United Journal of Quality and Validation

Global Recurrence Rates in Diabetic Nephropathy: A Pathological Systematic Review

Rupali Singh[1] and Madhav Nilakanth Mugale[1]*

Division of Toxicology and Experimental Medicine, Laboratory no. PCN-203, CSIR-Central Drug Research Institute (CSIR-CDRI), Lucknow, India – 226 031

Article Information
Article Type: Review Article
Article Received: 06-25-2021
Article Accepted: 06-29-2021
Article Published: 07-01-2021
Vol:2, Issue:1

OPEN ACCESS

Keywords: Diabetic Nephropathy; Glomerulus; Glycated hemoglobin; Histopathology; Hyperglycemia

*Corresponding Aurthor:
Nilakanth Mugale, Senior Scientist, CSIR-Central Drug Research Institute (CSIR-CDRI), Lucknow,
Email: madhav.mugale@cdri.res.in

ABSTRACT

Diabetes is a globally leading metabolic disorder and diabetic nephropathy (DN) is most serious long term complication associated with it. It accounts for approximately 30% to 40% Chronic Kidney Disease (CKD) and up to 45% of end-stage renal diseases. Diabetes mellitus (DM) starts from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency/ abnormalities that result in resistance to insulin action; it leads to hyperglycemia. In a diabetic population an increase in highly reactive free radicals inside blood cells and body that alters blood cell membrane properties which causes blood cell aggregation and increased blood viscosity leads to in impaired blood flow. Glycated hemoglobin (hemoglobin A1c, HbA1c, A1C) is a form of hemoglobin that is covalently bound to glucose. Therefore, increases in glycated hemoglobin used as prognostic marker for DM. Due to hyperglycemia the upper and lower urinary tract enriches the soil for various microorganisms. In DN observed the increase in protein excretion in urine which leads to thickening of glomerular and tubular basal membranes, with progressive mesangial expansion (diffuse or nodular) leading to progressive reduction of glomerular filtration surface. Specifically, glomerulus shown the more alterations. Microscopically; mainly found thickening of glomerular basement membrane/ degeneration, mononuclear cell infiltration, glomerular sclerosis is caused by intraglomerular hypertension and septicemic cases suppurtive nephritis. This review will shed light on the pathophysiology and role of glycated hemoglobin in DN due to proteinuria and histopathological changes. Subsequent pathological alterations and accumulation in the renal tissue shown by special staining PAS and Massons trichrome staining.

INTRODUCTION

DIABETES MELLITUS

Diabetes is leading metabolic disorder found in all communities with irrespective of race, age and sex. Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion/ insulin action or both (Landon et.al.2009) leads to a high morbidity and mortality worldwide & heavy economic loss and becomes burden to the family (Metzger et. al. 2010). Morbidity and mortality of DM due to the micro and macro vascular complications (Andrassy et. al. 2013). Pancreatic disorder leads to many complications including nephropathy, retinopathy, neuropathy, cardiovascular problem, gangrene and more than that. The prevalence of diabetes is increasing in developing countries like India. Currently, India is the world leader with the largest proportion of diabetic patients and is distinguished as the "*diabetes capital of the world*". India had an estimated 31,705,000 diabetics in the millennium year which is estimated to grow by over 100% to 79,441,000 by 2030 (Zhang et.al.2010). India is facing a major health care burden due to the high prevalence of type 2 diabetes and there are indications that it would

Citetion: Madhav Nilakanth Mugale / United Journal of Quality and Validation 1(2021): 1-8

increase further in the next few decades. Diabetes mellitus (types 1 and 2), is the foremost cause of incident and invite the chronic kidney disease (CKD). CKD accounts of approximately 30% to 40% and up to 45% of end-stage renal diseases (Whaley-Connell et.al. 2009).

Several pathogenic mechanisms are involved in the development of hyperglycemia/ diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action (Li et. al. 2010). The deficiency or resistance of insulin on target tissues leads to the abnormalities in carbohydrate, fat, and protein metabolism (Xu et. al. 2008). Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and due to the unknown cause. Clinical symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and in chronic affected population showed gangrene and blurred vision (Ntemka et. al. 2011). Life-threatening consequences of uncontrolled hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome but it's not common in the society. Long-term complications of diabetes include DN, gangrene and retinopathy with potential loss of vision. Nephropathy leads to renal failure, peripheral neuropathy causes numbness and with risk of foot ulcers, amputations, and charcot joints. Autonomic neuropathy causes gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular issues, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.

DIABETIC NEPHROPATHY

Hyperglycemia alters the redox equilibrium produces oxidative stress and elevation of reactive oxygen species (ROS) or inadequate antioxidant defense. Results in the molecular and structural damages at DNA, RNA, lipids, and proteins and develops the glomerular and tubular hypertrophy. The thickening of glomerular and tubular membranes ultimately leads to the cellular apoptosis or necrotic cell death. Ultimately leads to glomerular dysfunction characterized by albuminuria, proteinuria, glomerulosclerosis, and tubule-interstitial fibrosis.

Diabetic nephropathy (DN) refers to a characteristics of structural and functional abnormalities in the kidney. The structural abnormality includes hypertrophy, increase in glomerular basement membrane thickness, nodular and diffuse glomerulosclerosis, tubular atrophy, and interstitial fibrosis accumulation of extracellular matrix in these membranes leads to tubule-interstitial fibrosis, glomerular fibrosis and sclerosis. (American Diabetes Association Diagnosis and classification of diabetes mellitus, 2010). The secondary complications associated with the diabetes mellitus have raised and boosted the number of deaths in the last few years. Diabetic nephropathy occurs in patients having chronic hyperglycemia continuously from a longer duration of time. Specific pathological structural and functional changes seen in the kidneys of patients with chronic diabetes mellitus (Kim et. al. 2008).

Diabetes mellitus

Advanced glycation end products, increase in hemodynamic and growth factors etc.

