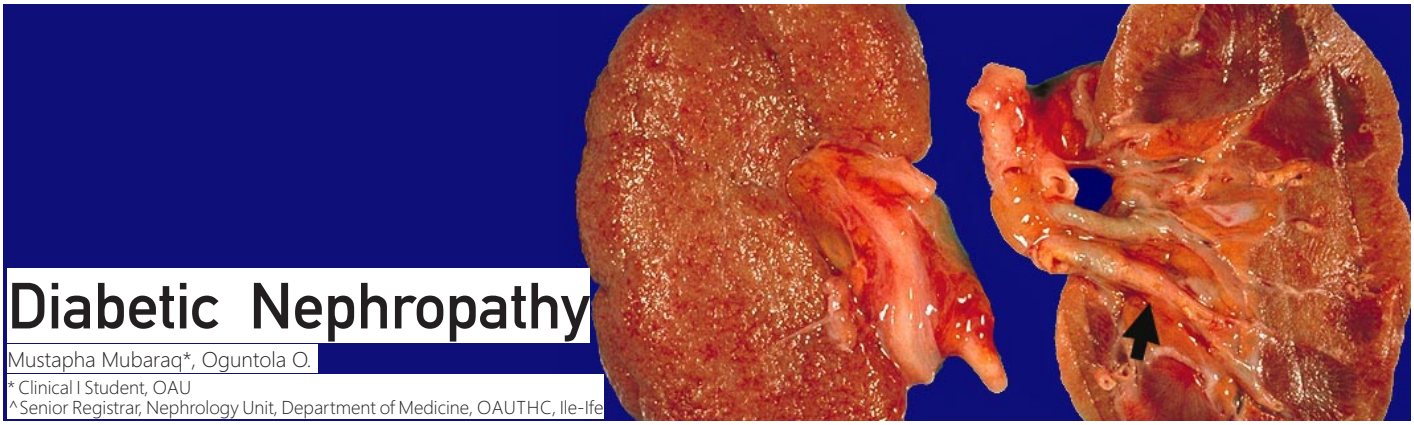

Diabetic Nephropathy

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INTRODUCTION

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism due to defects in insulin secretion, insulin action or both. About 366 million people worldwide have diabetes mellitus and 4 million deaths occur from diabetes mellitus yearly most of which are from vascular morbidity. [1]

Complications could be acute or chronic. Chronic include non vascular and vascular (micro and macro).

Diabetic nephropathy is one of the chronic microvascular complications of diabetes affecting the kidney. Renal failure is second only to myocardial infarction as a cause of death from diabetes.

Proteinuria was first recognized in DM in the late 18th century (Contunnius, 1764 and Rollo, 1798). In 1836, Richard Bright recognized albuminuria as a sign of "serious renal disease"

In 1936, Kimmelstiel and Wilson described the classic lesions of nodular glomerulosclerosis in diabetes associated with proteinuria and hypertension. [2] By 1950s, kidney disease was clearly recognized as a common complications of diabetes , with as many as 50% of patients with diabetes of more than 20 years having this complication. The risk of DM nephropathy is low in normo -albuminuric patients with DM duration of greater than 30 yrs. [2] Those without proteinuria after 20-25 years have a 1% risk per year of developing overt renal disease.

Diabetes nephropathy is characterized by:

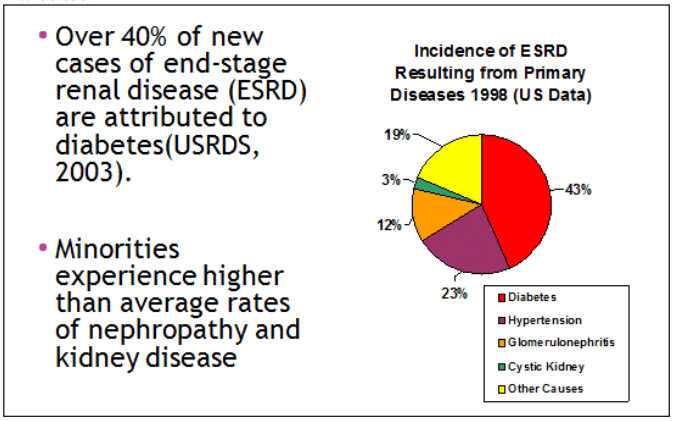
- Persistent albuminuria (30-299 mg/d or 20-200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart.
- Progressive decline in the glomerular filtration rate (GFR).
- Elevated arterial blood pressure.

Currently, diabetic nephropathy is the leading cause of chronic kidney disease in the western world. It is one of the most significant long-term complications in terms of morbidity and mortality for individual patient with diabetes[2].

