ASSOCIATION BETWEEN MICROALBUMINURIA AND RISK FACTORS AND COMPLICATIONS AMONG PATIENTS WITH TYPE II DIABETES MELLITUS

DISSERTATION SUBMITTED IN FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF M.D.GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

THE TAMIL NADU DR M.G.R MEDICAL UNIVERSITY

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PROPOSAL NUMBER	:	**10/105**

PROJECT TITLE

Association between microalbuminuria & risk factors and complications among patients with type II diabetes mellitus

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REVIEW TYPE	:	**Exempt**
DATE OF THE MEETING	:	**N/A**
DECISION	:	**Approved**
APPROVAL DATE	:	**15.04.2010**
VALIDITY OF THE APPROVAL	:	**One year**
CONTINUING PANEL REVIEW	:	**Not Needed**

15/04/2010

for **Dr S Bhuvaneshwari**
Secretary
Institutional Human Ethics Committee

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CERTIFICATE

*This is to certify that the thesis entitled "**ASSOCIATION BETWEEN MICROALBUMINURIA AND RISK FACTORS AND COMPLICATIONS AMONG PATIENTS WITH TYPE II DIABETES MELLITUS"** is a bonafide work of **DR.T.SUNIL KUMAR** done under my guidance and supervision in the department of General Medicine, PSG Institute Of Medical Sciences And Research, Coimbatore for fulfillment of the regulations of Tamilnadu Dr MGR Medical University for the award of M.D in General Medicine.*

Dr.K.Jayachandran, M.D

Guide & HOD

General Medicine

PRINCIPAL

DECLARATION

*I hereby declare that this dissertation entitled "**ASSOCIATION BETWEEN MICROALBUMINURIA AND RISK FACTORS AND COMPLICATIONS AMONG PATIENTS WITH TYPE II DIABETES MELLITUS"** was prepared by me under the direct guidance and supervision of **Professor Dr. K.Jayachandran MD,**PSG Institute Of Medical Sciences And Research, Coimbatore.*

This dissertation is submitted to Tamilnadu Dr MGR Medical University in fulfilment of the regulations for the award of M.D in General Medicine.This dissertation has not been submitted for the award of any degree or diploma.

ACKNOWLEDGEMENT

At the outset it gives me immense pleasure to express myheartfelt gratitude & sincere thanks to my beloved teacher Dr.K.Jayachandran Professor and Head Of The Department of General Medicine, PSGIMS & R, Coimbatore, for his constant encouragement, guidance and valuable suggestions without whose help this study would not have been possible.

I extend my heartfelt thanks to Dr.G.Venu, Professor, Department OF Nephrology, PSGIMS & R, Coimbatore, for his constant encouragement and guidance.

I thank all the unit chiefs for their constant help and support.

I sincerely thank our Principal, Dr. Ramlingam.S, PSGIMS & R, Coimbatore for his kind cooperation

I thank all the assistant professors, fellow post graduates, interns, hospital staff and all my friends who helped me in many ways during the study.

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INTRODUCTION

Diabetes mellitus, the most common endocrine disorder is characterised by metabolic abnormalities and long-term microvascular and macrovascular complications.

The prevalence of diabetes is on the rise, more alarming in the developing countries. Besides multiplying risk for coronary heart disease, diabetes enhances the incidences of cerebrovascular accidents. Moreover it is the leading cause of acquired blindness and accounts for about a quarter of the cases with end stage renal disease as well as half of the cases of non-traumatic lower limb amputations

Diabetic nephropathy occurs in as many as 30% of Type I diabetes mellitus patients and 25% of Type IIdiabetes mellitus patients. Diabetic nephropathy is a dreaded disease with progressive and continuous deterioration in glomerular function resulting in irreversible renal failure. Diabetic nephropathy is an important cause of morbidity and mortality and is now among the most common cause of end stage renal disease. However there is an early phase of diabetic renal disease called incipient diabetic nephropathy. In this stage there is a rise in urinary excretion of albumin i.e. microalbuminuria. But the rise is detectable only by use of sensitive assay for urinary albumin. At this stage urine is negative for macro albumin and renal function is normal by standard clinical tests. The presence of microalbuminuria precedes the development of overt diabetic nephropathy by 10 to 15 years. It is at this stage that one can hope to reverse diabetic renal disease or prevent its progression. Therapeutic interventions which reverse microalbuminuria include intensified insulin treatment, dietary protein restriction,and control of hypertension by ACE inhibitors and Beta-blockers.

Microalbuminuria thus is an important warning sign for both the physician and the patient which if ignored can lead to irreversible renal damage.

Microalbuminuria is most commonly associated with other microvascular complications of diabetes namely retinopathy, neuropathy, and ischemic heart disease. So microalbuminuria may be a marker for widespread microvascular damage in a patient of diabetes mellitus.

The aim of this study was to study the occurrence of microalbuminuria in patients with Type IIdiabetes mellitus and also to find out it its association with the risk factors of diabetes mellitus and the microvascular complications and macrovascular complications of diabetes mellitus

OBJECTIVES

- **To find the association between microalbuminuria and its risk factors and complications in south Indian type II Diabetes population attending PSGIMS&R, Peelamedu,**

- **Coimbatore,Tamil Nadu.**

REVIEW OF LITERATURE

HISTORICAL REVIEW:

1.Diabetes mellitus:

The knowledge of diabetes dates back to centuries before Christ. Polyuric disease, resembling diabetes was described as early as 150 BC in ancient Egyptian records discovered by George Beers. Celsius (30BC-50AD) had recognized the disease.Diabetes, a Greek term, which literally means to 'run thru' or a 'siphon' was initiallyused by Aretaeus in first century AD for the generic description of a condition causing increased urine output1. Roman physicians thought of diabetes as a "wonderful affection, not very frequent among men, being melted down of flesh and limbs into urine.

The association of polyuria with a sweet tasting substance in the urine was first reported in Sanskrit literature dating from fifth to sixth centuries AD at the time of two noted Indian physicians Susruth and Charaka4. It was in the seventeenth century that Thomas Willis (1621-1675) made the observation " as if imbibed with honey and sugar about the diabetic urine". A century after Willis, Mathew Dobson (1735-1784) demonstrated that the sweetness of urine was indeed due to sugars. It was John Rollo who was one of the first to use the adjectivemellitus (mellitus = honey) to distinguish it from other polyuric states in which the urine was unsavory (Greek – insipidus). Over the centuries, gradually the causes and complications of this disease were recognized. Aricanne, an Arab physician at around the tenth century had described gangrene 2, 3.

The diabetes world was overwhelmed with joy in 1921 when young physician and surgeon Fredrick Grant Banting (1891-1941) and Charles.H.Best, his graduate student assistant, working in Toronto through the summer on an almost non-existent budget in a lab loaned to them temporarily by a vacating professor, prepared active extracts ofpancreas which lowered the elevated level of sugars in diabetic dogs.

The first patient to be treated with pancreatic extract was Leonard Thomson in 1922.The long acting insulin preparation (isophane) was introduced in 1936 by Hans

Christian Hagedorn and colleagues. The testing of Sulfonylureas was done by Auguste Loubatieries in 1944.Thefirst therapeutic use of a Biguanide was done by G.Ungar in 1957.The efficacy of insulin in preventing the complications and retarding multisystem involvement was heralded by the fact that the untreated cases in the pre-insulin era had a high mortality rate which wasmostly due to diabetic ketoacidosis2, 3.

2.Diabetic nephropathy:

Diabetes was for many years regarded as the disease of the kidneys. This was the opinion of Aretaeus, Capadcian in second century AD. The view was still held by Erasmus Darwin in 1801. The presence of proteinuria in diabetes mellitus had long been known. Contunniues (1770), Rollo (1798), Darwin (1801), Rayer (1840), Van Noorden(1912), all had described the association of dropsy with diabetes. Vacuolization of tubular epithelium was observed by Armani (1875) and Ebstein (1881) and was shown to be due to glycogen infiltration by Ehlrich in 1888.

Kimmelstiel and Wilson were the first to attribute specific glomerular lesions entitled inter capillary lesions in the glomeruli of kidney. These peripheral hyaline masses are known as Kimmelstiel Wilson lesions. These histological features were associatedwith clinical features of diabetes, hypertension, nephrotic syndrome and renal failure.

3. **Microalbuminuria:**

In 1963 Keen and Chlouvervakis developed sensitive and specific
Radioimmunoassay for detecting human albumin in low concentration i.e. microalbuminuria, which indicate earliest stage of diabetic renal disease. Later various other methods were developed for detection of microalbuminuria.

INCIDENCE AND PREVALENCE OF MICROALBUMINURIA

The prevalence of microalbuminuria in Type I DM patients has been reported in range from 5-37% in different population based and diabetic clinic based studies. In Type IIDM patients' prevalence of microalbuminuria have been reported in between 8% and 46% in Europeans and 47% in indians. Microalbuminuria is found not only in patients with diabetes but also in patients with impaired glucose tolerance.

Age:

There is no correlation that has been found between Albumin Excretion Rate (ARE) and age.

Sex: There is male preponderance in Type I DM patients. There is no correlation between microalbuminuria and sex in Type IIDM patients.

Duration of diabetes:

Prevalence increase with duration of Type I DM with distinct variation in the rate of increase. Incidence of microalbuminuria is very high during the first 3 years after diagnosis of diabetes, declines at the end of first decade of diabetes and then increase again to a peak around 12-15 years duration. The prevalence is 8% in patientswith Type I DM of only 1-3 years of duration. The prevalence of microalbuminuria levels off after 10 years (prevalence of 20%) and then assumes its steep climb of around 32% after 30 years of post pubertal duration of diabetes.

Glycaemia:

The level of glycaemic control seems to be the strongest factor influencing transition from normoalbuminuria to microalbuminuria. In recent observational study ofthe dose response relationship between intensity of hyperglycemia (measuredas

average glycosylated hemoglobin HbA1C level during a 2-4 year period) and the rise tomicroalbuminuria was determined in a large cohort of Type I DMpatients. A threshold effect of hyperglycemia on the development of microalbuminuria was found. Below an HbA1C of 10.1% the risk of persistent microalbuminuria varied little. In contrast above a thresholdHbA1c of 10.1% the risk of microalbuminuria rose steeply with increasing levels of HbA1c. In comparison the risk of microalbuminuria increases six fold faster between HbA1 levels of 11 and 12% and that between 8 and 9%. This relationship between HbA1c and levels ofmicroalbuminuria was independent of the effect of duration of Type I DM.

Exercise:

Moderately strenuous exercise can provoke an exaggerated rise in AER in patients with diabetes whose resting values are normal. The severity of exercise inducedalbuminuria seems to be related to duration of diabetes and is modulated by level of glucose control

Blood pressure and heart rate:

Significant positive associations are found between microalbuminuria and diastolic blood pressure and resting heart rate. Other factors influencing the risk of developing microalbuminuria includecigarette smoking, elevated levels of serum LDL cholesterol49, 50.

ETIOPATHOGENESIS

1. **Hyperglycaemia:**

The development of clinically overt renal disease is not linearly related to duration of diabetes and affects only between 35-50% of patients. The majority of patients with diabetes escape renal failure, and although some histological changes occur in their kidneys, their renal function remain essentially normal till death. It appears that hyperglycaemia is necessary but not sufficient to cause renal damage that leads to kidney failure and that possibly non-environmental factors are needed for the manifestation ofthe clinical syndrome.

2.AGES:

Glycosylation of tissue proteins also may contribute to the development of diabetic nephropathy and other microvascular complications. In chronic hyperglycemia, some of the excess glucose combines with free amino acids on circulating or tissue proteins. This nonenzymatic process initially forms reversible early glycosylation products and later irreversible Advanced Glycosylation End Products (AGEs)

Circulating AGE levels are increased in diabetics, particularly those with renal insufficiency, since AGEs are normally excreted in the urine . The net effect is tissue accumulation of AGEs, in part by crosslinking with collagen, which can contribute to the associated renal and microvascular complications.

There are three possible mechanisms through which non-enzymatic glycation may contribute to diabetic complications1.

1) AGE may alter the structure and functions of extracellular matrix by cross-linking matrix proteins

2) AGE may affect the activity of signals such as cytokines, growth factors and free radicals, by interacting with AGE receptors on various tissues.

3) Glycation may directly affect the functions of enzymes and other key intracellular proteins1, 25.

Recent studies have shown that AGE products bind to specific AGE receptor identified by macrophages, endothelial cells and mesangial cells and thus induce the synthesis and secretion of cytokines, including Interleukin1 (IL-1) and insulin like growth factor 1 (IGF-1) 26,27. This could stimulate the proliferation of mesangial cells and also the glomerular synthesis of Type IV collagen28. On the other hand advanced glycation

appears to reduce mitogenic activity of basic fibroblast growth factor (b-FGF) in cultured endothelial cells29.

AGE can induces excessive cross linking of collagen molecules, affecting the assembly and architecture of glomerular basement membrane and mesangial cells via platelet derived growth factor (PDGF), causing them synthesize more extracellular matrix30. All these processes may lead to enhanced deposition of extracellular matrix proteins in the mesangium interfere with mesangial clearance of macromolecules and alter macrophage function, therefore contributing to mesangial expansion and gloemrular occlusion. AGE has also been shown to quench and inactivate nitric oxide (NO), a vasodilator and antiproliferative factor, in a dose dependent manner31.

3) The polyol pathway:

Sorbitol is produced in cells from glucose by reaction catalysed by aldolasereductase. In the normal kidney aldolase reductase is present in the papilla, glomerular distal tubular cells and also in mesangial cells. In the renal medullary cells of the kidney the primary role of aldolase reduction is in the generation of Sorbitol, an organic osmolyte in response to high salinity in medullary interstitial. Sorbitol would aid in preventing the osmotic stress. Chronic hyperglycaemia may lead to Sorbitol accumulation in a variety of tissues including renal tubules and glomerular. Sorbitol accumulation could cause tissue damage perhaps by disturbing cellular osmoregulation and depleting intracellular myoinositol. Depletion of phospoinositidase may result in reduced hydrolysis of phosphotidylinositol bi phosphate and decreased diacylglycerol formation. Diacylglycerol is a major endogenous cellular mediator of protein kinase C activation which itself has been implicated in pathogenesis of diabetic renal disease32.

4) Biochemical abnormalities of extracellular matrix:

Diabetic glomerulopathy is characterised by excessive accumulation of glomerular basement membrane and mesangial matrix. Glycosaminoglycans (GAG) polysaccharides account for approximately 90% of total carbohydrate component of glomerular basement membrane with sialoprotein constituting remainder. The principal GAG in the glomerular basement membrane is heparan sulfate that together with sialic acid contributes to negative charge of glomerular capillary wall and thereby to charge selective properties of the filtration barrier. In diabetes, there is reduced de novo synthesis of glomerular heparan sulphate and the totalGAG content in the glomerulus and the glomerular basement membrane is reduced. The heparan sulphate content of glomerular basement membrane has been found to be decreased in patients with Type I DM with nephropathy. Sialoglycoproteins are highly negatively charged and coat glomerular epithelial cells, their foot process and epithelial slit diaphragm. A loss of negative charge of glomerular membrane may be responsible for foot process fusion, with consequent obliteration of the slit diaphragm and could partly explain the albuminuria of diabetic nephropathy 30.

5) Glucotoxicity:

Glucose itself may have direct toxic effects on cells. Abnormalities include alteration in cell replication and maturation associated with evidence of damage to DNA. High glucose levels also lead to increased expression and synthesis of collagen, fibronectin and laminin, which may partly explain the enhanced products of extracellular matrix observed in diabetic kidneys. Mesangial cells in high glucose levels induce transcription and secretion ofTGF-B, which is unique among the cytokines in that it stimulates the matrix synthesis and inhibits its degradation.

Abnormalities in endothelial cell function have been implicated in the increased frequency of cardiovascular disease that is a feature of diabetic nephropathy.

6) **Hemodynamic and hypertrophic pathways:**

Glomerular hemodynamic disturbances with elevation of renal blood flow and GFR occur early in the course of diabetes have been suggested directly responsible for development of glomerulosclerosis and attendant proteinuria. Several observations support the notion that renal hyper perfusion and hyper filtration contribute to renal damage. Elevated intraglomerular pressure via increased mechanical stress and shear forces may damage the endothelial surface and disrupt the normal structure of glomerular barrier, and could eventually lead to mesangial proliferation, increased production of extracellular matrix and thickening of glomerular basement membrane.

Hemodynamic abnormalities are usually associated with hypertrophic changes in glomerulus. Marked renal hypertrophy is an early event in diabetes and it is argued that hyperplastic and hypertrophic changes in diabetic kidney may precede the hemodynamic abnormalities. Chronic overexpression of growth hormone or growth hormone releasing factors may lead to early glomerular enlargement followed by glomerulosclerosis. Growth hormone, insulin like growth factors, TGF-B, PDGF and other growth promoters may trigger mesangial cell proliferation and increase in mesangial matrix synthesis (and/or decrease its degradation), so causing pathognomonic features of diabetic glomerulopathy32.