⇩

Glycated hemoglobin causes an increase of highly reactive free radicals inside blood cells and free radicals alters the blood cell membrane properties

⇩

Aggregation of blood cells

⇩

Glomerular hyper filtration, Altered glomerular composition, Glomerular hypertension.

⇩

Deposition of extracellular matrix, Albuminuria,

⇩

Thickening of glomerular basement membrane, Renal hypertrophy,

⇩

Glomerulosclerosis, Interstitial fibrosis

⇩

End stage Kidney disease

The flow chart of progression of DN

Type 1 diabetes

Type 1 Diabetes, once known as juvenile diabetes or insulin dependent diabetes, is a chronic condition in which pancreas produces little or no insulin. Different factors contribute in pathogenesis of the type 1 diabetes including genetics and some viruses (Jacobsen et. al. 2006). It commonly appears during childhood or adolescence (Ruggenenti et.al 2008). Treatment of type 1 diabetes focuses on managing blood sugar levels with insulin, diet and lifestyle (**Fig. 1**) to prevent complications (Rossing et. al. 2007). Signs and symptoms of type1 diabetes can are increased thirst, frequent urination, extreme hunger, unintended weight loss, fatigue, weakness and blurred vision. Type 2 Diabetes is a long term metabolic disorder characterized by high blood sugar, insulin resistance and relative lack of insulin (Sato et. al. 2007). It commonly occurs due to obesity and lack of exercise (Brenner et.al. 2008) and found about 90% of cases of Diabetes cases (Gaede et.al. 2008).

NATIONAL AND INTERNATIONAL STATUS OF DIABETIC NEPHROPATHY

The prevalence of diabetes has extended epidemic magnitudes and is expected to affect more than 350 million people by the year 2035 globally (i.e. estimated to affect more than 8% of the global population) (Ramachandran et. al. 2010). Diabetic kidney disease (DKD) is a major complication that takes place in 20% to 40% of all diabetics. The incidence of end stage renal disorder is increasing year by year

(de Boer et.al. 2011). In the United States, the prevalence of diabetes among adults increased from 9.8% in the 1988–1994 to 12.3% in the 2011–2012-time period. In the year 2015 approximately 415 million people were estimated to have diabetes and by the year 2040, prevalence is projected to increase to 642 million, globally (WHO, 2014). Diabetic kidney disease is more frequent in African Americans, Asian-Americans, and Native Americans. The prevalence of diabetes especially type 2 is greater in certain races and ethnic groups. Affecting approximately 13% of African Americans, 9.5% of Hispanics, and 15% of Native Americans. In type 1 DM, nearly 20% to 30% morbid population leads to evident nephropathy and patients progress to ESKD (End Stage Kidney Disease). Arabic countries - Kuwait, Lebanon, Qatar, Saudi Arabia, Bahrain, and United Arab Emirates (UAE), are among the world's leaders in prevalence of type 2 diabetes. An increase in ESKD secondary to type 2 DM has been noted in countries known to have low incidences of type 2 DM, such as Denmark and Australia. Furthermore, the prevalence of any type of CKD and its rate of progression, especially DKD, is significantly higher in citizens of Asian origin, as observed both in the United Kingdom and in Canada presumably the result of different genetics and/or lifestyle and lack of awareness of kidney complications of diabetes.

In the national point of view; the number of people with diabetes in India increased from 26.0 million in 1990 to 65.0 million in 2016. Facing a major health care burden due to the high prevalence of type 2 diabetes and it may increase further in the next few decades (McCarty et. al. 2004). None the less attention towards diabetic nephropathy is not directed until the patient has progressed towards the stage of renal failure (Kaveeshwar et. al. 2014). The elderly diabetic population, DN accounts for 46% (Prakash et. al. 2006). The prevalence of DN and microalbuminuria was 2.2% and 26.9%, respectively, in the urban citizens of the chennai (Unnikrishnan et. al. 2007).

NATURAL HISTORY OF NEPHROPATHY

In the early 1980's independent investigators reported that there is a "preclinical" stage of

diabetic nephropathy; characterized by urinary albumin excretion. Normal individuals do not excrete more than 10-15 mg/day of albumin. However, routine laboratory tests do not detect these small amounts of albuminuria unless it is in excess of 300 mg/day (Greka et. al. 2012). This range (30-300 mg/day or 20-200 of gram/min) has been referred to as microalbuminuria and is the first laboratory evidence of diabetic renal disease (Greka et. al. 2012). Fortunately, microalbuminuria can be detected using more sophisticated techniques (Radioimmunoassay, Enzyme linked immunosorbent assay) and a highly accurate screening urine test for microalbuminuria now exists. Initial retrospective studies reported that approximately 80% of patients with type 1 diabetes would progress from microalbuminuria to overt albuminuria over 6 to 14 years. More importantly, tight glycemic control with insulin during the microalbuminuria stage has been shown to prevent the development of overt diabetic nephropathy.

The progression of nephropathy in type 1 diabetes has classically been described as a series of stages in a relentlessly deteriorating course from normal renal function to end stage renal disease marked by increasing amounts of albuminuria. At the time of initial diagnosis there are no significant renal abnormalities, and renal plasma flow (RPF) and glomerular filtration rate (GFR) are elevated. Within 3 years, histologic changes (increased mesangial matrix material and glomerular basement membrane thickening) of diabetic nephropathy are evident but GFR and RPF remain elevated (Caramoriet.al.2006). Over the subsequent 10-15 years there is progressive histologic damage but renal hyper filtration persists, approximately 15 years after the diagnosis of diabetes, albuminuria (> 300 mg/day; overt albuminuria, microalbuminuria) is detected and the elevated rates of RPF and GFR have returned to normal. This is an ominous sign and heralds the onset of progressive renal insufficiency. At this stage no intervention has been shown to slow the rate of decline of GFR. Within 5 years of the onset of albuminuria approximately half of the individuals will have experienced a 50% reduction in the GFR and a doubling of their serum creatinine (Vasylyeva et.al.2007). Within a mean of 3 to 4 years, half of these patients will have progressed to End Stage Renal Disease (ESRD) (Gariani et. al. 2012). At or just before the time of onset of over albuminuria, most patients will develop hypertension and the increase in blood pressure markedly accelerates the progression of renal disease (Giaccoet.al.2010). Effective treatment of the hypertension has been documented to slow, although not prevent, the progression to ESRD. Once clinically significant albuminuria (> 300 mg/day) has developed, tight glycemic control cannot prevent the development of renal insufficiency. It has been appreciated for more than a decade that microalbuminuria predicts risk for progression to overt albuminuria in both type 1and 2 diabetes (Parchwaniet.al.2012). It is an early warning system to alert clinicians to intervene at a time when future renal damage is still preventable. In type 2 diabetes, some might argue that the predictive value of microalbuminuria is less but most agree that it still indicates a need for appropriate evaluation and treatment. Further, a number of studies have shown that once proteinuria occurs, the decline in renal function continues at the same rate regardless of the type of diabetes and hence microalbuminuria is regarded as marker of progression of diabeticnephropathy (Su et.al.2010).

