Present	stage 2	Present	Absent	Present	6	7.6
30	309527	66	Male	5	Present	stage 2	Present	Absent	Present	6	5.7
31	308956	50	Female	5	Present	stage 2	Absent	Present	Present	4	8.4
32	319980	57	Female	10	Present	stage 2	Present	Absent	Present	6	9
33	292070	54	Female	10	Present	stage 3	Present	Absent	Present	6	9.5
34	317290	70	Male	6	Present	stage 3	Present	Absent	Present	6	9.7
35	291547	48	Female	10	Present	stage 3	Present	Present	Present	9	7.6
36	291092	55	Male	15	Absent	stage 3	Present	Present	Present	9	7.9
37	288707	56	Female	16	Present	stage 3	Present	Present	Present	9	9.6
38	274410	66	Male	7	Present	stage 3	Absent	Present	Present	4	7
39	272178	78	Male	15	Present	stage 3	Present	Absent	Present	6	7.5
40	268549	78	Male	12	Absent	stage 3	Present	Absent	Present	6	7.7
41	269386	57	Male	20	Absent	stage 3	Present	Present	Absent	8	9.4
42	300022	69	Male	7	Present	stage 3	Present	Absent	Present	6	6.1
43	309012	70	Female	5	Absent	stage 3	Present	Absent	Present	6	9.5
44	994930	45	Male	15	Present	stage 3	Present	Present	Present	9	8.6
45	294572	84	Male	15	Present	stage 3	Present	Present	Present	9	8.9
46	278039	57	Female	11	Present	stage 4	Absent	Present	Present	4	13.2
47	280285	58	Female	5	Absent	stage 4	Present	Absent	Present	6	9.2
48	308396	65	Male	10	Present	stage 4	Absent	Absent	Present	1	10
49	295400	70	Male	15	Present	stage 5	Present	Present	Present	9	5.3
50	320085	53	Male	10	Present	stage 5	Present	Present	Present	9	6.7

ANNEXURE III - KEY TO MASTER CHART

eGFR	Estimated Glomerular Filtration Rate
HbA1c	Glycosylated Hemoglobin
I.P. No.	In- Patient Number
MDRD Formula	Modification of Diet in Renal Disease formula
SI. No.	Serial Number