7) Familial and genetic pathways:

Diabetes induces important metabolic, hormonal and growth factor changes. These changes that are related in part to the degree of glycaemic control, occur in virtually all patients, but till now it has been impossible to isolate a subset of individuals in whom the severity of these environmental perturbations is convincingly linked to development of these complications. On the contrary, there is ever growing evidence that the diabetic control is only a necessary component but is not linearly related to development of renal failure. To explain the susceptibility of renal failure in a subgroup of patients who develop renal failure alternative hypothesis has been advocated taking into account the host response to diabetic induced environmental disturbances.

Familial clustering of diabetic kidney disease has been reported. In Type I DM 83% of siblings of proband with diabetic nephropathy haveevidence of nephropathy, compared with only 17% of diabetic sibling of probands without nephropathy36.

Familial influence on development of nephropathy has been described in Pima Indians with Type II DM

Sodium Lithium counter transport: Genetically determined red cell sodium-lithium counter transport, a cell membrane cation transport system whose elevated levels are associated with essential hypertension has given insight into predisposition to diabetic renal disease and also attendant cardiovascular disease38. The rate of sodium-lithium counter transport has been found to be higher in proteinuric patients with diabetes than in normoalbuminuric controls. Microalbuminuric diabetic patients have also been found to have higher sodium-lithium counter transport activity. Higher rate of counter transport were associated with elevated LDL cholesterol, total and VLDL triglycerides and reduced HDL cholesterol concentrations. The mechanism of association between sodium lithium counter transport activity, hypertension and lipid abnormalities and susceptibility to diabetic renal and vascular disease could be insulin resistant state.

These associations (i.e. albuminuria, left ventricular and renal hypertrophy and insulin resistance) were independent of actual level of blood pressure or duration of arterial hypertension. This combination of risk factors may not be confined to diabetic population but may be a manifestation of syndrome in general population (Syndrome X)
39, 40.

Sodium-hydrogen antiporter: Sodium-hydrogen antiporter is a cell membrane cation exchanger that catalyses the electroneural exchange of extracellular sodium ions for intracellular hydrogen ions with a stociometry of 1:1. Molecular ionic studies have so far revealed the presence of five subtypes of sodium hydrogen exchangers41.

The most widely studied sodium isoform is referred to as NHE-1, is expressed ubiquitously. The gene for NHE-1is located on short arm of chromosome 1; and encodes a protein of B15 amino acid with two distinct domains. Increased sodium-hydrogen antiport activity has been reported in leucocytes of Type I DM patients with nephropathy as well as patients with essential hypertension and on red cells from Type I DM patients with microalbuminuria. The cells of diabetic patients who

develop nephropathy have intrinsic enhanced capacity to proliferate and this phenomenon is associated with high rates of sodium hydrogen exchange activity. The activity of sodium hydrogen antiport seems to act as an indicator of some mechanism possibly genetically determined controlling cell growth and hypertrophy on one hand and intracellular homeostasis on the other. The environmental changes brought about by diabetes could lead to dysregulation of these mechanisms in susceptible individuals and induces cell hypertrophy and hyperplasia contributing to glomerular hypertrophy and mesangial expansion in the kidneys as well as tubular hypertrophy and hyperplasia. Increased renal sodium reabsorption would augment systemic and renal perfusion pressure to maintain sodium balance. The increasedperfusion pressure would be readily transmitted to glomerular capillaries because of generalised vasodilatation present in diabetes. This would lead to increased intraglomerular pressure, which determines at least in part, and increase in GFR may be responsible for disruption of glomerular permeability properties generating proteinuria. On the other hand progressive mesangial expansion would lead to glomerulosclerosis and further disruption of glomerular basement membrane permeability selective properties. The insulin resistance associated with excessive growth and the consequent hyperinsulinemia may cause lipid abnormalities that in the setting of vascularhyperpermeability characteristic of diabetic microvascular disease, would further aggravate the renal histological damage and contribute in combination with hypertension, and accelerated atherosclerosis of diabetic renal failure42, 43, 44.

PATHOLOGY

Appearence:

Gross Appearance:

The kidneys are of usually normal size. They may be enlarged in the early stages, but later becomes contracted with granular surface. The cut surface is usually pale and the renal arteries may show arteriosclerosis later stages.

Light microscopy:

Glomerular lesions1, 45, 46, 47:

1) Nodular
2) Diffuse
3) Exudative
4) Glomerular hyalinization

Nodular lesions:

The nodular lesions described by Kimmelstiel and Wilson in 1936 has for a long time been considered virtually specific for diabetes.

The nodules are well-demarcated hard masses, eosinophilic, and periodic acid schiff positive, located in the central regions of peripheral lobules. When not acellular they contain pyknotic nuclei and infrequently foam cells can be seen surrounding them. They are characteristically

irregular in size and distribution, both within and between glomerular loops and located away from the hilus. A rim of mesangial cells can sometimes be seen between them and adjoining capillary, which is often distended. Recent evidence seems to establish mesangium as their site of origin and extends the original suggestion that mesangial disruption and lysis of lobule center was related to prior microaneurysmal dilatation of the associated capillary followed by a laminar reorganization of mesangial debris. Its incidence varies considerably from 12-46% in different series, which included both Type I DM and Type II DM cases. Nodules are not seen in the absence of diffuse lesions, and this reflects their appearance only after a long period of disease.

Diffuse glomerular lesions:

Diffuse glomerular lesions comprise an increase in mesangial area and capillary wall thickening with the mesangial matrix extending to involve the capillary loops. The accumulated material has staining properties similar to those of nodules. In its early stages it may be difficult to distinguish the minor mesangialexpansion from changes present with aging or from other glomerular pathology. In more severe cases capillary wall thickening and mesangial expansion lead to capillary narrowing and eventually to complete hyalinization. In advanced lesions periglomerular fibrosis is often present. As with nodules the distribution of diffuse lesion is non-uniform, both among lobules of the same glomerulus and between different glomeruli, leading to appearances suggestive of transition to nodule formation. The thickening of capillary walls also tends to be non-uniform, and this is particularly evident when the histological changes are notvery severe. The diffuse lesions represent earlier stage in the evolution of the disease. In patients with Type II DM the reported prevalence of these changes ranges between 25-51%.

Exudative Glomerular lesions:

Exudative lesions are highly eosinophilic rounded homogenous structures seen in capsular space overlying a capillary loop (fibrin cap) or lying on the inside of Bowman's capsule (capsular drop). They are non-specific, containing various proteins and sometimes lipid materials.

Glomerular hyalinization:

As a consequence of above lesions increasing number of glomeruli becomes hyalinised in advanced cases. In some of the ischemic glomeruli, the tufts shrink with fibrous thickening of the inner surface of Bowman's capsule.

Arterial lesions:

Diffuse intimal fibrosis in these vessels has been found to be more frequent

Arteriolar lesions:

Arteriolar lesions are prominent in diabetics with hyaline material progressively replacing the entire wall structure.Both afferent and efferent arterioles could be affected. Bell also established lesions were often present in absence of hypertension and the involvement of efferent vessel was highly specific for diabetes. These arteriolar changes may be the first change detectable by light microscopy in the diabetic kidney as judged by their recurrence at 2 years in non-diabetic kidneys transplanted into diabetic patients.

Tubular and interstitial changes:

Tubules and interstitium may show a variety of changes that are non-specific and similar to those seen in other forms of progressive renaldisease.

Armanni-Ebstien lesions are the result of accumulation of glycogen in tubular cells of the corticomedullary region in patients with profound glycosuria. More subtle tubular changes consisting of vacuolization, a decrease in the intercellular spaces normally present between the macula densa and a significant increase in the contact areabetween them and extraglomerular mesangial cell48.

Immunopathology:

Westberg and Michael confirmed previous observation of linear staining of glomerular basement membrane for IgG, IgM, albumin and fibrinogen in kidneys of patients with IDDM. The findings were later extended for IgG and albumin not only inthe glomerular basement membrane but also in the Bowman's capsule and especially in the outer aspect of tubular basement membrane were considered specific for diabetes.

Immunofluoroscence techniques have shown increased mesangial amounts of type I, IV, V and VI collagens. Immunochemical analysis has also showed reduced levels laminin and markedly decreased amounts of heparan sulphates, proteoglycan where as levels of fibronectin were normal in diabetic mesangium.

Electron microscopy:

Salient features are:

1) Thickening of glomerular basement membrane

2) Maintenance of fine detail of epithelial foot process and abundant epithelial cytoplasm containing enlarged mitochondria.

3) Accumulation of basement membrane like material within the mesangium.

4) Fibrin deposition in the mesangium and along endothelial aspect of capillary basement membrane.

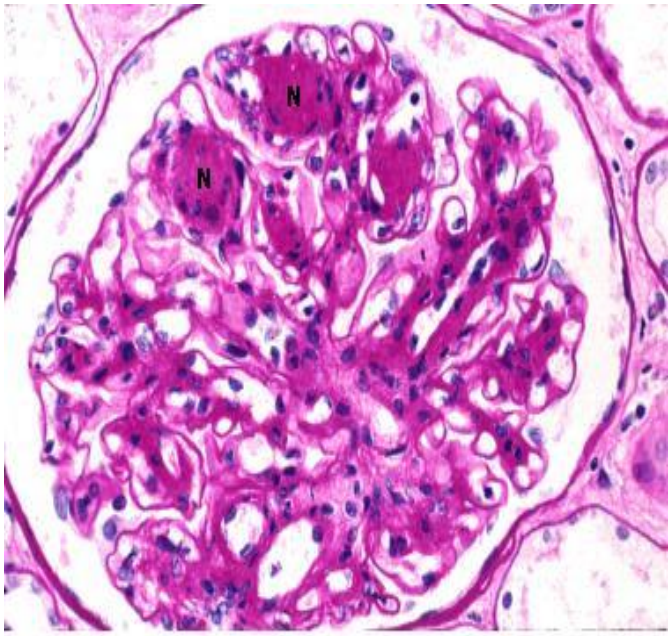
Structure-function relationship:

In early phases of IDDM the increase in luminal volume and filtration surface area may explain the increase in GFR. With advancing renal disease, a close association is observed between thefunctional changes and mesangial expansion but not thickness of glomerular basement membrane. Mesangial expansion also correlates inversely with capillary filtration surface area, a variable closely associated with glomerular filtration rate from levels of hyperfiltration to markedly reduce renal function. Therefore it has been suggested that expansion of mesangium with attendant reduction in glomerular filtration surface areathat is responsible for the progressive loss of renal function in Type I DM

In Type I DMpatients with low levels of microalbuminuria (i.e. AER of 20-30mcg/min) no consistent glomerular abnormalities have been found. Above these levels of urinary albumin excretion, however the fractional volume of mesangium is on averagesignificantly increased, and minor reduction in creatinine clearance and rise in bloodpressure are observed. Similar findings have been reported in Type II DM patients withmicroalbuminuria and proteinuria47.

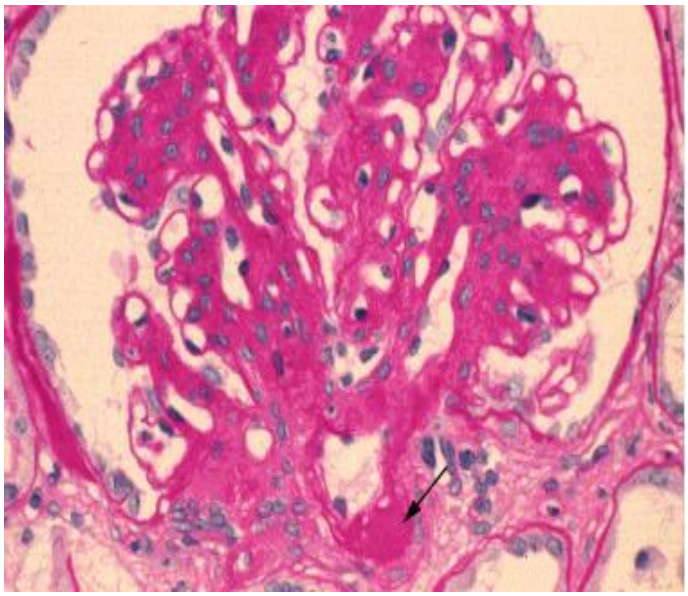
HISTOPATHOLOGY OF DIABETIC NEPHROPATHY

DIABETIC NEPHROPATHY



Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules.

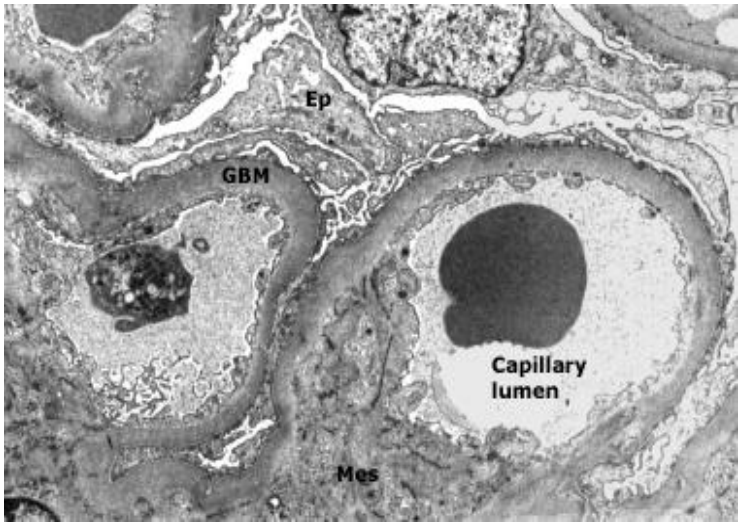
ADVANCED DIABETIC NEPHROPATHY



Light micrograph in advanced diabetic nephropathy shows diffuse and nodular mesangial expansion and characteristic hyaline thickening of the arteriole at the glomerular hilum (arrow). Although not shown, diabetes typically affects both

afferent and efferent arterioles.

Basement membrane thickening in diabetic nephropathy



Electron micrograph in diabetic nephropathy shows a 2 to 3 fold increase in the thickness of the glomerular basement membrane (GBM). Although not seen, the mesangium is also expanded by basement membrane-like material, a process that contributes to nodule formation and glomerulosclerosis.

STAGES OF DIABETIC NEPHROPATHY

Diabetic nephropathy can conveniently be categorized into different stages, which differ with respect to renal hemodynamic, systemic blood pressure, urinary findings and susceptibility to therapeutic interventions.

Stages of diabetic nephropathy- typical findings49

STAGE	***GFR***	***ALBUMINURIA Mcg/ml***	***BP***	***YERAS AFTER DIAGNOSIS***
RENAL HYPERFUNCTION	Elevated	Absent	Normal	At diagnosis
CLINICAL LATENCY	High normal	Absent	Normal	At diagnosis
MICROALBUMINURIA	With in normal range	20-200	within or >normal	5-15
MACROALBUMINURIA	Decreasing	>200	Increased	10-15
END STAGE NEPHROPATHY	diminished	massive	increased	15-30

PROGNOSTIC SIGNIFICANCE OF MICROALBUMINURIA

Prevalence —

The reported prevalence of microalbuminuria among patients with type 2 diabetes approximately 10 years after the diagnosis ranges from 25 to 40 percent [16-20] . In a systematic review of 28 studies in type 2 diabetes (10,298 patients), the prevalence of microalbuminuria was 26 percent at a mean diabetes duration of 10 years [16] . The prevalence was similar (27 percent at eight years) in the ADVANCE trial of 11,140 patients with type 2 diabetes that was published after the systematic review [17] .

The prevalence of microalbuminuria in patients with type 2 diabetes varies with ethnicity, being higher in Asians and Hispanics than in whites [19,20] . The magnitude of this difference was illustrated in an international cross-sectional study of over 24,000 patients with type 2 diabetes without known albuminuria [20] . At a mean duration of diabetes of almost eight years, the rate of microalbuminuria was significantly higher in Asians and Hispanics (43versus 33 percent in whites). As noted in the following section,there arealso racial and ethnic differences in the rate of progression to macroalbuminuria.Some patients with type 2 diabetes have microalbuminuria at the time of diagnosis [18,21,22] .

A higher rate of microalbuminuria (17.9 percent) was noted in another report of over 3600 newly diagnosed patients who were recruited for the UKPDS [21] . The rate of microalbuminuria was significantly higher in the 39 percent of patients with hypertension (24 versus 14 percent in those without hypertension).

The rate of microalbuminuria at the time of diagnosis of type 2 diabetes may be higher in older patients. This was illustrated in a cross-sectional population study in Finland (age 65 to 74 versus a mean of 52 years in the previous two studies) [22] .Microalbuminuria was present in 44 percent and hypertension in 68 percent of these patients; these values were significantly higher than in the subjects who did not develop diabetes.