Hyperglycemia is well known risk factor for Diabetic Kidney Disease (DKD) and it recognized that intensive glucose control reduces the risk of DKD. Other hyperglycemia-dependent metabolic abnormalities that may also play a role in the development of nephropathy includes AGEs and polyols. AGEs are the result of nonenzymatic covalent attachment of glucose to proteins which not only changes the tertiary structure of proteins but also results in intra and intermolecular crosslinking. Proteins of many types are affected by this process, and levels of circulating and tissue. Hypertension is probably both a cause and an effect of diabetic nephropathy. In the glomerulus, an early effect of systemic hypertension is dilatation of the afferent arteriole, contributing to intraglomerular hypertension, hyper filtration, and hemodynamically mediated damage. ACE inhibitors specifically decrease the efferent arteriolar pressure, thereby decreasing intraglomerular pressure and helping to protect the glomerulus from further damage, as seen in their beneficial effect on microalbuminuria.

Complications

Complications of diabetic nephropathy may develop gradually over

period of time including fluid retention, which could lead to swelling in legs and arms, high blood pressure, pulmonary edema, hyperkalemia, heart and blood vessels disease leads to stroke. Damages to the blood vessels of the retina and leads diabetic retinopathy, foot sores, erectile dysfunction, diarrhea and neuropathy. Irreversible damage to kidneys eventually leads to end-stage kidney disease.

The pathophysiology of DN

Diabetic Nephropathy (DN) usually observed 15 to 25 years after the onset of type 1 and 2 diabetes (Heshmatollah and Isa 2013) and 3.5 to 4 months of hyperglycemic condition in experimental animals. DN is a clinical syndrome characterized by the consistent albuminuria that should be confirmed on at least two occasions separated by 3-6 months, by continuous decline in the glomerular filtration rate (GFR), and by increased arterial blood pressure (Di Landroet.al. 2010). A clinically asymptomatic point of failure follows with development of microalbuminuria (30 mg albumin per day) to microalbuminuria (>300 mg albumin per day). Once microalbuminuria has established, renal function falls at a significant but at alterable rate (decline in GFR of 220 ml/min/ year) (Wanner et.al. 2016). The rate of decline depends on type of diabetes, genetic predisposition, glycemic control and, very significantly, blood pressure. The characteristic occurrence is thickening of the glomerular basement membrane(GBM) and renal damage (Kitadaet.al2014). After renal damage, the thickening of the basement membrane starts, which leads to pathologic modifications in mesangial and vascular cells. It includes formation of AGEs, accumulation of polyols, and activation of protein kinase C. It leads to activation of the inflammatory pathway playing a significant role in the damage of Glomerular Basement Membrane (Cooper et.al.2008). Secondly, the renal hemodynamic anomaly is similar in both types of diabetes. An initial physiologic abnormality is glomerular hyper-filtration related to intra-glomerular hypertension (Remuzziet.al.2010). This is complemented by the onset of microalbuminuria. Microalbuminuria is considered the first sign indicating the onset of DN (Parving et.al. 2010).

Hyperglycemia leads to thickening of GBM and Glomerular hyper-filtration. Which leads to impaired endothelial integrity and onset of microalbuminuria and impairment of nitric oxide synthesis. Impairment of nitric oxide transport causes loss of afferent/efferent auto-regulatory control.

Sustained hyperglycemia in diabetes increases free fatty acid (FFA) synthesis and triglyceride (TG) accumulation in adipose tissue (Eidet.al.2016). Further elevation of serum TGs, FFAs, and modified cholesterol levels causes ectopic accumulation of lipids in the parenchymal organs including the pancreas, liver, heart, and kidneys (Rudberget. al.2011). This process of lipotoxicity serves as an aggravating factor in the pathogenesis of DN in association with glomerulosclerosis and tubule-interstitial injury (Cherneyet.al.2012). This lipid byproduct accumulation in DN may arise from altered lipid metabolism resulting from a mismatch between lipid uptake and disposal, featuring enhanced lipid uptake and reduced peroxidation, catabolism, and efflux of residues in the kidney.

Stage 1	Glomerular hypertension and hyper filtration, Raised GFR ,Raised creatinine level
Stage 2	Silent Phase (Structural changes on biopsy but no clinical manifestations), Normoalbuminuria.
Stage 3	Microalbuminuria, Normal serum creatinine, There may be increased blood pressure
Stage 4	Macroalbuminuria, Hypertension, Increase in the progression of nephropathy
Stage 5	End stage renal failure

Development of renal changes in diabetes is recognizable

Stage 1: Early hypertrophy and hyper function

Stage 2: Glomerular lesion without clinical disease

Stage 3: Incipient diabetic nephropathy/ microalbuminuria stage: urine albumin excretion 30-300mg/day

Stage 4: Overt diabetic nephropathy/microalbuminuria stage: urine albumin excretion > 300 mg/day

Stage 5: End-stage renal disease

The major histological changes (Jenkins et.al.2010).

(1) Mesangial expansion is directly induced by hyperglycemia, perhaps viaincreased matrix production or glycosylation of matrix proteins. Tubular hypertrophy/ degeneration (Fig. 1) thickening of the tubular basement membrane and interstitial inflammation (**Fig. 2**) with mononuclear cell infiltration early histological alterations in the diabetic kidney.

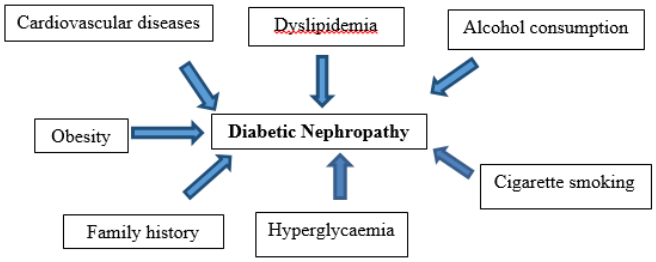

Figure 1. Risk Factors: Depicting different mechanisms and risk factors for Diabetic Nephropathy

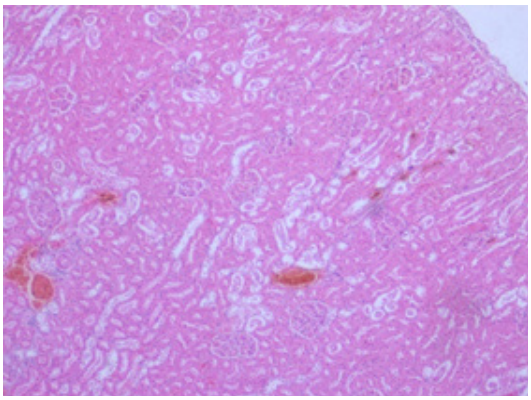

Figure 2: Kidney- Glomerular - tubular degeneration (red arrow)- basement membrane thickening (green arrow)- and interstitial inflammation (black arrow) - H & E staining 10X

(2) Glomerular basement membrane thickening occurs, cell shape and function, cell vacuolization of tubules. Progress of tubulointerstitial abnormalities leads to tubulointerstitial fibrosis and tubular atrophy. Eosinophilic deposition (**Fig. 3**) is an early sign of the renal fibrosis due to glycation of extra cellular matrix (ECM) and the loosening of the balance of ECM protein synthesis and degradation.

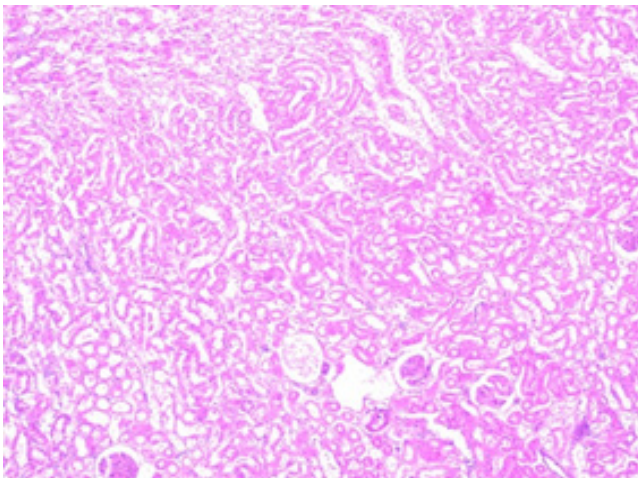

Figure 3: Kidney- Increase in Bowman's space (red arrow) - tubular degeneration - and interstitial inflammation (black arrow)- Eosinophilic accumlation - H & E staining.

(3) Glomerular sclerosis is caused by intraglomerular hypertension and in upper urinary tract infection cases suppuration and necrosis (**Fig. 4**) and septicemia.

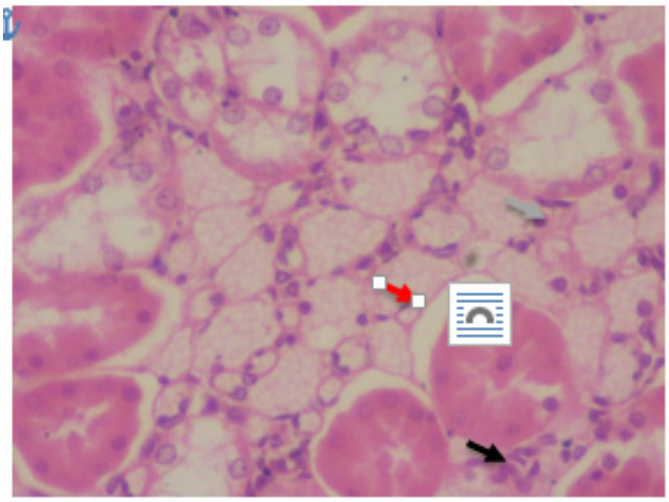

Figure 4: Kidney- Medullary area-tubular degeneration (red arrow) - and interstitial inflammation black arrow) - Eosinophilic deposition (green arrow) -H & E staining.

These different histologic patterns appear to have similar prognostic significance.

Special staining - Massons Trichrome staining

Masson's trichrome is a three-colour staining protocol used in histopathology for checking the status of chronic alteration in the tissue. It's used for distinguishing thecells from the surrounding connective tissue.The bluish green staining indicates interstitial sclerosis/ fibrosis/ collagen formation in the glomeruli or interstitial parenchyma (**Fig. 5**).