There are at least two possible explanations for the presence of microalbuminuria at the time of diagnosis of type 2 diabetes: the patients had previously undiagnosed diabetes or some other disease (eg, benign nephrosclerosis) was responsible for the microalbuminuria.

Progression to macroalbuminuria —

As noted above, macroalbuminuria (also called overt proteinuria, clinical renal disease, or dipstick positive proteinuria) is defined as albumin excretion greater than 300 mg/day or 20 µg/min or a urine albumin-to-creatinine ratio greater than 300 mg/g of creatinine or, using standard units, 34 mg/mmol of creatinine.

Among the approximately 5100 patients (81 percent Caucasian) with newly diagnosed type 2 diabetes in the UKPDS described in the preceding section, the prevalence of macroalbuminuria was 5.3 percent at 10 years after diagnosis, compared to 25 percent for microalbuminuria [18] . The rate of progression from microalbuminuria to macroalbuminuria was 2.8 percent per year, which is similar to the 20 to 40 percent rate within a 10-year period noted in other studies of mostly Caucasian patients [4,23,24]

In the systematic review cited above, patients with microalbuminuria had a significantly higher risk than those with normoalbuminuria of progressing to macroalbuminuria (relative risk 7.5, 95% CI 5.2-10.9) [16] .

Other risk factors contributing to progression to macroalbuminuria include higher baseline levels of albuminuria, worse glycemic control as estimated from the hemoglobin A1c concentration, higher blood pressure, and cigarette smoking [23-25] .

Ethnicity may also be important as four- to five-year rates of progression to macroalbuminuria as high as 37 to 42 percent have been described in Pima Indians and Israeli patients [26,27] . In older patients, other causes for proteinuria (such as benign nephrosclerosis) that might progress more slowly than diabetic nephropathy could have accounted for the lower rate of progression to macroalbuminuria.

Macroalbuminuria in patients with type 2 diabetes is typically associated with a progressive reduction in glomerular filtration rate (GFR). In the Pima Indian study, for example, the initial mean GFR was 143 mL/min in patients with newly diagnosed diabetes, 155 mL/min in those with microalbuminuria, and 124 mL/min in those with macroalbuminuria [26] . During four-year follow-up, the GFR increased by 18 percent in the patients with newly diagnosed diabetes, decreased by 3 percent in those with microalbuminuria, and decreased by 35 percent in those with macroalbuminuria.

Microalbuminuria is unlikely to be a marker for susceptibility to the development of clinical nephropathy bur it is more likely to be a sign of early disease. This interpretation has been recently corroborated by the finding that patients with persistent microalbuminuria have more severe histological lesions than do patients with normal AER.

MICROALBUMINURIA AND CARDIOVASCULAR DISEASE.

Multiple studies in different patient populations have suggested that, in addition to its relation to renal disease, microalbuminuria is an important risk factor for cardiovascular disease and early cardiovascular mortality in patients with and without diabetes and/or hypertension.

Clinical trials — HOPE (Heart Outcomes Prevention Evaluation) trial, the presence of microalbuminuria was associated with an increased relative risk of the primary aggregate end point (myocardial infarction (MI), stroke, or cardiovascular death) in those with and without diabetes (1.97 and 1.61, respectively) [12] . The risk of an adverse cardiovascular event increased progressively with increasing absolute levels of microalbuminuria.

LIFE trial of patients with hypertension and electrocardiographic evidence of left ventricular hypertrophy, For every 10-fold increase in the albumin-to-creatinine ratio, the risk of the composite end-point of cardiovascular death, MI, or stroke increased by 57 percent and the risk of cardiovascular death by 98 percent among nondiabetics. The respective increases in risk for diabetics were 39 and 47 percent. A subsequent analysis of this trial showed that the risk of the composite

end-point of cardiovascular death, MI, or stroke was reduced among participants who had a substantial reduction in microalbuminuria at the one-year follow-up [32] .

Population-based studies — have identified microalbuminuria as a significant predictor of cardiovascular risk [14,15,33] . In PREVEND study, urinary albumin excretion was measured in a general population sample of 40,548 participants who were followed for a median of 2.6 years [14] . When adjusted for age and sex, there was a graded increase in the relative risk of cardiovascular mortality of 1.35 for each doubling of urinary albumin excretion.

The mortality risk in postmenopausal women was evaluated in a population-based cohort study of 12,239 postmenopausal women [15] . Cardiovascular mortality was increased in those in the highest quintile of urinary albumin excretion (>21 mg/g creatinine [>2.41 mg/mmol]) compared to women without detectable albuminuria (13.2 versus 2.6 per 1000 years, age-adjusted rate ratio 4.4) [15] . This relationship was independent of diabetes and hypertension.

Low-grade microalbuminuria — Low levels of microalbuminuria, well under the above definitions (≥ 30 mg/day [20 µg/min] or urine albumin-to-creatinine ratio ≥ 30 mg/g), are associated with an increase in cardiovascular risk that is additive to conventional risk factors [16,17,34-37] . In the Third Copenhagen Heart Study, 2726 patients underwent a urine collection for measurement of albumin and were followed for the development of coronary heart disease or death [16] . The adjusted relative risk for coronary heart disease and mortality were 2.0 and 1.9, after adjustment for other risk factors.

Framingham Heart Study of 1568 nonhypertensive, nondiabetic men and women (mean age 55) [34] . The increase in risk remained significant in participants with a low or intermediate pretest probability of cardiovascular disease..

ST and T wave changes — The presence of microalbuminuria also enhances the predictive value of ST and T wave changes for cardiovascular disease. This was illustrated in population-based PREVEND study [18] . Among 7330 subjects, 1244 had ST-T changes; 885 had microalbuminuria. At a median follow-up of six years, the patients with both ST-T changes and microalbuminuria compared to those with ST-T changes alone had marked increases in the incidence of all-cause mortality

(7.2 versus 1.1 percent) and cardiovascular mortality (2.7 versus 0.5 percent). Microalbuminuria had a greater impact on the risk of all-cause mortality than hypertension, hypercholesterolemia, cigarette smoking, obesity, or diabetes mellitus.

Possible mechanisms — How microalbuminuria is associated with cardiovascular disease is not well understood. Microalbuminuria in nondiabetics appears to be a signal from the kidney that the vasculature, particularly the endothelium, is not functioning normally. As examples: Vasodilation in response to certain stimuli is relatively reduced in older "normal individuals" with microalbuminuria compared to those without microalbuminuria [38] . Among nondiabetic patients with essential hypertension, those with microalbuminuria had higher plasma levels of von Willebrand factor (vWf) antigen than patients with normal albumin excretion [39] ; furthermore, individual vWf and albumin excretion values were significantly correlated. vWf has been associated with occlusive thrombosis; thus, the increased plasma vWf levels might directly contribute to the enhanced cardiovascular risk.

Endothelial dysfunction is also present in diabetic patients [20] and the degree of coronary endothelial dysfunction appears to be greater in patients with microalbuminuria [40] . One important factor may be hyperglycemia-induced alterations in extracellular matrix, such as decreased density of heparan sulfate proteoglycans. This abnormality can lead to increased microvascular permeability, resulting in microalbuminuria at the glomerulus and perhaps increased lipoprotein deposition in peripheral vessels. in the Diabetes Control and Complications Trial, progressive increases in albuminuria were associated with elevations in proatherogenic intermediate-density lipoprotein and small dense LDL particles [41] .

Microalbuminuria, the fifth pillar of syndrome X:

Reavon in a seminar article has proposed that insulin resistance /hyperinsulinemia forms the common denominator between conventional cardiovascular risk factors and the development of atherosclerosis. Thus individual risk factors such as hypertension, obesity, hyperlipidemia and glucose intolerance, which commonly aggregate, simply represent the “rainbow colors” of a clinical syndrome

characterised by an underlying state of insulin resistance and a devastating cardiovascular outcome in what Reavon referred to collectively as syndrome X. Interestingly there is now evidence to promote microalbuminuria as a distinct and independent facet of this disorder. Investigating theinfluence of microalbuminuria and hypertension on insulin resistance in Type II DM patients, Group et al reported that glucose metabolism, as measured during insulin clamp technique, was impaired in normotensive Type II DM patients with microalbuminuria compared with normotensive normoalbuminuric patients. The defect in insulin action wasshown to correlate with urinary albumin excretion. Furthermore, diabetic subjects with a combination of hypertension and microalbuminuria had a greater reduction in insulin mediated glucose disposal and widespread disturbances in lipid metabolism. Perhaps the most surprising finding of these studies was the observation that insulin-stimulated glucose disposal was remarkably normal in normotensive Type II DM patients who did not have microalbuminuria54. A similar conclusion has also been reached by Nosadini and Zambon et al who showed that insulin sensitivity was not compromised in healthy Type II DM patients unless either microalbuminuria or hypertension or both existed55. The relationship between insulin resistance and albuminuria in Type II DM subjects was alsoconfirmed by Niskanen and Laaksa who showed that insulin mediated glucose uptake determined during euglycemic clamp study was significantly lower in Microalbuminuric when compared with normoalbuminuric patients, independent of the confounding effectof hypertension. Thus, the association between insulin resistance and microalbuminuria in Type II DM as revealed by the findings of these studies raises the interesting question of whether the two phenomena might in some way be causally related. However, the presence of microalbuminuria in Type II DM has not been marked by a reduction in insulin sensitivity in all of the studies thus far reported. For the present, therefore the mechanism relating insulin resistance/hyperinsulinemia to albuminuria remains largely speculative56.

Finally, two recent reports have shed further insight into the significance of microalbuminuria in Type II DM. Haffner et al in a cross-sectional study, and Mykannen et al in a prospective study, have reported that microalbuminuria in non-diabetic individualsmay precede and even predict the onset of Type II DM. Moreover, microalbuminric subjects who remained glucose tolerant after 3.5 years of follow-up still demonstrated multiple cardiovascular abnormalities, including elevated blood

pressure, high triglyceridesconcentration, high insulin concentration, and low HDL cholesterol concentration, i.e. a cardiovascular risk profile akin to that observed in prediabetic individuals. Microalbuminuria may be regarded as a prominent feature of the prediabetic state. The above findings therefore provide probably the most damaging evidence against microalbuminuria as a serious phenomenon in the evolution of Type II DM and atherosclerotic disease57, 58.

TREATMENT OF INCIPIENT NEPHROPATHY

Microalbuminuria indicates early stage of development of diabetic nephropathy and also a marker of increased mortality from cardiovascular risk factors. Microalbuminuria is also associated with other microvascular and macrovascular complications of diabetes. It is a warning sign for the patient, which should not be neglected. Progress of microalbuminuria to macroalbuminuria or overt nephropathy can
be reversed or delayed by intervention at this stage.

The strategies for treatment at this stage include1, 5, 7, 8, 61:

1) Optimum glycaemic control-diet, intensified insulin treatment, oral hypoglycemic agents
2) Blood pressure control and ACE inhibitors
3) Dietary treatment
4) Newer treatment modalities which are under study
 Aldolase reductase inhibitors
 Glycosaminoglycans
5) Correction of cardiovascular risk factors and other diabetic complications.
 Stopping of cigarette smoking
 Correction of dyslipidemia

Optimum glycaemic control

In patients with Type I DM with microalbuminuria, strict metabolic control by continuous subcutaneous insulin infusion has been effective in reducing AER. Similar reduction in AER is seen after multiple injection therapy, provided that similar levels of blood glucose control are achieved, a finding suggesting that it is the attained blood glucose control concentration rather than the modality of treatment that matters62

Blood pressure control:

ACE inhibitors/ARBs — Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have similar efficacy in type 2 diabetic patients with microalbuminuria. The only randomized comparative trial (DETAIL) of these agents in type 2 diabetic patients compared enalapril to the ARB telmisartan in 250 patients with early nephropathy as defined by albuminuria (82 percent microalbuminuria and 18 percent macroalbuminuria to a maximum of 1.4 g/day) and a baseline GFR (measured isotopically) of approximately 93 mL/min per 1.73 m2 [33] . A greater fall in GFR of at least 10.0 mL/min per 1.73 m2 at five years was predefined as suggesting a clinically significant difference between the two treatment groups.

At five years, there was a smaller decline in GFR with enalapril that was not significant (14.9 versus 17.9 mL/min per 1.73 m2 with telmisartan). Both groups had similar rates or findings for the secondary end points, which included annual changes in the GFR, blood pressure, serum creatinine concentration, urinary albumin excretion, end-stage kidney disease, cardiovascular events, and mortality.

Preferential renoprotective benefits with ACE inhibitors or ARBs compared to that observed with placebo have also been noted in a number of trials [27,34-38] . The potential magnitude of benefit can be illustrated by the results of the RENAAL trial in which 590 hypertensive patients with type 2 diabetes and microalbuminuria were randomly assigned to either irbesartan (150 or 300 mg/day) or placebo and then followed for two years [34] .

The primary end point was the time from baseline to first detection of overt nephropathy (urine albumin excretion >200 µg/min [macroalbuminuria] and at least a 30 percent increase from baseline on two consecutive visits). This end point was significantly more common in the placebo group compared to irbesartan (14.9 versus 9.7 and 5.2 percent with 150 and 300 mg of irbesartan). This benefit was not related to differences in blood pressure, although the systolic blood pressure was 3 mmHg lower with 300 mg irbesartan than with placebo or 150 mg irbesartan (141 versus 144 mmHg), a difference that was statistically significant.

In patients with type 2 diabetes and microalbuminuria, either an ACE inhibitor or an ARB is recommended to slow or prevent progression to macroalbuminuria and overt diabetic nephropathy. The renal goal of ACE inhibitor therapy is a modest reduction in urine albumin excretion.

Calcium channel blockers — Calcium channel blockers have less antiproteinuric effect than ACE inhibitors or ARBs, and the antiproteinuric effect is primarily seen with diltiazem and verapamil, not the dihydropyridines.

The difference between these drug classes was evaluated in the MARVAL trial in which 332 patients with type 2 diabetes and microalbuminuria were randomly assigned to valsartan or amlodipine [39] . Albumin excretion was reduced by 92 percent with valsartan compared to 56 percent with amlodipine, a difference that was highly significant.

Dietary and Behavioural modification:

Reductions of dietary protein by approximately 50% has been shown to reduce the fractional clearance of albumin in patients with microalbuminuria, and to lower GFR in patents with hyperfiltration, independently of changes in glucose control and pressure.

Diets restricted 0.5-0.6gm of protein /kg body weight per day is ideal and does not have long-term detrimental effect on nutritional status of an individual. Cessation of cigarette smoking should always be advised in a patient with microalbuminuria61.

Other treatment modalities:

Aldolase reductase inhibitors, which have been studied in a few studies, show reduction in GFR and decreases in AER in Type II DM patients who had either a normal AER or microalbuminuria. But study in subjects with Type II DM with microalbuminuria it failed to show any effects on renal function. Further studies are needed to confirm the finding.

Recent observation suggests that oral administration sulodexide (a naturally occurring glycosaminoglycan) extracted from pig intestinal mucosa, containing a fast moving heparan like fraction (80%) and a dermatan sulphate fraction (20%) along with ACE inhibitors seems to retard progression from incipient to overt nephropathy in Type II DM patients. Mechanism is possibly by restoring glomerular basement

membrane charge and size selectivity to albumin molecules as well as reducing glomerular capillary pressure. Further studies are needed to confirm this finding68.

Correlation of cardiovascular risk factors and other complications:

A detailed cardiovascular examination is necessary early in the course of diabetic nephropathy. Hypertension must be treated energetically. Left ventricular hypertrophy and function should be assessed echocardiographically at the stage of microalbuminuria and thereafter every 6 –12 months. Effective antihypertensive therapy can reverse leftventricular hypertrophy. In addition cardiac assessment should includeelectrocardiography, stress testing, coronary angiography and Holter monitoring is indicated whenever needed. Ischemic heart disease should be treated aggressively.

Peripheral vascular disease must be assessed and treated as necessary. Doppler flow studies and arteriography may be useful to assess the severity of the disease69, 70.

Microalbuminuria is frequently associated with hyperlipidemia and lipid profile is an essential investigation and dyslipidemia should be treated71.

Testing vibration perception threshold and thermal discrimination may identify the risk of neuropathic ulceration. The test should be repeated regularly as sensation may become impaired later, during the course of nephropathy. Autonomic dysfunction is very common in nephropathic patients. The important manifestations are postural hypotension and incomplete bladder emptying which predisposes to urinary tract infection72.

Microalbuminuria is frequently associated with retinopathy. Retinopathy almost always accompanies diabetic nephropathy. Early and regular ophthalmic review and prompt treatment is necessary to prevent blindness73, 74.

PRIMARY PREVENTION —

In addition to treating microalbuminuria to prevent progressive disease, clinical trials have also demonstrated efficacy of ACE inhibitors and ARBs and of glycemic control for the primary prevention of microalbuminuria and subsequent overt nephropathy in patients with type 2 diabetes.