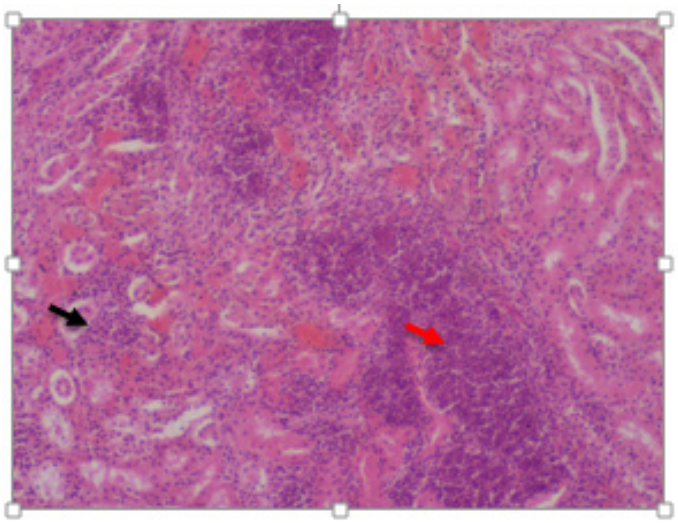

Figure 5: Kidney- Medullary area - suppurative nephritis (red arrow) - and interstitial inflammation (black arrow) - H & E staining 10X

PAS Staining

The accumulation of glycogen in minute glomerular capillaries leads thickening of mesangial layer of bowman's capsule and also takes dark pink coloration in the glomeruli which leads to hindrance in glomerular filtration and its function (**Fig. 6**) (Alsaad and Herzenberg 2007).

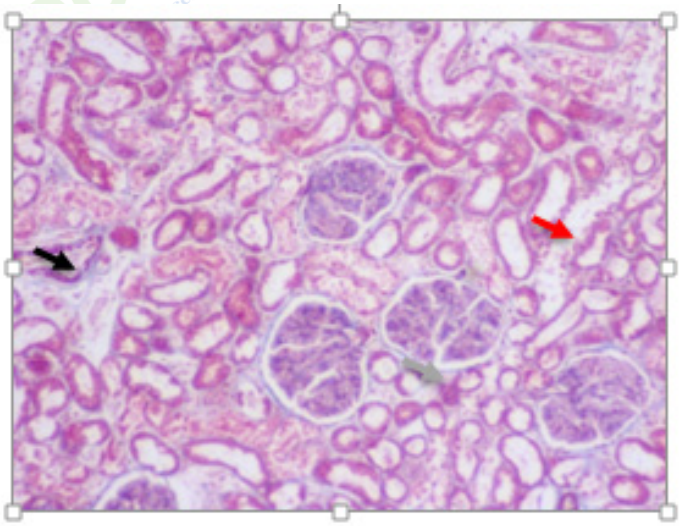

Figure 6: Kidney- Cortical area- glomeruli- mild bluish-green coloration showed chronic changes with collagen formation& interstitial fibrosis (black arrow) - tubular degeneration (red arrow) - Eosinophilic deposition (green arrow)– Massons trichrome staining 10X.

Hemodynamic abnormalities

There is a wealth of evidence from experimental diabetic models that intraglomerular pressure is raised, due to relative constriction of the efferent glomerular arteriole. The increased pressure is thought to precipitate glomerular damage directly by pressure effects and indirectly by increasing proteinuria (Li et al 2004).

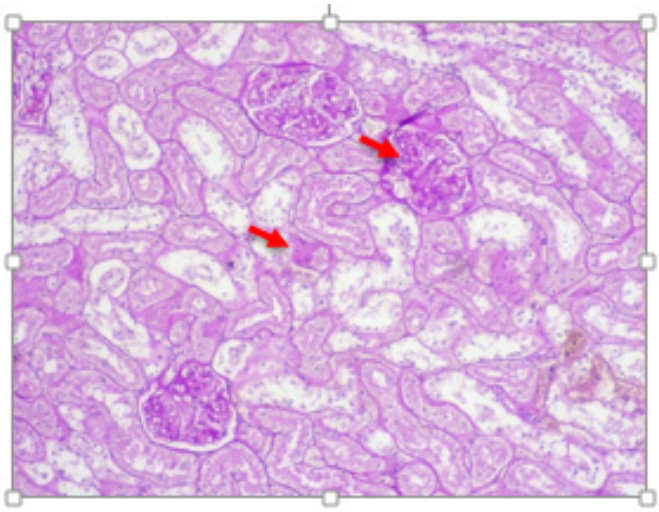

Figure 7: Kidney- Cortical area- glomeruli-dark pink coloration - showed accumulation of glycogen at central matrix accumulation, and the restriction of the surrounding glomerular capillaries – multifocal pink deposition in parenchyma– PAS staining 10X.

Genetic influences

The fact that only a subset of people with diabetes develop nephropathy has long been interpreted as evidence that there is a genetic susceptibility to the development of nephropathy (Ryuet.al.2013). Many studies have demonstrated an excess of hypertension, dyslipidemias, insulin resistance, and premature cardiovascular disease in individuals with diabetic nephropathy compared with diabetic individuals with normal albumin excretion. (Zanchi et.al.2013). Family studies have also demonstrated an excess of these features in first degree relatives of diabetic nephropathy patients compared with first degree relatives of patients with diabetes but no nephropathy (Zoja et. al.2014).

Thus it may be that the genetic factor in the development of nephropathy also influences the susceptibility to cardiovascular risk factors and premature cardiovascular disease.

Role of Glycated Hemoglobin in Diabetic Nephropathy

Glycated hemoglobin (hemoglobin A1c, HbA1c, A1C, or less commonly HgbA1c, hemoglobin A1c, HbA_{1c}, Hb1c, etc.) is a form of hemoglobin that is covalently bound to glucose (Shimazaki .et. al 2007). It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Glycated hemoglobin causes an increase of highly reactive free radicals inside blood cells and alters the blood cell membrane properties. This leads to blood cell aggregation and increased blood viscosity which results in impaired blood flow (Selvin et.al.2010). The lifespan of a red blood cell is four months (120 days) due to this reason the test is limited to a three-month average (Pradhan et.al.2007). However, since red blood cells do not all undergo lysis at the same time, HbA1C is taken as a limited measure of three months. HbA_{1c} is a measure of the β-N-1-deoxy fructose component of hemoglobin. Diabetes mellitus (DM) is the leading cause of chronic kidney disease (CKD) worldwide, accounting for end-stage renal disease (ESRD) (Kumar et.al.2014). Measuring glycated hemoglobin (HbA1c) has been suggested as a means of assessing glycemic control in patients with diabetes. HbA1c is the gold standard to measure severity and level of control of diabetes mellitus (Raman et.al.2016). Glycated compounds are formed when glucose reacts with primary amines of proteins non-enzymatically. Hyperglycemia exerts harmful effects on kidney functioning by directly changing the signaling pathways of cells.

Kidney infections in Diabetes mellitus

Urinary tract infection (UTI) is the most common infection in subjects having chronic diabetes. Certain renal tract infections includecystitis, candidiasis. These together with the renal papillary necrosis forms the basis for the UTI. Diabetic patients have been found to have more folds of frequency of having UTI. These infections lead to severe kidney damage and cause renal failure (Raptiset.al.2001). Gram negative bacillus are the most common organisms to cause UTI in diabetic patients. E. coli causes maximum UTI in Diabetic patients (Pickup et.al.1997).

PRIMARY PREVENTION AND TREATMENT FOR DIABETIC NEPHROPATHY

Blood glucose control

The ultimate aim is to prevent the development of diabetic nephropathy. Both the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the UKPDS (United Kingdom Prospective Diabetes Study) in type 2 diabetes demonstrated that in individuals with normal albumin excretion at outset, the lower the blood glucose level long term, the lower the risk of developing microalbuminuria (Mosenzonet.al.2017). In neither study was a threshold of glycated hemoglobin (HbA1c) demonstrated, below which further reduction in risk was not gained. Thus for prevention of nephropathy, the lowest possible HbA1c for the individual patient is the target (Cristobal-Garcia et.al.2015). Several studies in type 1 diabetes suggest that the effect of tight blood glucose control in delaying the onset of nephropathy may persist for longer than the actual period of tight control.

Blood pressure control

Good control of systemic blood pressure also reduces the risk of nephropathy. In the UKPDS (United Kingdom Prospective Diabetes Study), the lower the blood pressure, the lower the risk of developing microalbuminuria (Kanasakiet.al. 2017). Again, there was no threshold blood pressure below which further reduction did not result in further lowering of risk. However, an upper limit of acceptable blood pressure has generally been agreed at 140/80 mm Hg. There is no great evidence to support the use of one particular class of anti-hypertensive agent over another in the primary prevention of nephropathy, the most important point is to lower the blood pressure.

Treatment targets

In type 1 diabetes, target blood pressure,120/70 mm Hg are recommended, with130/75 mm Hg in type 2 diabetes (Bjornstadet. al.2015). However, in the belief that the passage of protein through the glomerulus accelerates damage, some authorities advocate adding additional antihypertensive therapy regardless of blood pressure, aiming to reduce albuminuria into the normal range.

Hypolipidemic treatment

Treatment of all DN patients with statins is recommended. Statins decrease the risk of atherosclerotic cardiovascular disease in CKD patients. However, they have a minimal effect on CKD progression (Tomaschitzet.al.2010).

Diet control

Dietary salt restriction to less than 5–6 g (100 m mol)/day significantly reduces BP in T1DM and T2DM. It seems that salt restriction should be advised very early in the course of diabetes mellitus (Zanchiet.al.2013).

Quitting smoking

Smoking is one of the important factors responsible for DN progression. Cigarette smoking can damage your kidneys and make existing kidney damage worse.

Maintain a healthy weight

Maintenance of a healthy weight, and to maintain it by being physically active most days of the week. Talk with your doctor about strategies for the weight loss. Often this involves increasing daily physical activity and reducing calories each and every day.

Table: 1: Commonly used therapies for management of hyperglycemia

Medicine	Uses	Side effects	Mechanism
Metformin	Improves insulin sensitivity	Long term use impairs vitamin B12 absorption	It acts through AMPK pathway
DPP-4 inhibitors	Increase insulin release	Caution in patients with heart failure	It prolongs incretin activity
Thiazolidinediones	Increase insulin sensitivity	It worsens condition of heart patients	It decreases gluconeogenesis

Novel therapies (Table: 1)

- DPP 4 inhibitors- Sitagliptin, Saxagliptin,Vildagliptin, Linagliptin.
- SGLT 2inhibitors (Sodium Glucose Co Transporter 2 Inhibitors)- Dapagliflozin, Empagliflozin.
- Selective endothelin receptor antagonists

In the last few years there has been an exponential growth in the field of herbal medicine. These drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Medicinal antidiabetic plants with proven and related beneficial effects and of herbal drugs includes,

Allium sativum, Eugenia jambolana, Momordicacharantia, Ocimumsanctum, Phyllanthusamarus, Pterocarpus marsupium, Allium cepa, inosporacordifolia, Trigonellafoenumgraecum and Withaniasomnifera and various others (Goh et al 2008).

Acknowledgement

CSIR -CDRI institute communication number for this manuscript is 10265.

Conclusion

This review will shed light on the recurrence rate of diabetes and its complication. Diabetes and its complication rate increasing and awareness shold be there in all affected population. Pathophysiology and role of glycated hemoglobin in DN due to proteinuria and subsequent histopathological findings in the end-stage renal disease. In future use of this reviewed pathogenesis and mechanism of action will help to know the sytematic pathogenesis and management of hypergycaemia to alleviate the diabetic nephropathy.

References

1. Alsaad K O and Herzenberg A M. Distinguishing diabetic nephropathy from other causes of glomerulosclerosis: an update. J ClinPathol. 2007; 60(1): 18-26.

2. Andrassy KM. Comments on 'KDIGO 2012clinicalpractice guideline for the evaluation and management of chronic kidney disease'. Kidney Int. 2013; 84(3): 622-623.

3. American Diabetes Association Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010; 33: S62-9.

4. Brenner BM, Cooper ME, de Zeeuw D. Effects of losartan on renal andcardiovascular outcomes in patients with type 2 diabetes mellitus andnephropathy. N Engl J Med. 2008; 345(12): 861-869.