Glycemic control — As noted above, worse glycemic control is a risk factor for both the development of microalbuminuria and for progression to macroalbuminuria in patients with type 2 diabetes. Strict glycemic control is recommended in all patients because of its beneficial effects on the microvascular complications.

The UKPDS evaluated the importance of strict glycemic control in 3867 patients with newly diagnosed type 2 diabetes [43] . The patients were randomly assigned to intensive or conventional therapy. Over 10 years, the average hemoglobin A1C value was 7.0 percent in the intensive therapy group, compared to 7.9 percent in the conventional therapy group (an 11 percent reduction).

ADVANCE trial in which 11,140 patients with type 2 diabetes (mean duration eight years) were randomly assigned to intensive therapy to achieve a hemoglobin A1c below 6.5 percent or to standard therapy [17] . At a median follow-up of five years, the intensive and standard groups achieved mean hemoglobin A1c values of 6.5 and 7.3 percent, respectively.

ACE inhibitors or ARBs — There have been variable results related to the efficacy of ACE inhibitors [36,44-49] or ARBs [50] for the primary prevention of nephropathy in clinical trials of patients with type 2 diabetes

Among normotensive patients, the rate of progression to microalbuminuria was significantly lower with enalapril compared to placebo [45,46] and, in the ABCD trial, enalapril was equivalent to nisoldipine [46] . Among hypertensive patients, the rate of progression to microalbuminuria was similar with captopril and atenolol in the United Kingdom Prospective Diabetes Study [47] , significantly lower with trandolapril compared to verapamil

A meta-analysis and the BENEDICT trial illustrate the magnitude of these effectsACE inhibitors significantly reduced the progression to microalbuminuria or macroalbuminuria compared to placebo and to calcium channel blockers. The benefit was similar in patients with and without hypertension. Based upon these observations, administration of an ACE inhibitor is recommended in hypertensive normoalbuminuric patients with type 2 diabetes. Although ARBs are likely to provide similar benefits, this has not yet been proven for these agents.

There is insufficient evidence to recommend ACE inhibitor therapy for primary prevention in patients with type 2 diabetes who are normotensive. These patients should be screened yearly for microalbuminuria and an ACE inhibitor initiated if persistent microalbuminuria is documented.

METHODS OF MEASURING MICROALBUMINURIA

Small concentration of albumin in the urine can be measured qualitatively by several methods.Radioimmunoassay was the first and most widely used method. Various methods to determine microalbuminuria are given in the table59.

METHOD	SENSITIVITY	TIME OF ASSAY
Single radio immune diffusion(Manini1965)	1.25 mg/ml	1 day
Electroimmuno assay (Laurel1966)	5 mg/l	4-6 hrs
Immunoturbidimetric assay (Teppor1982)	5 mg/l	20-30 min
Radio immuno assay (Keen and Chlouvervakis, 1963)	6.2 mcg/l	1-2 days
ELISA (Filding 1983)	250 mcg/l	12-18 min
Fluorescent immuno assay (Chavers 1984)	500 mcg/l	4-6 hrs
Latex agglutinates immuno nephelometry(Vasquez 1984)	750 mcg/l	6 hrs
Immuno chemical semi quantitative dipstic (MICRAL)	20-300 mg/l	5 sec – 5 min

In our study we have used Micral test for estimation of microalbuminuria. Micral test (Boehringer Mannheim, Germany) is dipstick method of estimation of microalbuminuria. Test principle is immunochemical in nature. Sensitivity of Micral test was 93% and its specificity was 93% when compared to radioimmunoassay in a study by Gilbert PE et al60. Micral test has also been compared with immunoturbidimetricassay and radioimmunoassay methods. In all studies Micral test is comparable in sensitivity and specificity to the other methods of estimation of microalbuminuria.

MATERIALS AND METHODS

One hundred patients of Type II DMadmitted to PSGIMS & R were studied. The patients were taken from both IP and OP of the hospital, based on random selection. Patients were considered to be diabetic based on WHO (2) criteria for diagnosis of diabetes mellitus

which is : -

1) Symptoms of diabetes mellitus plus a random glucose concentration >200 (11.1mmol/l). The classic symptoms of diabetes mellitus include polyuria, polydipsia and unexplained weight loss

OR

2) Fasting blood glucose >126 mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for at least 8 hours

OR

3) 2 hour post prandial glucose > 200mg/dl (11.1 mmol/l). Among diabetics, the above criteria were considered to include the patients for the study.

OR

4)HbA1C> 6.5

Inclusion criteria for case selection:

1) Urine sugar – positive

2) Fasting blood sugar > 126 mg/dl

Exclusion criteria for case selection:

1) Patients with macroalbuminuria

2) Patients with congestive cardiac failure, urinary tract infection.

3) Ketonuria

4) Pregnant patients

5) Patients with overt diabetic nephropathy

The selected patients were studied in detail with history and physical examination

History:

- Patient's characteristics age, sex, age of onset and duration of diabetes.
- All details regarding the presenting complaints were noted.
- Total duration of diabetes, the drugs the patient was taking and the dosages were noted. The regularity of the treatment taken by the patients was also noted. The family history regarding diabetes was taken.
- Personal history regarding smoking, alcohol consumption, bowel and bladder habits and drug intake were noted.

A complete clinical examination was carried out in each patient with particular reference to the complications of diabetes like retinopathy, neuropathy, diabetic foot and ischemic heart disease.

Height and weight were measured in all cases and body mass index (BMI) was calculated by weight in kg / height in m_2

Hypertension was said to be present when there was a history of hypertension or the systolic blood pressure was recorded greater than 160mm of hg and/or diastolic pressure greater than 90 mm of hg on 3 consecutive occasions. Ischemic heart disease was recorded to be present in the presence of suggestive history of angina or myocardial
infarction with electrocardiographic evidence.

Peripheral neuropathy was judged to be present if there was historical evidence of neuropathic pain, numbness or tingling sensation in the extremities and or absence of ankle jerks along with diminished vibratory threshold or pin prick sensation in hands or feet on examination.

Fundus examination was done in all patients for evidence of diabetic retinopathy. Retinopathy was said to be present when there was evidence of microaneurysm, soft or hard exudates and hemorrhages. Neovascularity was considered as evidence for proliferative retinopathy.

Peripheral vascular disease was considered to be present with history of amputations and /or absent of one or more peripheral pulses and /or presence of gangrenous foot.

T*he following investigations were done in all the patients.*

- Microalbuminuria was estimated by Micral test in all the cases.
- Fasting Blood sugar and Postprandial blood sugar
- Glycosylated hemoglobin
- Blood urea and serum creatinine
- Fasting lipid profile
- Urine routine and culture
- Electrocardiogram
- Ultrasonography of the abdomen, echocardiogram and chest x-ray were done in selected cases only.

Estimation of Microalbuminuria by Micral test: **A**ll patients having overt macroalbuminuria detected by albustic were excluded from study. Micral test, a immunological rapid dip stick semi qualitative technique for detection of microalbuminuria, was used for estimation of microalbuminuria.

Micral test components: 1 test strip contains monoclonal antibodies against human albumin (immunoglobulin G) labeled with colloid gold 2.2mg, fixed albumin 7.7 mg

TEST PRINCIPLE:

There is a serial arrangement of several reagent pads, which are in fluid communication by a reaction controlling chromatographic process. This step combines one step handling with a complex chemistry. The single reaction steps are as follows:

- Urine of the sample is transported through the wick fleece to the buffer fleece, where acidic urine is adjusted to proper pH. Upon entering the conjugate fleece the antigen – antibody reaction takes place Albumin of the sample is specifically bound to a soluble conjugate of antibodies and marker enzyme resulting in an antigen – conjugate complex
- The excess antibodies are bound to immobilized albumin on the capture matrix and removed from the sample in this way.
- Only the complex of conjugate with sample-albumin reaches the substrate pad. Here the color reaction takes place, the marker enzyme B-Galactosidase cleaves off

the purple dye chlorophenol red from the Yellow substrate (chlorophenol red galactoside) in a kinetic reaction. The intensity of the color produced is proportional to the albumin concentration in the urine.

SPECIMEN COLLECTION:

All patients were afebrile during the course of collection of urine and were kept at rest during the collection of urine. Urine of the patient was first tested for albumin by albustix method. Patients who were negative for albumin by the albustix method were only included in this study.

First morning mid stream urine sample that was collected in a sterile container was used for determining microalbuminuria. Test strip was immersed in urine such that fluid level was between the two black bars provided on the strips. Strip was withdrawn after 5 seconds. Strip was placed horizontally across the urine vessel and color change inthe test zone was compared with color scale after one minute. Sensitivity of the kit is 0.4ng/ml and measuring range is 0.8 to 10ng/ml.

Microalbuminuria was graded as follows:

Mild (20-50mg/L)- +

Moderate (50-100mg/L) - ++

Severe (100-300mg/L)- +++

Depending on the color change in the strip.

Severity of diabetes was graded based on the HbA1c levels, as follows:

Mild - <7.0%

Moderate- 7.0% to 7.5%

Severe- > 7.5%

Blood urea, serum creatinine and lipid profile were estimated in all cases.

STATISTICAL METHODS [75, 76]

Chi-square and Fisher Exact test have been used to find the significance of proportion of incidence of microalbuminuria between various levels of study parameters namely BMI, Age, Duration of DM, GHB %, abnormal lipid profile and complications etc. The Odds ratio has been used to find the strength of relationship between the incidence of microalbuminuria and other study parameters. Student t test has been used to find the significance of mean levels of lab parameters between the presence and absence of microalbuminuria

Statistical software: The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS AND STATISTICALANALYSIS

Study design

A Prospective clinical study consisting of 100 Type 2 DM patients is undertaken to investigate the pattern and magnitude of microalbuminuria and its relationship with microvascular and macrovascular complications of Type 2 DM

Table 1 shows the age and sex distribution of patients

Table1: Age and sex distribution

Age in years	Male		Female		Total
	No	%	No	%	
30-40	9	15.7	7	16.28	16
41-50	14	24.56	9	20.93	23
51-60	15	20.32	16	37.21	31
61-70	14	24.56	6	13.95	20
>70	5	8.77	5	11.63	10
Total	57	100	43	100	100
Mean age SD	54.82+/-12.38		54.82+/-11.08		54.87+/-11.59
Mean age of detection of DM	48.84+/-10.11		48.75 +/- 8.68		48.79 +/-9.27
P value	**Mean age between male and female = 0.965** **Mean age of detection of diabetes= 0.964**				

16 patients were in the age group between 30 and 40 years, among whom 9 were maleand 7 were female patients. 23 patients were in the age group between 41 and 50 years,among whom 14 were male and 9 were female patients. 31 patients were in the age groupbetween 51 and 60 years, among whom 15 were male and 16 were female patients. 20patients were in the age group between 61 and 70 years, among whom 14 were male and6 were female patients. 10 patients were in the age group greater than 70 years, amongwhom 5 were male and 5 were female patients. The mean age of male patients in thestudy was 54.82 + 12.38 years and that of the female patients was 54.82 + 11.08 years.The mean age of detection of diabetes mellitus among the male patients was 48.84+ 10.11years and in the patients was 48.75 + 8.68 years.

The mean age between male and female is not statistically significant withp=0.964 and the mean age of detection of DM is not statistically significant with P=0.965

FIGURE 1

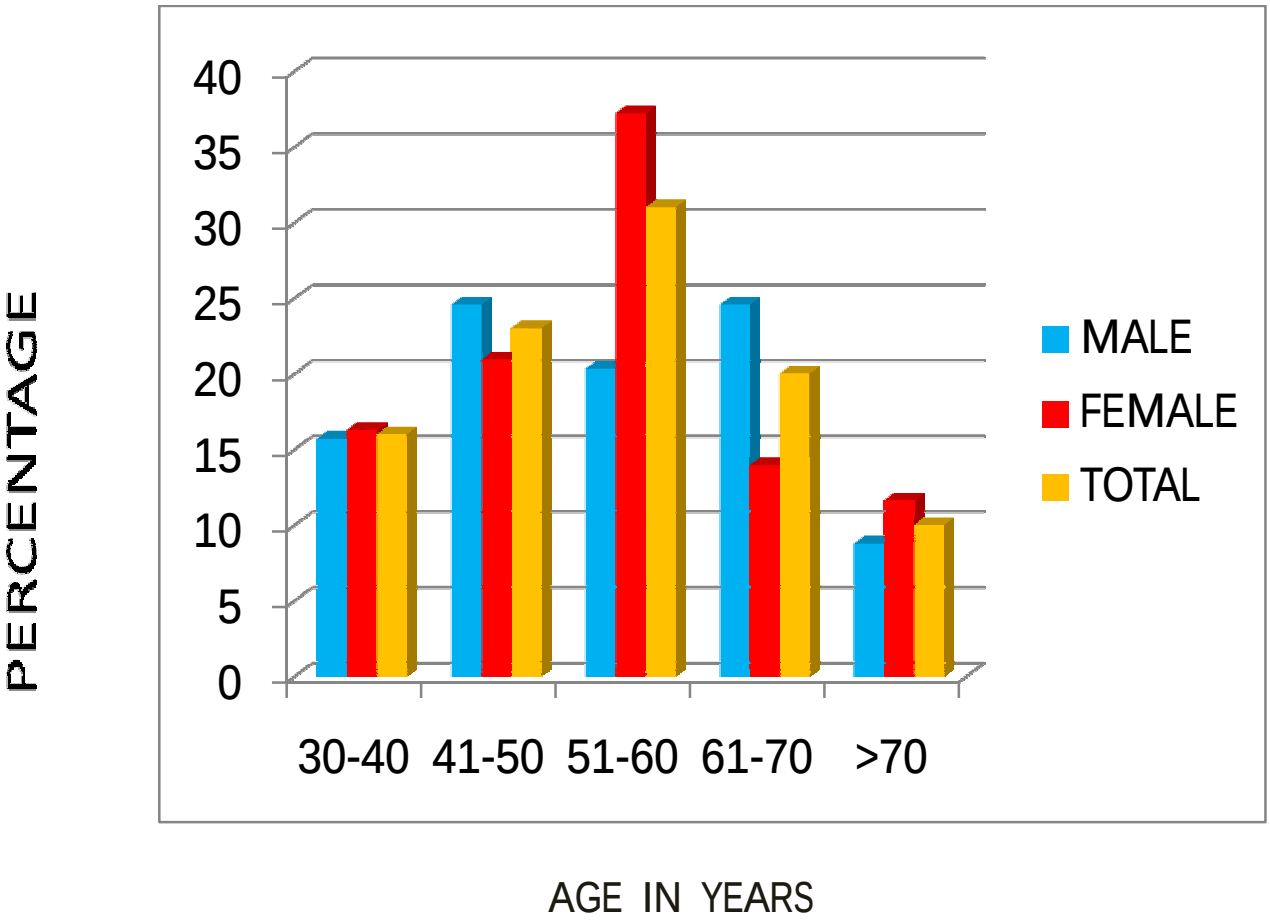

PERCENTAGE
40
35
30
25
20
15
10
5
0
30-40
41-50
51-60
61-70
>70
MALE
FEMALE
TOTAL
AGE IN YEARS

Table 2 shows the duration of diabetes mellitus since diagnosis

Table2: Duration of diabetes mellitus since diagnosis

Duration of DM	MALE (n=57)		FEMALE (n=43)		Total (n=100)
	N0	%	NO	%	
<5	35	61.4	24	55.81	59
5.1-10	12	21.05	11	25.58	23
10.1-15	5	8.77	6	13.95	11
>15	5	8.77	2	4.65	7
Mean duration of DM □ SD	6.19□4.31		6.11□4.75		6.14□4.54
P value	0.930				

A total of 59 patients had duration of diabetes since diagnosis less than 5 yearsamong which 35 were male and 24 female patients. 23 patients had duration of diabetessince diagnosis between 5 years and 10 years among which 12 were male and 11 werefemale patients. 11 patients had duration of diabetes since diagnosis between 10 years and15 years among which 5 were male and 6 were female patients. 7 patients had duration ofdiabetes since diagnosis greater than 15 years among which 5 were male and 2 werefemale patients. The mean duration of diabetes since diagnosis was 6.19 +4.31 yearsamong the male patients and 6.11+4.75 years among the female patients. The meanduration of DM is not statistically significant between male and female patients withp=0.930

FIGURE 2

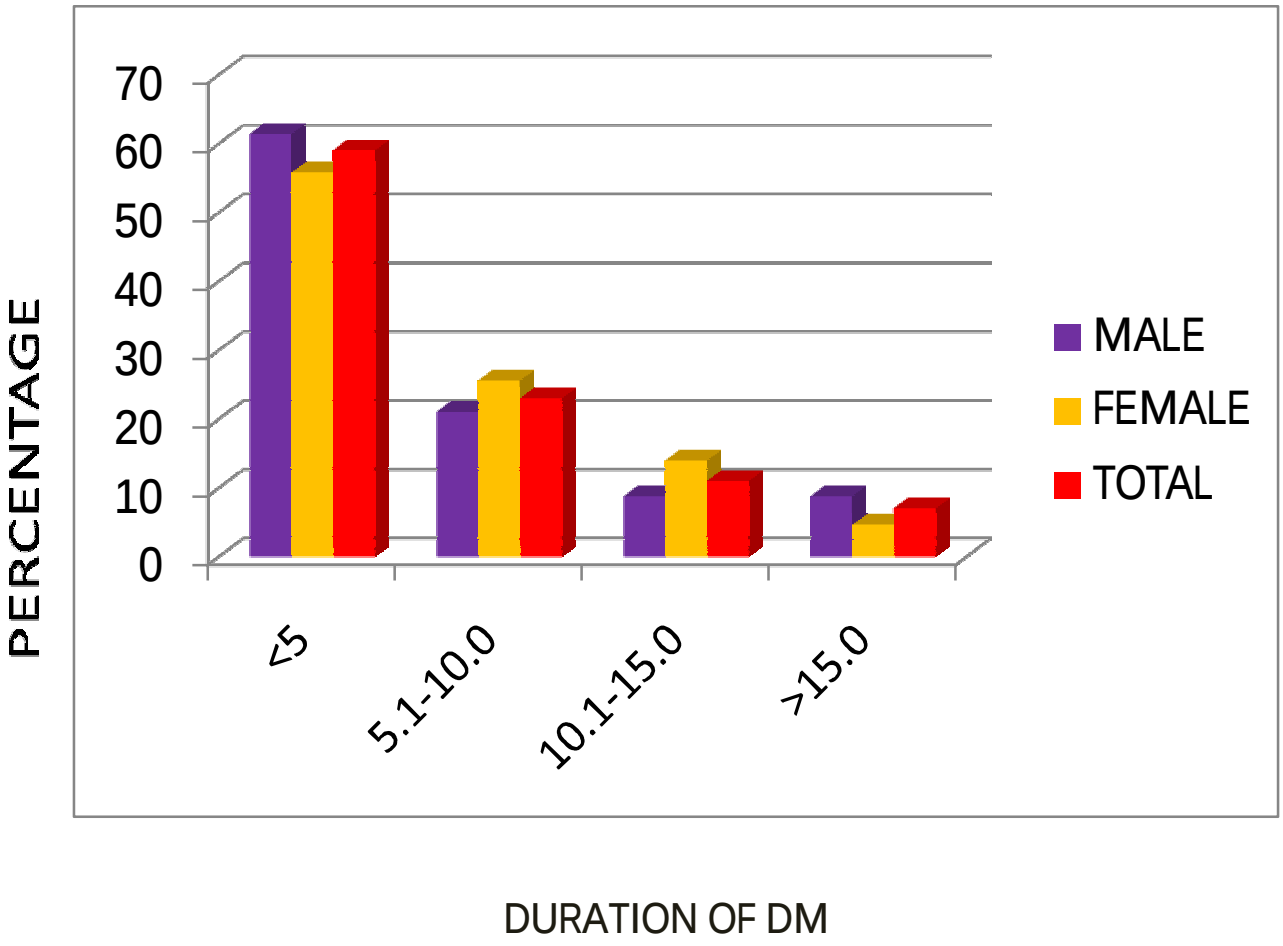
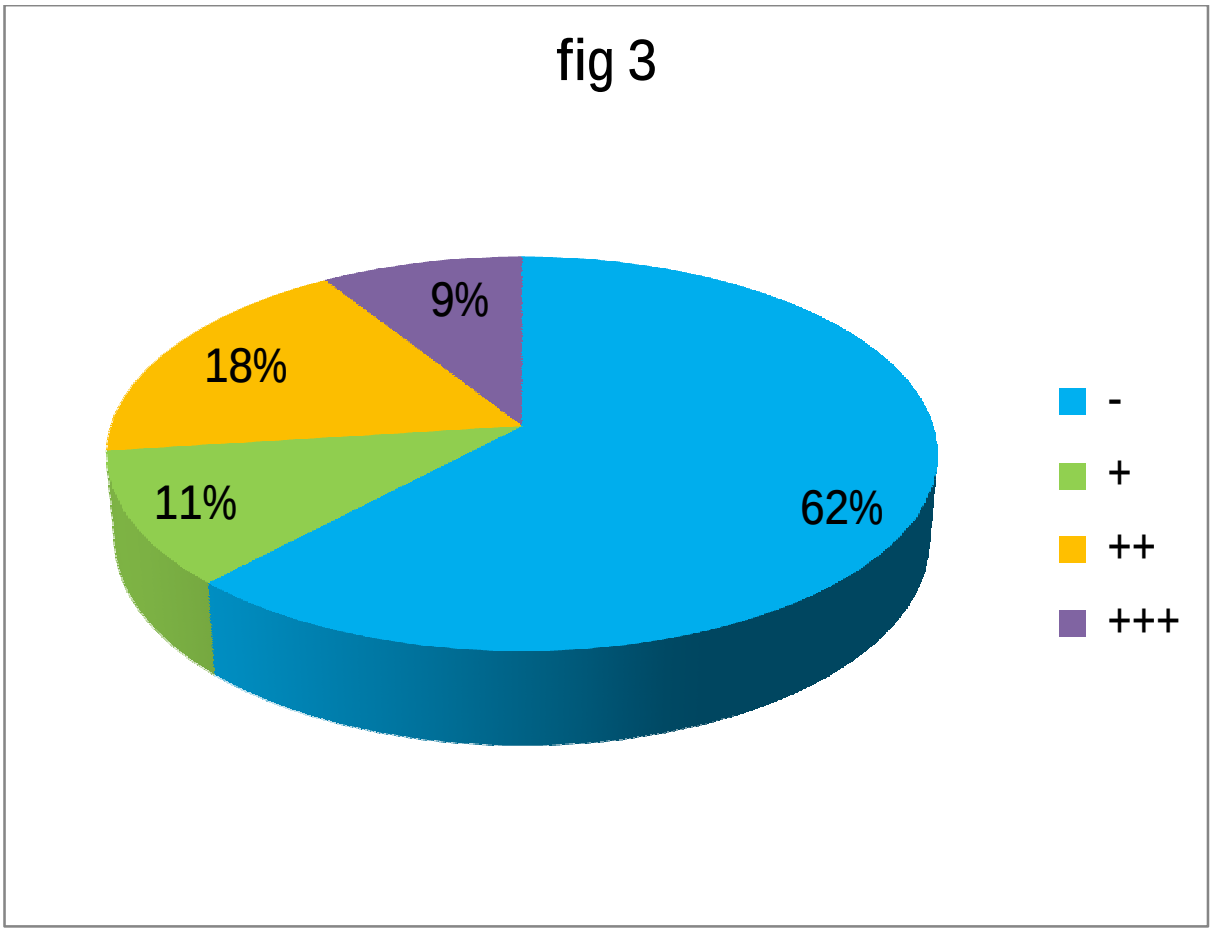

70
60
50
40
30
20
10
0
PERCENTAGE
<5
5.1-10.0
10.1-15.0
>15.0
MALE
FEMALE
TOTAL
DURATION OF DM

Table 3 shows the number of patients with microalbuminuria in this study.

Table3: Number of patients with Microalbuminuria

Microalbuminuria	Number (n=100)
-	62
+	11
++	18
+++	9

There were 62 patients negative for microalbuminuria. 11 patients had microalbuminuria between 20 to 50 mg/l. 18 patients had microalbuminuria between 50 to100 mg/l. finally 9 patients had microalbuminuria between 100 to 300 mg/l.



MICROALBUMINURIA

Table 4 shows the number of patients on different treatment for diabetes mellitus

Table4: Treatment

TREATMENT	NUMBER n =100
INSULIN	4
OHA	84
INSULIN +OHA	12

4 patients were on treatment with Insulin and 84 patients were on treatment withoral hypoglycaemic agents whereas 12 patients were on both insulin and oral hypoglycaemic drugs.

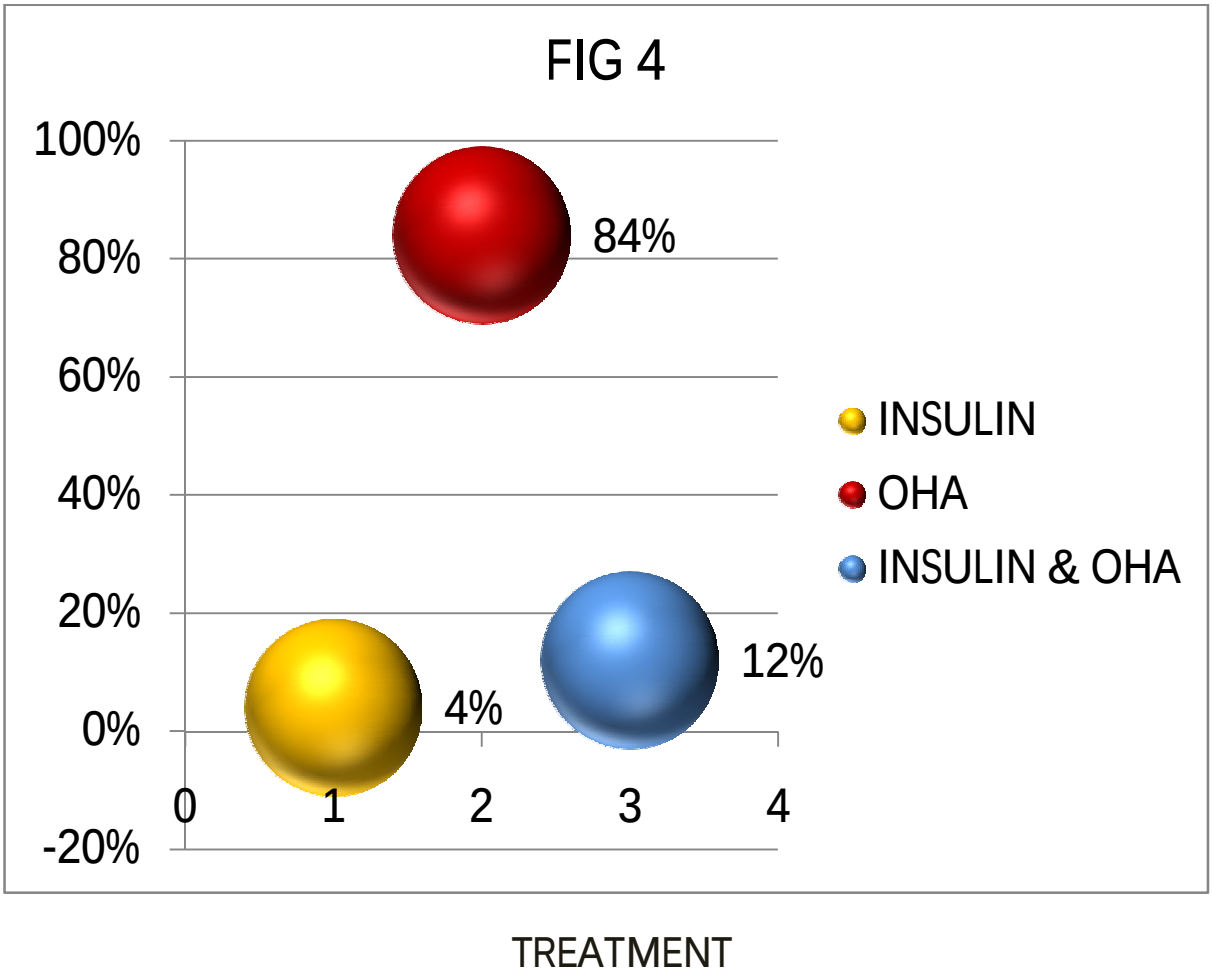


FIG 4
100%
80%
60%
40%
20%
0%
-20%
84%
4%
12%
0
1
2
3
4
INSULIN
OHA
INSULIN & OHA
TREATMENT

Table 5 shows the association of age with microalbuminuria

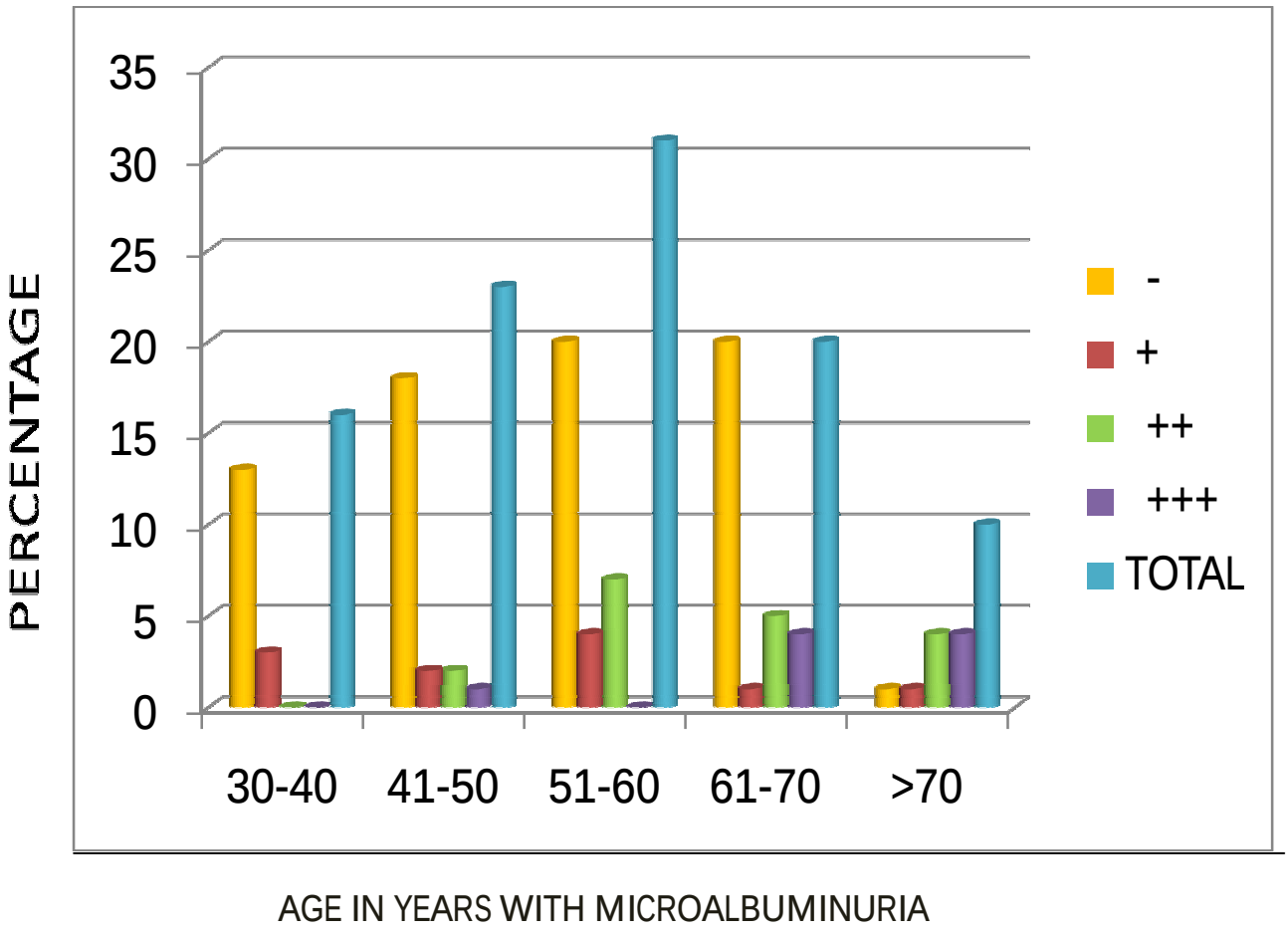
Table5: Association of Age with Microalbuminuria

AGE IN YEARS	MICROALBUMINURIA				
	-	+	++	+++	TOTAL
30-40	13	3	-	-	16
41-50	18	2	2	1	23
51-60	20	4	7	-	31
61-70	20	1	5	4	20
>70	1	1	4	4	10
TOTAL	62	11	18	9	100
P VALUE	***Incidence of microalbuminuria is 2.54 times more likely for age group > 50 years P=0.053***				

Among the 16 patients in the age group between 31 to 40 years 3 patients hadmicroalbuminuria. 23 patients were in the age group between 41 to 50 years amongwhom 5 patients had microalbuminuria. 31 patients were in the age group between 51 to60 years among whom 11 patients had microalbuminuria. 20 patients were in the agegroup between 61 to 70 years among whom 10 patients had microalbuminuria. 10 patientswere in the age group greater than 70 years among whom 9 patients hadmicroalbuminuria.