5. Bjornstad P, Lanaspa MA, Ishimoto T, Kosugi T, Kume S. Fructose and uric acid in diabetic nephropathy. Diabetologia. 2015; 58(9): 1993-2002.

6. Caramori M, Fioretto P, Mauer M. Enhancing the predictive value of urinary albumin for diabetic nephropathy. J Am SocNephrol. 2006; 17(2): 339-352.

7. Cherney DZ, Scholey JW, Jiang S, Har R, Lai V, et al. The effect of direct renin inhibition alone and in combination with ACE inhibition on endothelial function, arterial stiffness, and renal function in type1 diabetes. Diabetes Care. 2012; 35(11): 2324-2330.

8. Cooper M. Pathogenesis, prevention, and treatment of diabetic nephropathy. Lancet. 2008; 352(9123): 213-219.

9. Cristobal-Garcia M, García-Arroyo FE, Tapia E, Osorio H, Arellano-Buendia AS. Renal oxidative stress induced by long-termhyperuricemia alters mitochondrial function and maintains systemic hypertension. Oxid Med Cell Longev. 2015; 53: 56-86.

10. Di Landro D, Catalano C, Lambertini D, Bordin V, Fabbian F, Naso A. et al, The effect of metabolic control on development and

progression of diabetic nephropathy. Nephrol Dial Transplant. 2010; 13(Suppl 8): 35-43.

11. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA. 2011; 305(24): 2532-2539.

12. Eid S, Boutary S, Braych K, Sabra R, Massaad C. mTORC2 Signaling Regulates Nox4-Induced Podocyte Depletion in Diabetes. Antioxid Redox Signal. 2016; 25(13): 703-719.

13. Expert Committee on the Diagnosis andClassification of Diabetes Mellitus (2007) Reportof the Expert Committee on the Diagnosisand Classification of Diabetes Mellitus. Diabetes Care 20:1183–1197.

14. Fioretto P, Sutherland DE, Najafian B, Mauer M. Remodeling of renal interstitial and tubular lesions in pancreas transplant recipients. *Kidney Int.* 2006; **69(5)**: 907-912.

15. Gaede P, Vedel P, Larsen N. Multifactorial intervention andcardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2008; 348(5): 383-393.

16. Gariani K, de Seigneux S, Pechere-Bertschi A, Philippe J, Martin PY. Diabetic nephropathy: an update. Rev Med Suisse. 2012; 8(330): 473-479.

17. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010; 107(9): 1058-1070.

18. Goh SY, Jasik M, Cooper ME. Agent sin development for the treatment to diabetic nephropathy. Expert OpinEmerg Drugs. 2008; 13(3): 447-463.

19. Greka A, Mundel P. Cell biology and pathology of podocytes. Annu Rev Physiol. 2012; 74: 299-323.

20. Hansen HP, Tauber-Lassen E, Jensen BR. Effect of dietary proteinrestriction on prognosis in patients with diabetic nephropathy. Kidney Int. 2009; 62(1): 220-228.

21. Heshmatollah S, Isa R. Diabetic kidney disease; review of the current knowledge. J Renal Inj Prev. 2013; 2(2): 73-80.

22. Jacobsen P, Andersen S, Jensen BR. Additive effect of ACE inhibitionand angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. J Am SocNephrol. 2006; 14(4): 992-999.

23. Jenkins AJ, Lyons TJ, Zheng D, Otvos JD, Lackland DT, McGee D, et al. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. Kidney Int. 2010; 64: 817-828.

24. Kanasaki K, Shi S, Kanasaki M, He J, Nagai T, Nakamura Y. Linagliptinmediated

25. DPP-4 inhibition ameliorates kidney fibrosis in Streptozotocin induceddiabetic mice by inhibiting endothelial-to-mesenchymal transitionin a therapeutic regimen. Diabetes 63sx. 2014; 63(6): 2120-2131.

26. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australasian Medical Journal. 2014; 7(1): 45-48.

27. Kitada K, Nakano D, Ohsaki H, Hitomi H, Minamino T. Hyperglycemia causes cellular senescence via a SGLT2- and p21-dependent pathway in proximal tubules in the early stage of diabetic nephropathy. J Diabetes Complications. 2014; 28(5): 604-611.

28. Kim DJ, Kim YM, Yun YS. Therapeutic effect of recombinant humanerythropoietin on anemia with erythropoietin deficiency in diabetic patients. Diabetic Med. 2008; 20(8): 661-664.

29. Kumar S, Aneja GK, Trivedi A, Atam V, Shankhwar SN, Panwar A, et al. Correlation of diabetic nephropathy and hba1c in newly diagnosed type 2 diabetic patients of Western UP. Int J Sci Res Publ. 2014; 4(12):1-4.

30. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009; 361(14): 1339-1348.

31. Li J, Wu HM, Zhang L, Zhu B, Dong BR. Heparin and related substances for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2010; (8)9: 5631-5634.

32. Li B, Yao Yukiko k, Tanaka O, Hoshiyama M, Morioka T, Gejyo F, Real-time observation of glomerular hemodynamic changes in diabetic rats: Effects of insulin ARB. Vascular Biology – Hemodynamics – Hypertension. 2004; 66(5): 1939-1948.

33. McCarty D, Zimmet P. Diabetes 1994 to 2010: Global Estimates and Projections. Melbourne: International Diabetes Institute. 2004;

34. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, DammP, et al. International Association of Diabetes and Pregnancy Study Groupsrecommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010; 33(3): 676-682.

35. Mosenzon O, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, Wei C. Effect ofSaxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial. Diabetes Care. 2017; 40(1): 69-76.

36. Ntemka A, Iliadis F, Papanikolaou N, GrekasD. Network-centric Analysis of Genetic Predisposition in Diabetic Nephropathy. Hippokratia. 2011; 15(3): 232-237.