Incidence of Microalbuminuria is 2.54 times more likely for the age group > 50years of age as compared to the age group <50 years with □2=3.757, P=0.053

FIGURE 5



AGE IN YEARS WITH MICROALBUMINURIA

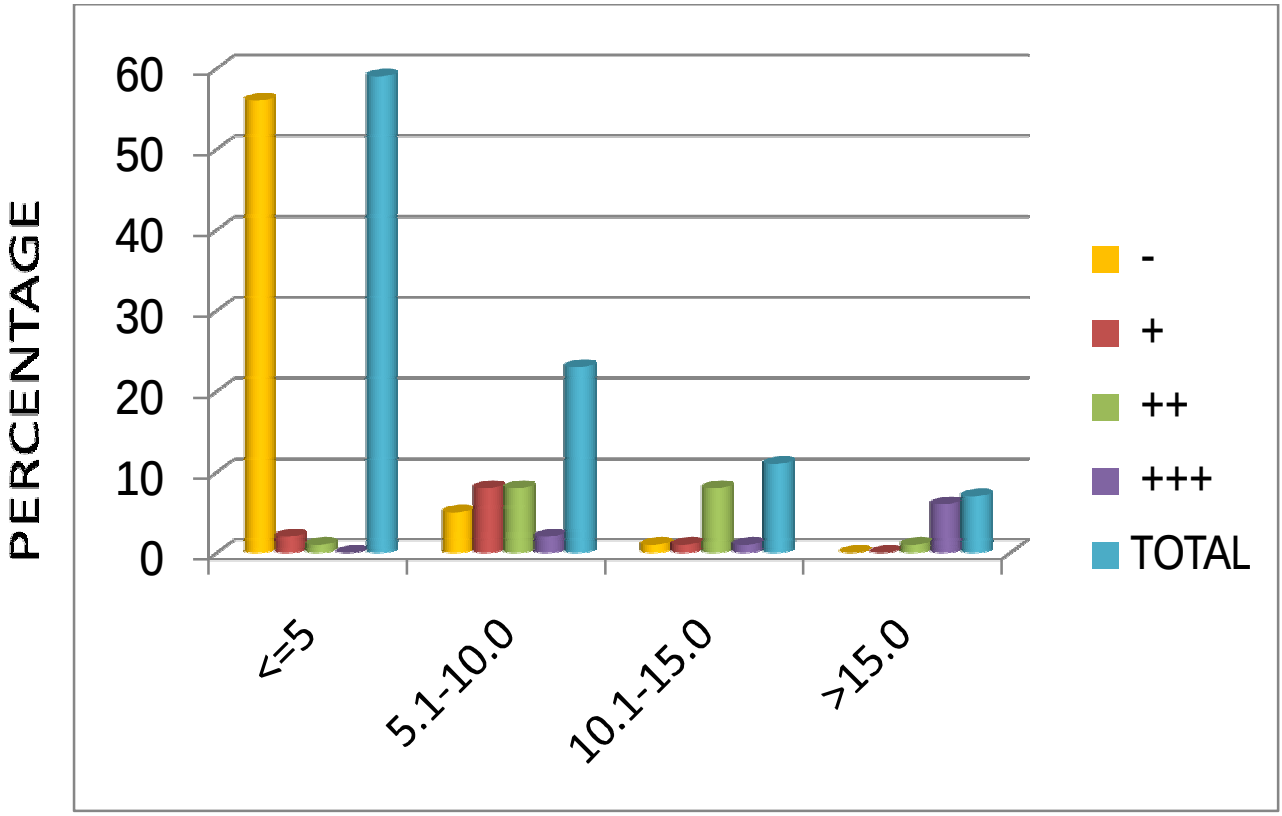
Table 6 shows the association of the duration of diabetes since diagnosis with the incidence of microalbuminuria

Table6: Association of Duration of DM since diagnosis with the incidence of Microalbuminuria

DURATION OF DM	MICROALBUMINURIA				
	-	**+**	**++**	**+++**	**TOTAL**
<=5	56	2	1	-	59
5.1-10.0	5	8	8	2	23
10.1-15.0	1	1	8	1	11
>15.0	-	-	1	6	7
P value	**P < 0.001**				

The number patients with the duration of diabetes since detection less than 5 years were 59 and among them 3 were positive for microalbuminuria. The number patients with the duration of diabetes since detection 5 years and 10 years were 23 andamong them 10 were positive for microalbuminuria. The number patients with theduration of diabetes since detection 10 years and 15 years were 11 and among them 10were positive for microalbuminuria. All the patients i.e. 7 with duration more than 15years were positive for microalbuminuria.

FIGURE 6



DURATION OF DM WITH MICROALBUMINURIA

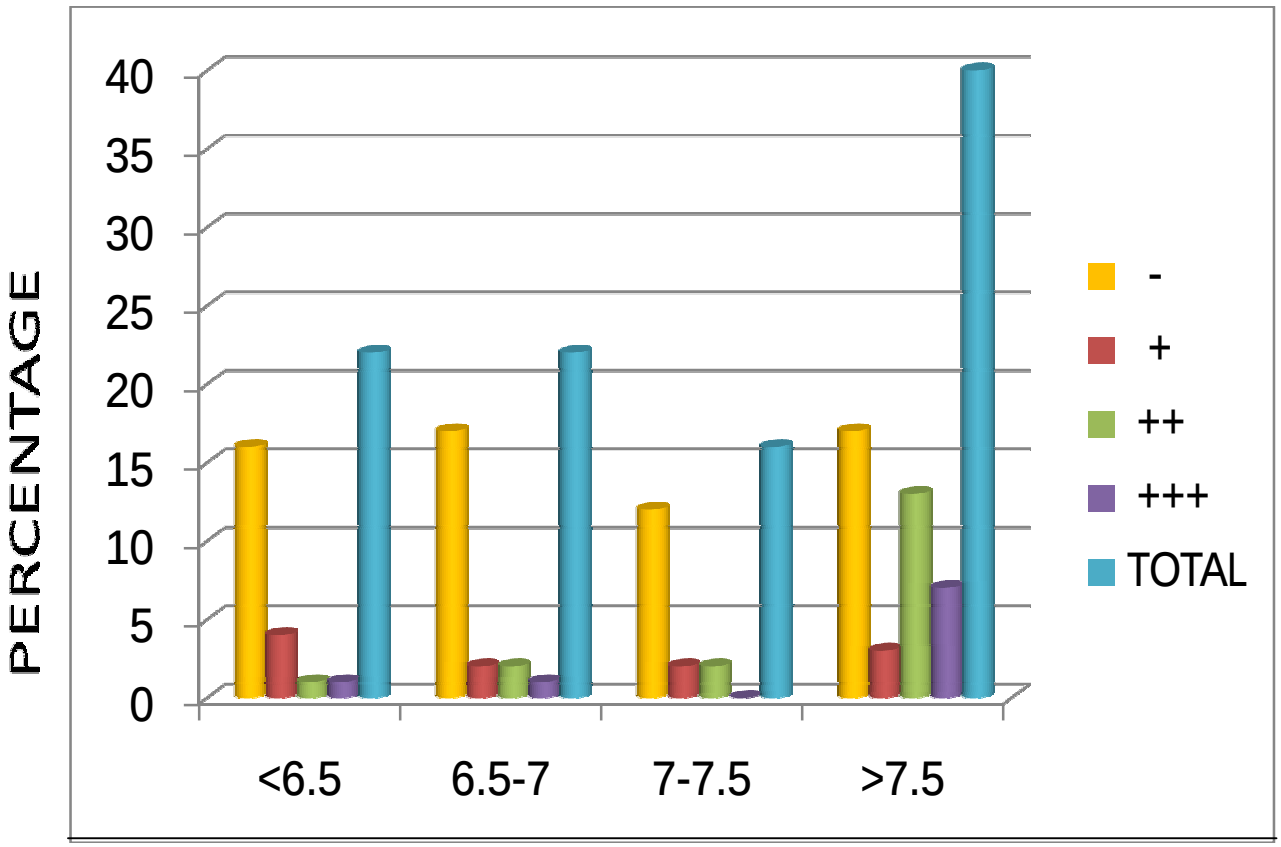
Table 7 shows the association of HbA1c with the incidence of microalbuminuria

Table 7:Association of HbA1c with the incidence of Microalbuminuria

HbA1c	Microalbuminuria (n=100)				
	-	+	++	+++	TOTAL
<6.5	16	4	1	1	22
6.5-7.0	17	2	2	1	22
6.5-7.0	12	2	2	-	16
>7.5	17	3	13	7	40
P value	**7.0%, p= 0.018** **7.5%, p= 0.001**				

22 patients had HbA1c values less than 6.5% and among them 6 were positive formicroalbuminuria. 22 patients had HbA1c values between 6.5% and 7.0%, among them 5were positive for microalbuminuria. 16 patients had HbA1c values between 7.0% and7.5%, among them 4 were positive for microalbuminuria. 40 patients had a HbA1c valuesmore than 7.5%, among them 23 were positive for microalbuminuria

FIGURE 7



HbA1C WITH MICROALBUMINURIA

Table 8 shows the association of body mass index with microalbuminuria

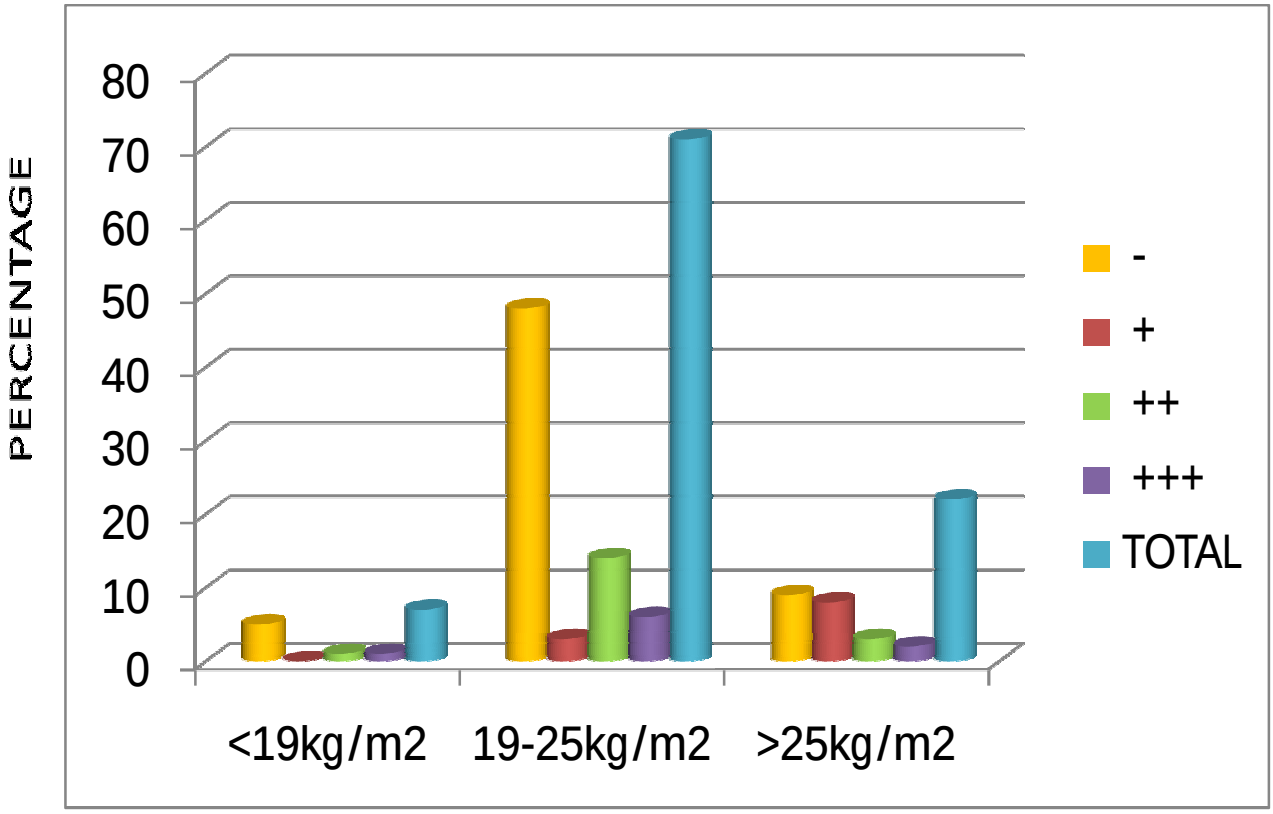
Table 8:Association of body mass index with the incidence of Microalbuminuria

Body mass index (Kg/m2) (n=100)	Microalbuminuria					
	-	+	++	+++	TOTAL	OR
<19	5	-	1	1	7	0.63 (P=0.706)
19-25	48	3	14	6	71	0.44 (P=0.071a
>25	9	8	3	2	22	3.06 (P=0.027*)
P value	**P< 0.05**					

a Near significance * Significance at 5% ** Significance at 1%

7 patients had a BMI less than 19kg/m2 and out of them 2 patients were positivefor microalbuminuria. 71 patients had a BMI between 19kg/m2 and 25 kg/m2 and out ofthem 23 patients were positive for microalbuminuria. 22 patients had a BMI above 25kg/m2 and out of them 13 patients were positive for microalbuminuria. Incidence of Microalbuminuria is significantly associated & Positively with BMI>25 and Negatively associated with BMI <25 kg/m2 with P<0.05

FIGURE 8



BMI WITH MICROALBUMINURIA

Table 9 shows the association of lipid parameters with the incidence of microalbuminuria

Table 9: Association of Lipid Parameters with the incidence of Microalbuminuria

Body mass index (Kg/m_2) (n=100)	Microalbuminuria					OR
	-	+	++	+++	TOTAL	
T.Cholesterol (>200 mg/dl)	20	4	3	3	30	1:0.65 (P=0.359)
Triglycerides (>160 mg/dl)	21	6	7	3	37	1:1.42 (P=0.408)
LDL (>150 mg/dl)	6	-	3	2	11	1:1.41 (P=0.744)
HDL (<30 mg/dl)	17	3	8	5	33	1:1.41 (P=0.744)

30 patients had Total cholesterol greater than 200 mg/dl and among them 11 patients were positive for microalbuminuria. 37 patients had Triglycerides greater than160 mg/dl and among them 16 patients were positive for microalbuminuria. 11 patientshad LDL greater than 150 mg/dl and among them 5 patients were positive formicroalbuminuria. 33 patients had HDL lesser than 30 mg/dl and among them 16 patientswere positive for microalbuminuria.Incidence of microalbuminuria is not significantly associated with the abnormallipid parameters, however, the incidence of microalbuminuria is 1.93 times more likelyfor the patients presented with HDL <30 mg/dl.

FIGURE 9

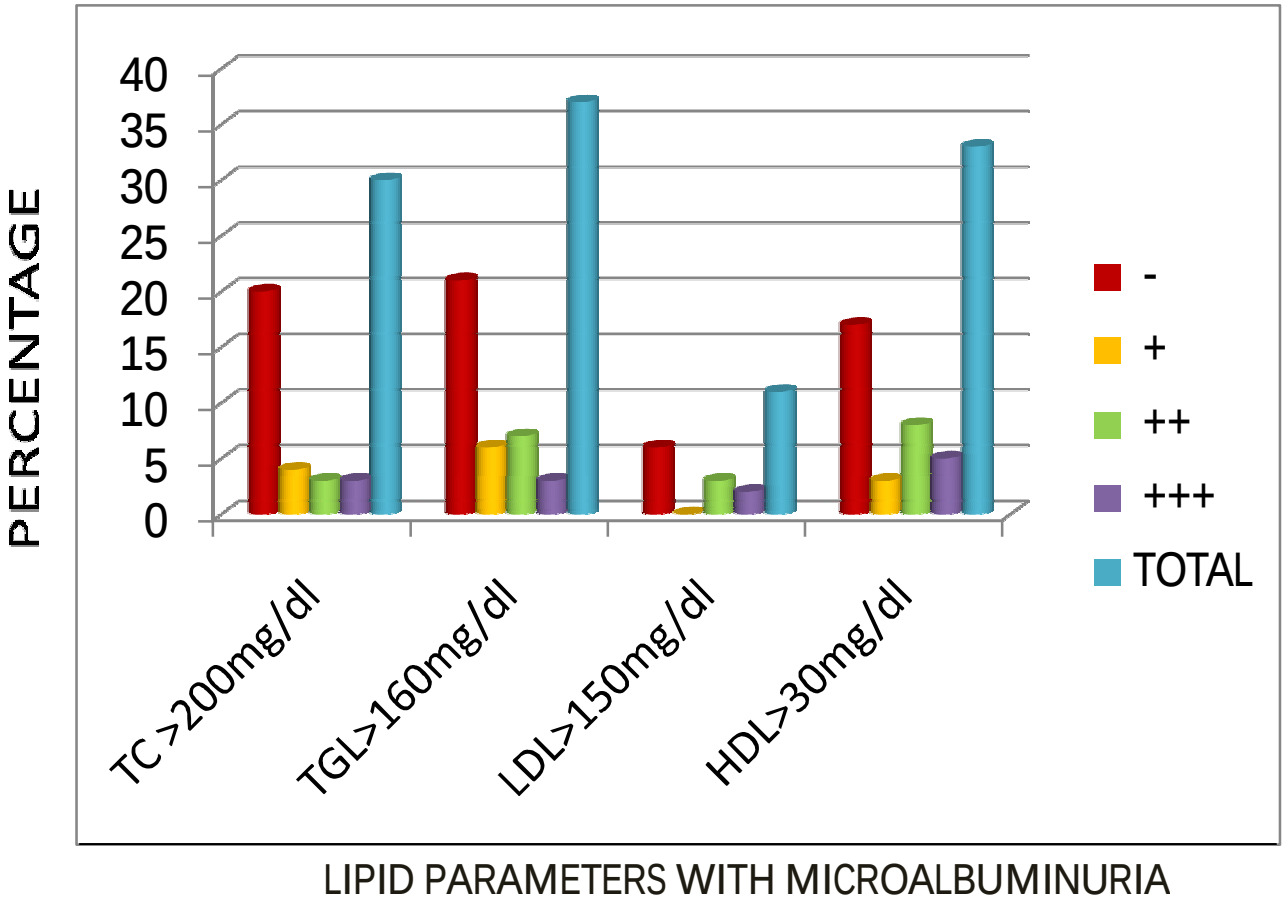

PERCENTAGE
40
35
30
25
20
15
10
5
0
TC >200mg/dl
TGL>160mg/dl
LDL>150mg/dl
HDL>30mg/dl
-
+
++
+++
TOTAL
LIPID PARAMETERS WITH MICROALBUMINURIA

Table 10 shows the association of complications with the incidence of microalbuminuria

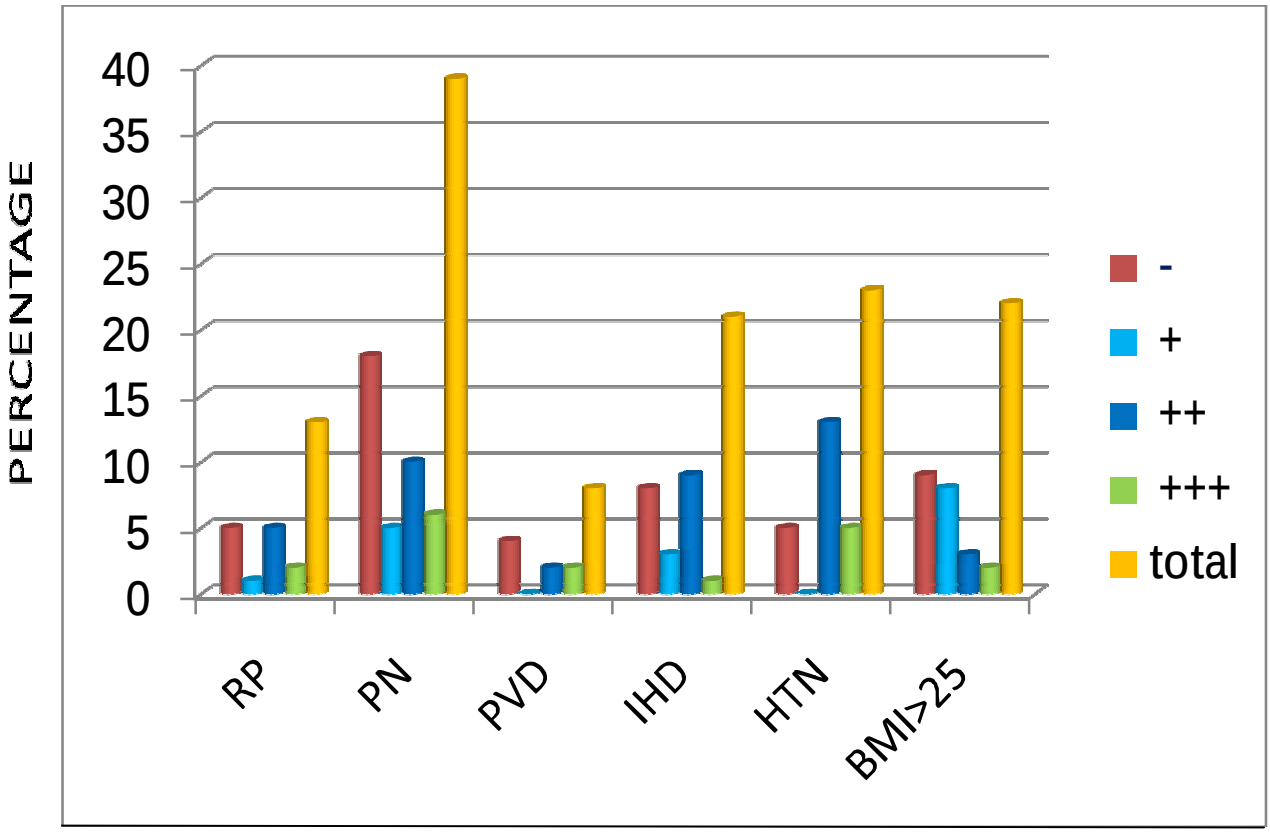
Table 10:Association of Complications with the incidence of Microalbuminuria

Complications (n=100)	**Microalbuminuria**					**OR**
	-	**+**	**++**	**+++**	**TOTAL**	
Retinopathy	5	1	5	2	13	1:3.04 (P=0.073a)
Peripheral Neuropathy	18	5	10	6	39	1:3.02 (P=0.009**)
Peripheral vascular diseases	4	-	2	2	8	1:1.71 (P=0.474)
Ischemic heart Disease (IHD)	8	3	9	1	21	1:3.51 (P=0.011*)
Hypertension	5	-	13	5	23	1:10.26 (P<0.001**)
BMI (>25 kg/m2)	9	8	3	2	22	1:3.06 (P=0.027*)

a Near significance * Significance at 5% ** Significance at 1%

13 patients had retinopathy, among them 8 patients were positive for microalbuminuria. 39 patients had peripheral neuropathy, among them 21 patients werepositive for microalbuminuria. 8 patients had peripheral vascular disease, among them 4patients were positive for microalbuminuria. 21 patients had Ischemic heart Disease(IHD), among them 13 patients were positive for microalbuminuria. 23 patients hadhypertension, among them 18 patients were positive for microalbuminuria. 22 patientshad a BMI above 25 kg/m2 and out of them 13 patients were positive for microalbuminuria

FIGURE 10



COMPLICATIONS WITH MICROALBUMINURIA

Table 11 shows the mean pattern of laboratory parameters in the presence of Microalbuminuria

Table 11: Mean Pattern of Lab parameters in the presence of Microalbuminuria

Lab parameters	Microalbuminuria Lab parameters (Mean ±SD)		Significance by student t test
	Absent	Present	
FBS mg/dl	172.39 ± 26.22	194.44 ± 34.39	P<0.001**
PPBS mg/dl	244.97 ±30.19	273.92 ± 48.49	P<0.001**
GHB %	7.06 ± 0.81	8.06 ±1.41	P<0.001**
Blood Urea mg/dl	29.19 ±6.02	29.95 ± 6.81	P=0.555
S. Creatinine mg/dl	1.04 ± 0.16	1.05±0.19	P=0.915
T.Cholesterol mg/dl	188.09 ±29.61	188.74 ± 38.75	P=0.926
TGL mg/dl	153.31 ±60.06	164.61 ± 63.52	P=0.374
LDL mg/dl	125.97±21.75	125.58 ± 26.82	P=0.937
HDL mg/dl	31.46 ± 3.52	30.23 ± 3.40	P=0.089a

a Near significance * Significance at 5% ** Significance at 1%

The mean value of FBS in the presence of microalbuminuria was 194.44 ± 34.39 mg/dland 172.39 ± 26.22 mg/dl in the absence of microalbuminuria. The mean value of PPBSin the presence of microalbuminuria was 273.92 ± 48.49 mg/dl and 244.97 ±30.19 mg/dlin the absence of microalbuminuria. The mean value of GHB% in the presence ofmicroalbuminuria was 8.06 % ± 1.41 % and 7.06% ± 0.81% in the absence ofmicroalbuminuria. The mean value blood urea of in the presence of microalbuminuriawas 29.95 ± 6.81 mg/dl and 29.19 ± 6.02 mg/dl in the absence of microalbuminuria. Themean value serum creatinine of in the presence of microalbuminuria was 1.05 ±0.19mg/dl and 1.04 ±0.16 mg/dl in the absence of

microalbuminuria. The mean value oftotal cholesterol in the presence of microalbuminuria was 188.74 ± 38.75mg/dl and188.09 ± 29.61 mg/dl in the absence of microalbuminuria.

The mean value oftriglycerides in the presence of microalbuminuria was 164.61 ± 63.52 mg/dl and 153.31 ±60.06 mg/dl in the absence of microalbuminuria. The mean value of LDL cholesterol inthe presence of microalbuminuria was 125.58 ± 26.82 mg/dl and 125.97 ± 21.75 mg/dl inthe absence of microalbuminuria. The mean value of HDL cholesterol in the presence ofmicroalbuminuria was 30.23 ±3.40 mg/dl and 31.46 ±3.52 mg/dl in the absence ofmicroalbuminuria.

DISCUSSION

Type 2 diabetes mellitus is being increasingly recognized as a disease, which is characterised by dysfunction of the endothelium. Endothelial dysfunction occurs in a generalized and widespread manner in diabetic subjects. The severity of the dysfunction is directly proportional to the age of the patient and duration of the diabetes. The clinical markers of the generalized endothelial dysfunction becomes manifest in several forms. Microalbuminuria marks the onset of endothelial dysfunction related to the kidney. Since its original description by Mogensen, the estimation of microalbuminuria is made easy and practical. Microalbuminuria serves as a warning for imminent nephropathy. But its true value is that it heralds generalized endothelial dysfunction. Thus diabetic subjects with microalbuminuria not only have ongoing progressive nephropathy but are also likely to have retinopathy, nephropathy and cardiovascular problems including coronary artery disease and hypertension. An effort has been made in this study to highlight this issue. Even among randomly selected patients an incidence of 38% for microalbuminuria is evident. Among various other studies the prevalence of microalbuminuria ranges from 25% to 35% 78, 79, 80, 81. A slight increase in the percentage of microalbuminuria in our study can be attributed to several factors such as, large number of elderly patients, longer duration of diabetes and poor glycemic control.

It is very well recognized that microalbuminuria occurs more commonly in diabetic subjects who are more than 50 years of age. In our study microalbuminuria tended to be 2.54 times more common in the age group of above 50 years as compared to the age group of less than 50 years. There are many reasons for this phenomenon. Firstly deterioration in the □-cell function, which occurs parripassu with increasing duration of diabetes, is likely to contribute to worsening glycemic control. Poor values of HbA1c are known to be associated with increasing incidence of microalbuminuria. In our study only 11 out of 44 patients who had a normal HbA1c (< 7.0%) manifested Microalbuminuria, whereas with HbA1c values more than 7, 27 out of 56 (nearly 50%) had microalbuminuria. It is seen from the above result that even small increments of HbA1c more than 7.0% result in almost doubling of the incidence of

microalbuminuria. It is also interesting to note that when HbA1c rises above 7.0%, 22 out of 27 patients tended to have more than 50mg/l and 7 out of 27 had microalbuminuria touching 300mg/l.

Although this is a cross sectional study, these findings raise concern regarding the blatant association between poor glycemic control and microalbuminuria in a rural setting.

This study has also brought out a significant association of microalbuminuria with body mass index of more than 25kg/m2. Of the 22 patients with BMI of more than 25, 13 had microalbuminuria (52%). Similar findings have been brought forth by other studies79, 80, 81. The possible explanation for this could be

1. Increasing body mass index is a reflection of insulin resistance which inturn leads to endothelial dysfunction and microalbuminuria.
2. Associated hypertension may also be responsible for microalbuminuria.
3. Poor glycemic control which inturn is an outcome of insulin resistance is also held responsible.

Our study has also brought out the correlation between lipid parameters and microalbuminuria. Although no correlation could be found between microalbuminuria and hypertriglyceridemia and hypercholesterolemia, the incidence of microalbuminuria is 1.93 times more likely for the patients who present with HDL values of less than30mg/dl. A similar inverse relationship between HDL and icroalbuminuria has been described in many studies77, 78, 79, 81, 82, 83.

The incidence of microalbuminuria is significantly associated with the presence of retinopathy (p=0.073), peripheral neuropathy (p=0.009), ischemic heart disease (p=0.011), hypertension (p=0.001) and body mass index (p=0.027) more than 25kg/m2. Peripheral neuropathy and hypertension have the most significant association with microalbuminuria. This association is not surprising since both hypertension and neuropathy are dependent on similar risk factors. It is also well known that retinopathy and microalbuminuria have a high concordance rate. Several studies have highlighted the occurrence of microalbuminuria as a marker of ischemic heart disease 78, 81, 83. Our study also underscores this point. Out of the total 38 patients with microalbuminuria, 13 of them had ischemic heart disease.

SUMMARY

- We studied 100 Type II DM patients for detection of microalbuminuria through the dipstick method.

- The mean age between male and female and the mean age detection of DM is not statistically significant

- 9 patients had severe microalbuminuria between 100 and 300 mg/dl

- Incidence of microalbuminuria is 2.5 times more likely for the age group more than 50 years

- All patients with HbA1C 7 with duration of DM > 15 years were positive for microalbuminuria

- Incidence of microalbuminuria is significantly associated with BMI > 25 kg/m^2

- Incidence of microalbuminuria is 1.9 times more in patients with HDL < 30 mg /dl

CONCLUSIONS

- The incidence of microalbuminuria is estimated to be **38%** in this study.

- Microalbuminuria shows a **direct relationship with increasing age of patients and increasing duration of diabetes mellitus** since diagnosis.

- A HbA1c value **above 7% is associated with 50% or higherincidence** of microalbuminuria.

- Patients with a **body mass index of more than 25kg/m2 have significant increasein the incidence** of microalbuminuria.

- Incidence of microalbuminuria is significantly associated with presence of hypertension, neuropathy, Ischemic heart disease, retinopathy and high body mass index.

- Microalbuminuria is **inversely associated with HDL.**

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ANNEXURE

PROFORMA

Name:

IP/OP No:

Age: Date of admission:

Sex: Date of discharge:

Religion: Marital status:

Address:

Occupation:

Education:

Income group: High/middle/poor

CHIEF COMPLAINTS:

Polyuria/ Polydipsia / Blurring of vision

Weight loss / Tiredness Polyphagia

Pruritus /Aches and pains Skin infections

HISTORY OF PRESENTING ILLNESS

1) **Cardiovascular symptoms:**

Angina/ myocardial infarction/ exertional dyspnea /orthopnea

PND /palpitations/ syncope /sweating/Swelling of feet

2) Peripheral vascular symptoms:

Intermittent claudication/ Gangrene /Impotence/ thrombophlebitis

3) Cerebrovascular symptoms:

Giddiness /headache/ vomiting/ transient ischemic attacks/Stroke

4) Visual symptoms:

Blurring of vision/ Progressive loss of vision /sudden loss of vision

5) Renal symptoms:

a) Symptoms of urinary tract infection:

Dysuria Fever with chills Flank pain

b) Symptoms of nephropathy:

Swelling of feet Puffiness of face Distension of abdomen

Increasing sensitivity of insulin

6) Symptoms of neurological complications:

a) Symptoms of polyneuropathy:

Tingling Numbness Paraesthesia Nocturnal pain

Sensory ataxia Trophic ulcers Charcot joints

b) **Symptoms of mononeuropathy:**

Wrist drop Foot drop

c) Cranial nerves:

Diplopia Squint Deviation of the angle of mouth

Inability to close the eyes

d) Symptoms of radiculopathy:

e) Symptoms of autonomic neuropathy

Dysphagia vomiting Nocturnal diarrhea Syncope

f) Symptoms of amyotrophy:

Paraesthesia of the anterior thigh Thinning of proximal muscle

Weakness of proximal muscles

7**) Symptoms of Diabetic skin complications:**

Recurrent skin infections Abscesses Carbuncles

8) Gastro intestinal symptoms:

Dysphagia Abdominal pain Nausea/Vomiting Diarrhea

Weight loss Loss of appetite

9) Genito urinary symptoms:

Polyuria/Nocturia Balanoprosthitis Impotence Dysuria

Discharge per urethra Discharge per vagina

DIABETES HISTORY

Diabetes diagnosed in the year:

Duration of Diabetes:

Diabetes onset at the age of:

Mode of onset of Diabetes:

Family history of Diabetes:

Drugs used for Diabetes: OHA / INSULIN/ INSULIN + OHA

PAST HISTORY

History of hypertension

History of Angina / Myocardial infarction

History of Transient ischemic attack / stroke

PERSONAL HISTORY

HABITS YES NO STOPPED

Smoking

Sweets

Alcohol

Tobacco

Appetite /bowel /bladder

FAMILY HISTORY

MEMBERS PRESENT ABSENT

Father

Mother

Sisters

Sons

Daughters

Spouse

Others: History of Hypertension, Ischemic heart disease , Cerebrovascular accidents