37. Parchwani DN, Dhanani JV, UpadhyahAA, Sharma MH, Shah AM, Maheria PB, et al. Relationship between cardiovascular autonomic(dys)function and microalbuminuria in type 2 diabetes mellitus. Natl J Physiol Pharm Pharmacol. 2012; 2: 84-92.

38. Parving HH, Lehnert H, Brochner-Mortensen J. The effect of irbesartanon the development of diabetic nephropathy in patients with type 2 diabetesmellitus. N Engl J Med. 2010; 345(12): 870-878.

39. Pickup JC, WilliamsG,eds. Textbook of Diabetes mellitus. 2nd edition. Oxford: Blackwell ,1997.

40. Pradhan AD, Rifai N, Buring JE, Ridker PM. Hemoglobin A1c predicts diabetesbut not cardiovascular disease in non-diabeticwomen. Am J Med. 2007; 120(8): 720-727.

41. Prakash J, Hota JK, Singh S, Sharma OP. Clinical spectrum of chronic renal failure in the elderly: A hospital based study from eastern India. Int Urol Nephrol. 2006; 38(3-4): 821-827.

42. Raman S, Dai H, DeLurgio SA, Williams DD, Lind M, Patton SR. High hemoglobin A1c variability is associated with early risk of microalbuminuria in children with T1D. Pediatr Diabetes. 2016; 17(6): 398-406.

43. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. Lancet. 2010; 375(9712): 408-418.

44. Raptis AE, Viberti G. Pathogenesis of DiabetesExpClinEndocrinol Diabetes. 2001; 109(suppl 2): S424-S437.

45. Remuzzi G, Ruggenenti P. Prognosis of diabetic nephropathy: how to improve the outcome. Diabetes Res ClinPract. 2010; 39(Suppl): S49-53.

46. Rossing K, Jacobsen P, PietraszekL. Renoprotective effects of addingangiotensin II receptor blocker to maximal recommended doses of ACEinhibitor in diabetic nephropathy: a randomised double-blind crossover trial. Diabetes Care. 2003; 26(8): 2268-2274.

47. Rudberg S, Osterby R. Diabetic glomerulopathy in young IDDM patients: preventive and diagnostic aspects. Horm Res . 2010; 50(Suppl 1): 17-22.

48. Ruggenenti P, Perna A, Remuzzi. G. Retarding progression of chronicrenal disease: the neglected issue of residual proteinuria. Kidney Int. 2003; 63: 2254-2261.

49. Ryu ES, Kim MJ, Shin HS, Jang YH, Choi HS. Uric acid inducedphenotypic transition of renal tubular cells as a novel mechanism of chronic kidney disease. Am J Physiol Renal Physiol. 2013; 304(5): F471-F480.

50. Sato A, Tabata M, Hayashi K. Effects of the angiotensin II type 1 receptorantagonist candesartan compared with angiotensin-converting enzymeinhibitorson the urinary excretion of albumin and type IV collagen in patientswith diabetic nephropathy. ClinExpNephrol. 2007; 7(3): 215-220.

51. Selvin E, Steffes MW, Zhu H, MatsushitaK, WagenknechtL,Pankow J. Glycated hemoglobin, diabetes,and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010; 362(9): 800-811.

52. Shimazaki T, Kadowaki T, Ohyama Y, Ohe K, Kubota K. Hemoglobin A1c(HbA1c) predicts future drug treatmentfor diabetes mellitus: a follow-up studyusing routine clinical data in a Japaneseuniversity hospital. Translational Research. 2007; 149:196-204.

53. Su J, Li SJ, Chen ZH, Zeng CH, Zhou H, et al. Evaluation of podocyte lesion in patients with diabetic nephropathy.Diabetes Res ClinPract. 2010; 87(2):167-175.

54. DCCT. The Diabetes Control and Complications Research Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the diabetes control and complications trial. Kidney Int. 1995; 47(6): 1703-1720.

55. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C. Independent association between 1,25-dihydroxyvitamin D,25-hydroxyvitamin D and the renin-angiotensin system: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Clin Chim Acta. 2010; 411: 1354-1360.

56. Unnikrishnan RI, Rema M, Pradeepa R, Deepa M, Shanthirani CS, Deepa R, et al. Prevalence and risk factors of diabetic nephropathy in an urban South Indian population: The Chennai Urban Rural Epidemiology Study (CURES 45) Diabetes Care. 2007; 30: 2019-2024.

57. Vasylyeva TL, Ferry RJ. Novel roles of the IGF-IGFBP axis in etiopathophysiology of diabetic nephropathy. Diabetes Res ClinPract. 2007; 6(2): 177-1786.

58. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in Type 2 diabetes. NEngl J Med. 2016; 375(4): 323-334.

59. Zanchi C, Locatelli M, Benigni A, Corna D, Tomasoni S, Rottoli D. Renalexpression of FGF23 in progressive renal disease of diabetes and the effect ofACE inhibitor. PLoS ONE. 2013; 8(8): e70775.

60. World Health Organization. Global Status Report on Noncommunicable Diseases, Geneva, Switzerland, World Health Organization. 2014;

61. Xu M, Chen X, Yan L, Cheng H, Chen W. Association between (AC)n dinucleotide repeatpolymorphism at the 5'-end of the aldose reductase gene and diabetic nephropathy: ameta-analysis. J MolEndocrinol. 2008; 40(5): 243-251.

62. Zanchi C, Locatelli M, Benigni A, Corna D, Tomasoni S. Renal expression of FGF23 in progressive renal disease of diabetes and the effect of ACE inhibitor. PLoS One. 2013; 8: e70775.

63. Zhang X, Gregg EW, Williamson DF, Barker LE, Thomas W, Bullard KW, et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care. 2010; 33(7): 1665-1673.

64. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001; 414(6865): 782-787.

65. ZojaC, Benigni A, Remuzzi G. The Nrf2 pathway in the progression of renaldisease. Nephrol Dial Transplant. 2014; 29(Suppl 1): i19–i24.

66. US Renal Data System. USRDS Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2004;