Obesity and Sudden death

OBSTETRIC AND GYNECOLOGICAL HISTORY

Menarche/ Menopause

Gravida/Para/Abortion/History of stillbirths/History of delivery of large babies

GENERAL PHYSICAL EXAMINATION

1) BUILT: Well / moderately /poor/ emaciated

2) WEIGHT:

HEIGHT:

BODY MASS INDEX:

3) PULSE:

4) BLOOD PRESSURE:

5)PALLOR/EDEMA/CLUBBING/KOILONYCHIA/CYANOSIS/ICTERUS/LYMPHADENOPATHY

6) JUGULAR VENOUS PULSE

7) PERIPHERAL PULSE

8) SKIN CHANGES:

Diabetic dermopathy

Acanthosis nigricans

Scleroderma

Xanthoma

Fungal infection

Skin tags

9) EYES:

Normal/ Xanthoma / Arcus / Cataract

10) FUNDUS

SYSTEMIC EXAMINATION

1) <u>CARDIOVASCULAR SYSTEM</u>

- INSPECTION
- PALPATION
- PERCUSSION
- AUSCULTATION
- OTHER FINDINGS

<u>2) RESPIRATORY SYSTEM</u>

- INSPECTION
- PALPATION
- PERCUSSION

- AUSCULTATION
- OTHER FINDINGS

3) ABDOMEN

- INSPECTION
- PALPATION
- PERCUSSION
- AUSCULTATION
- OTHER FINDINGS

4) CENTRAL NERVOUS SYSTEM

- HIGHER MENTAL FUNCTIONS
- CRANIAL NERVES
- MOTOR SYSTEM
- NUTRITION
- TONE
- POWER
- CO-ORDINATION
- INVOLUNTARY MOVEMENTS
- SENSORY SYSTEM

  TOUCH / PAIN / TEMPERATURE/VIBRATION /

  POSITION SENSE
- DIABETIC RETINOPATHY: PRESENT/ ABSENT

INVESTIGATIONS

1) URINE:

- Macroalbuminuria
- Microalbuminuria
- Sugar
- Microscopy
- Ketone bodies

2) BLOOD:

- Fasting blood glucose
- Post prandial blood glucose
- Glycosylated hemoglobin:
- Blood urea:
- Serum creatinine:
- Lipid profile
    1. Total cholesterol
    2. Triglycerides
    3. HDL
    4. LDL

3**) ELECTROCARDIOGRAM**

4) ECHOCARDIOGRAM (selected cases only)

5) ABDOMINAL ULTRASONOGRAPHY

DIAGNOSIS

TREATMENT GIVEN:

1) Diet

2) Diet + OHA

3) Diet + OHA + insulin

4) Diet + insulin

SN	AGE yr	SEX	AO / DUR. yr	Rx	BMI	MA L B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
1	40	M	38/2	OHA	26.3	-	170 250 7.2	34 1.1	235 250	155 30	- - - - -	-
2	65	M	55 10	OHA	19.8	++	189 232 6.8	23 1	170 120	118 28	- - - - +	-
3	68	M	55 13	OHA	20.1	+++	270 355 10.1	36 1	189 155	126 32	+ + - - -	-
4	72	M	54 18	OHA INS	16.4	+++	221 291 9.8	22 0.9	175 145	118 28	- - + - -	CVA
5	60	M	55 5	OHA	17.8	-	173 212 7.8	38 0.8	165 135	108 30	- - + - -	DIABETIC FOOT
6	58	M	50 8	OHA	22.5	-	164 250 6.8	33 1.2	184 100	132 32	- - - - -	-
7	50	F	48 2	OHA	18.2	-	160 280 7.6	24 1.2	240 285	145 38	- - - - -	DIABETIC FOOT
8	65	M	53 12	OHA INS	26.3	+	201 294 9.3	26 1.4	212 260	130 30	- + - + -	-
9	52	F	46 6	OHA	30.1	+	230 289 10.2	27 1	240 290	146 36	- - - + -	-

SN	AGE yr	SEX	AO / DUR. yr	Rx	BMI	MALB	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
10	43	f	39/4	OHA	18.4	-	214 261 6.9	25 0.8	180 100	124 36	- - - - -	-
11	46	m	44/2	OHA	22.5	-	210 280 6.8	22 0.8	165 105	112 32	+ + - - -	-
12	70	f	54 /16	INS	22.6	+++	190 286 8.1	26 0.9	192 170	128 30	- + - - +	-
13	48	M	45/3	OHA	29.7	-	185 270 8.4	38 1.3	144 120	92 28	- - - + -	-
14	60	M	58/2	OHA	21.9	++	170 250 7.8	34 1.2	180 170	120 26	- + - - +	BPH
15	65	M	47/ 18	OHA	24.3	+++	210 290 8.4	29 1.1	140 85	95 28	- - - - +	-
16	60	M	55/5	OHA	23	-	165 260 7.6	30 1.2	200 130	146 28	- + - - -	-
17	40	F	38/2	OHA	28.3	-	192 280 9.2	24 1.1	190 90	136 36	- - - - -	-
18	44	M	40/4	OHA	21.8	-	160 247 6.8	29 1.2	178 170	112 32	- - - - -	

SN	AGE yr	SEX	AO / DUR. yr	Rx	BMI	MA L B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
19	46	M	40/6	OHA	26.2	+	180 240 7	24 0.9	188 190	122 28	- - - - -	-
20	57	M	50/7	OHA	26.3	+	180 212 6.6	34 1.1	186 180	120 30	- + - - -	-
21	60	F	61/4	OHA	22.6	-	180 256 7.1	24 1.1	165 115	108 34	- - - + -	-
22	60	F	48 12	OHA	19.8	++	196 272 8.1	28 0.9	160 140	102 30	- + - + -	-
23	48	M	45/3	OHA	20.3	-	154 230 6.4	20 0.8	168 130	110 32	- + - - -	-
24	40	F	38/2	OHA	21.9	-	146 212 6.3	28 0.9	212 210	134 26	- - - - -	-
25	44	F	40/4	OHA	22	-	149 219 6.4	29 1	180 120	122 34	- - - - -	Viral hepatitis
26	80	F	68 12	OHA	18.2	++	214 356 10.2	29 1.2	190 130	134 30	- - - + +	-
27	62	M	58/4	OHA	22.6	-	241 317 9.5	34 1.3	210 140	150 32	- + - - -	-

SN	AGE yr	SEX	AO / DUR. yr	Rx	BMI	MA L B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
28	65	F	61/4	OHA	30.1	-	200 290 7.8	42 0.9	185 100	135 30	- - - - -	-
29	55	M	51/4	OHA	24.2	-	210 290 7.4	26 1.1	210 180	144 30	- + - - -	-
30	50	M	40/ 10	OHA	23.3	++	140 196 6.1	29 1	175 125	118 32	- + - - -	-
31	65	M	60/5	OHA	23	-	156 240 7.4	20 1.1	146 100	98 28	+ + + - +	-
32	55	M	53/3	OHA	22.5	-	148 240 7	29 1.1	155 105	106 28	- - - + -	Pneumonia
33	40	m	38/2	OHA	21.1	-	150 226 5.9	31 1.2	224 260	144 28	- + - - +	-
34	45	F	42/3	OHA	31.2	-	136 200 1.6	28 1	250 275	155 40	- - - - -	Lumbar sponylosis
35	45	M	43/2	OHA	20.8	-	158 250 7.2	29 0.9	140 90	96 26	- + - - -	OLD PTB
36	55	F	53/2	OHA	23.3	-	170 300 8.4	33 1	224 225	149 30	- - - - -	

SN	AGE yr	SEX	AO / DUR. yr	Rx	BMI	M A L B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
37	65	F	60/5	OHA	22.4	-	223 247 7.2	25 0.9	165 65	122 30	- - - + +	-
38	72	M	66/6	OHA	20.8	-	220 280 8	25 0.8	220 230	146 28	- - - + -	-
39	70	F	53/ 17	OHA INS	24.5	++	180 260 7.8	29 1.2	200 195	132 29	+ + - - -	-
40	66	M	62/4	OHA	20.9	-	220 280 8	34 0.7	196 100	144 32	- - + - -	-
41	53	F	46/7	OHA	21.6	-	212 280 8.2	26 0.9	220 260	138 30	- - - - -	
42	80	F	70/ 10	OHA	32.5	++	280 340 10.8	26 0.8	190 120	140 26	- - - + +	-
43	71	M	55/ 16	INS	22.5	+++	158 267 9.8	34 0.8	130 90	88 24	- + - - +	-
44	48	F	44/4	OHA	21.3	-	190 235 7.6	40 1.2	140 130	80 34	- - - - -	OLD PTB
45	61	M	57/4	OHA	23	-	180 240 7.2	36 1	166 70	122 30	- + - - -	

SN	AGE Yr	SEX	AO / DUR. yr	Rx	BMI	MA L B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
46	64	M	60/4	OHA	18.8	-	164 232 7	32 1.2	182 120	130 28	- - - - +	-
47	48	M	40/8	OHA	23.1	++	200 280 8.1	20 0.9	181 85	136 28	- + + + -	-
48	53	M	50/3	OHA	21.6	-	162 240 7.3	27 1.2	213 120	160 29	- - - - -	-
49	48	M	44/4	OHA	26.3	-	156 242 6.7	30 1	201 170	140 27	- - - - -	-
50	52	F	44/8	OHA	24.9	++	149 232 6.2	29 1.3	 170 120	116 30	- + - + -	-
51	66	M	58/8	OHA	24.3	+++	149 232 6.2	27 0.7	 161 135	102 32	- + - - -	-
52	70	M	58/ 12	OHA INS	30.4	++	186 260 7.1	31 0.8	153 115	98 32	- + + - +	OLD CVA
53	55	M	43/ 12	OHA	25	-	188 239 6.8	27 1.1	181 95	132 30	- + - - -	OLD PTB
54	57	M	50/7	OHA	32.5	+	181 252 7.2	28 1.2	187 90	140 29	- - - - -	-

'SN	AGE Yr	SEX	AO / DUR. yr	Rx	BMI	MALB	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
55	40	M	37/3	OHA	21.9	+	129 189 6.1	29 0.7	165 115	110 32	- - - - -	-
56	51	F	48/2	OHA	26.4	-	130 198 6	23 1.1	160 190	112 30	- - - - -	APD
57	50	F	40/ 10	OHA INS	28.2	+++	163 280 7	39 0.9	274 280	178 40	- - - + -	-
58	66	M	61/5	OHA INS	21.9	-	166 250 6.8	34 1.2	200 185	136 27	- - - + -	-
59	45	F	41/4	OHA	21.5	-	160 240 6.6	28 0.9	 158 120	102 32	- - - - -	-
60	66	F	58/8	OHA	19.8	++	205 380 8.2	27 1.3	 258 270	178 26	- - - + +	-
61	57	F	47/ 10	OHA INS	24.5	++	174 250 7.3	19 1.1	291 285	196 38	+ - - - +	-
62	52	F	43/9	OHA INS	21.3	++	235 310 8.9	18 1.2	280 310	186 32	- + - + -	-
63	40	M	38/2	OHA	19.8	-	127 203 5.9	18 0.8	200 180	134 30	- - - - -	-

SN	AGE Yr	SEX	AO / DUR. yr	Rx	BMI	MA L B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
64	45	M	43/2	OHA	25	-	130 201 5.9	32 0.9	250 225	176 29	- - - - -	APD
65	55	F	50/5	OHA	21.9	-	140 180 6.1	23 0.8	160 130	102 32	+ - - - -	-
66	38	F	35/3	OHA	26.2	+	210 257 7.2	22 0.8	212 170	140 38	- - - - -	-
67	60	F	55/5	OHA	22.5	-	190 280 8.1	29 1.1	204 120	148 32	- + - - -	-
68	35	M	30/7	OHA	31.2	+	149 190 5.9	32 1.1	222 245	143 30	- + - - -	-
69	47	M	44/3	OHA	26.3	-	200 251 7.8	22 0.9	219 260	138 29	- - - - -	APD
70	50	M	48/2	OHA	22.1	-	141 210 6	33 1.1	190 105	140 29	- + - - -	-
71	55	F	43/ 12	OHA	31.2	++	195 260 8	39 0.9	175 190	110 27	- - - + +	-
72	78	M	60/ 18	OHA	26.7	+++	210 292 9.2	43 1.3	161 110	112 27	- + + - +	-

SN	AGE yr	SEX	AO / DUR. yr	Rx	BMI	MAL B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
73	33	F	32/1	OHA	25	-	155 230 6.8	29 0.9	200 160	130 28	- + - - -	
74	45	F	39/6	OHA	22	+	167 198 6.3	44 1.4	155 115	103 29	- - - + -	
75	65	M	62/3	OHA	22.5	-	200 250 6.8	32 1.2	166 140	108 30	+ - - - -	
76	37	M	35/2	OHA	32.5	-	170 250 7.2	38 1.2	178 185	109 32	- - - - -	
77	45	M	37/8	OHA	21.9	-	165 291 7.7	28 1.1	190 125	129 36	- - - - -	
78	36	M	33/3	OHA	23.3	-	161 245 6.8	22 1.1	215 115	160 32	- + - - -	
79	55	M	49/6	OHA	24	+	176 290 8	40 0.9	170 140	112 30	- - - - -	
80	55	M	52/3	OHA	23.2	-	190 290 7.9	39 1.1	168 140	108 29	- + - - -	
81	52	M	50/2	OHA	23	-	166 270 8	26 1.3	265 280	180 34	+ - - + +	

SN	AGE Yr	SEX	AO / DUR. yr	Rx	BMI	MAL B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
82	40	M	39/1	OHA	22.6	-	145 190 5.8	28 0.8	160 110	104 34	- + - - -	-
83	62	M	50/ 12	OHA INS	24.7	++	210 290 8.2	29 1.3	180 215	108 29	+ - - + +	-
84	55	M	52/3	OHA	22.5	-	140 242 6.2	27 1.2	200 220	130 26	- + - - -	
85	68	F	62/6	OHA	20.8	-	168 250 6.6	40 1.1	206 225	127 34	- - - - -	
86	72	F	66/6	INS	29.7	+	178 212 6	42 1.3	153 115	98 32	+ + - - -	
87	78	F	65/ 13	OHA INS	20.3	++	220 320 10.7	22 1.3	140 110	88 30	+ + - - +	
88	60	F	57/3	INS	20.1	-	129 190 6	33 1	176 130	118 32	- - + - -	
89	60	F	55/5	OHA INS	22.6	-	145 184 5.9	22 1.2	218 280	128 34	- - + - -	
90	44	M	43/1	OHA	20	-	180 263 7.2	23 1	150 135	93 30	- - - - -	

SN	AGE yr	SEX	AO / DUR. yr	Rx	BMI	MA L B	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
91	60	M	55/5	OHA	18.8	-	170 219 6.4	21 0.9	184 160	121 31	- + - - -	-
92	75	M	57/ 18	OHA INS	22.4	+++	272 348 9.2	29 1.1	234 190	168 28	+ + - - +	-
93	74	F	60/ 14	OHA	21.1	++	200 326 8.8	32 0.9	172 155	108 33	- + - - +	
94	55	F	53/2	OHA	19.8	-	172 250 7.4	22 1.1	210 210	138 30	- - - - -	
95	35	F	33/2	OHA	24.2	-	195 240 6.4	31 1.3	175 145	108 38	- - - - -	
96	50	F	48/2	OHA	21.9	-	165 230 6.8	33 1.2	145 120	88 33	- - - - -	
97	36	F	34/2	OHA	19.5	-	190 230 6.6	39 0.9	150 110	86 42	- - - - -	
98	40	F	39/1	OHA	20.9	-	182 270 7.2	42 1	181 115	122 36	- - - + -	
99	38	M	35/3	OHA	21.9	-	165 230 6.8	22 1.2	150 90	108 24	+ - - - +	

SN	AGE Yr	SEX	AO / DUR Yr	Rx	BMI	MALB	FBS PPBS HBA1C	UREA / CREA	CHO / TGL	LDL / HDL	RP PN PVD IHD HT	OTHERS
100	55	F	44/ 11	OHA	24.2	++	215 321 8.9	41 1	161 130	105 30	+ - - - + -	

KEYS TO MASTER SHEET

AO	AGE OF ONSET OF DM
DUR	DURATION OF DM
MALB	MICROALBUMINURIA
FBS	FASTING BLOOD SUGAR
PPBS	POST PRANDIAL BLOOD SUGAR
HbA1C	GLYCOSYLATED HAEMOGLOBIN
CREA	CREATININE
BMI	BODY MASS INDEX
CHO	TOTAL CHOLESTROL
RP	RETINOPATHY
PN	PERIPHERAL NEUROPATHY
IHD	ISCHEMIC HEART DISEASE
PVD	PERIPHERAL VASCULAR DISEASE
HT	HYPERTENSION