EPIDEMIOLOGY

Approximately 40% of patients with Types 1 & 2 DM develop nephropathy, but due to higher prevalence of type 2 diabetes (90%) compared to Type 1 (10%) the majority of patients with DN have Type

2 disease.



In Nigeria, there are several hospital based studies reporting different statistics on diabetic nephropathy.

In Enugu, Neboh E et al studied 100 diabetic patients and reported that 49% had positive micro-albuminuria .Those with established renal failure were excluded.

Onovughakpo-Sakpa, O.E et al reported the incidence of diabetic nephropathy of 72.63% in Ekpoma. The study population was made up of 95 diabetic patients attending a tertiary health facility .[8]

Alebiosu et al demonstrated a 28.4% prevalence of nephropathy amongst diabetics in OOUTH, Sagamu.[13]

In 1989, a study done by Akinsola et al, DM 2% of patients with Chronic Renal Failure.[11]

In 2011, a study done by Arogundade et al on the epidemiology of chronic kidney disease in Ile-Ife, Nigeria showed that diabetic nephropathy is the 4th leading cause of CKD in Nigeria. [7]

A similar rising pattern was also found by Onavughakpo-Sakpa et al.

Its incidence was seen to increase by 150% in the US alone with a similar trend in Europe and Japan between 1990 and 2000.[9]

This has been attributed to an increased in the prevalence of diabetes mellitus especially type 2 and an increase in the lifespan of diabetic patients.[10]

A similar trend of an increase in the proportion of patients with CKD due to diabetes mellitus has also been reported in the developing nations.

For example in Southwestern Nigeria, diabetes accounted for 2% of those with CKD in 1989 but by 2000, had increased to 5%.

RISK FACTORS

Age: The onset of diabetes at a younger age is associated with a higher risk of progression to end-stage kidney disease.

Sex : Male to Female ratio(2:1).

Race : Incidence is high in blacks (3-6B : 1W) .

The prevalence of DN is relatively increased in African Americans, Native Americans, Mexican Americans, Polynesians, Australian Aborigines, and Urbanized Indo-Asian immigrants in the UK compared with Caucasians.

Hyperglycaemia.

Hypertension.

Dyslipidemia .

Family History.

Smoking.

ACE Gene Polymorphisms.

In a type 1 diabetic patient who has a 1st degree relative with diabetes and nephropathy, the risk for development of DN is 83%.

The frequency is only 17% if there is a 1st degree relative with diabetes but without nephropathy.

PATHOPHYSIOLOGY

The precise mechanisms that cause diabetic nephropathy are incompletely understood. However, pathogenesis is multifactorial, although persistent hyperglycaemia and genetic predisposition seem to be the key mediator.

Four mechanisms have been postulated that explain how hyperglycaemia causes tissue damage:

- Nonenzymatic glycosylation that generates advanced glycosylation end products(AGEs).
- Activation of Protein Kinase C (PKC).
- Acceleration of the aldose reductase pathway.

Generation of N-acetyl glucosamine via the Hexosamine pathway .

- A Unifying Mechanism proposed by Brownlee showed that an increase intracellular glucose concentrations stimulates glucose oxidation in the TCA cycle. This pushes more electron donors (NADH, FADH2) into the electron transport chain. When a critical threshold is reached and electrons are donated to molecular oxygen, superoxide is generated. This mitochondrial overproduction of superoxide activates the 4 major pathways that are involved in DN.

(A) Formation of Advanced Glycation End Products (AGE): These are formed as a result of non enzymatic reactions between intracellular glucose derived dicarbonyl precursors with the amino groups of both intracellular and extracellular proteins. AGE bind to RAGE receptor and the detrimental effect of AGE-RAGE signaling axis within the vascular compartments include (1) release of pro-inflammatory cytokines and growth factors from intimal macrophages; (2) generation of reactive oxygen species in endothelial cells; (3) increased procoagulant activity on endothelial cells and macrophages (4) enhanced proliferation of vascular smooth muscles and synthesis of extracellular matrix[9].

(B) Activation of Protein Kinase C. Hyperglycemia activate PKC by formation of ca ions and diacyl glycerol (DAG) . Effects of PKC activation include; production of profibrogenic factors like transforming growth factor B(TGF B), production of pro-inflammatory cytokines by the vascular endothelium[9].

(C) Aldose Reductase (POLYOL) Pathway. Increased sorbitol leads to generation of reactive oxygen species, alteration in redox potential and increased cellular osmolarity. This action promotes vasodilatation and hyperfiltration, which are the early processes in diabetic nephropathy[10].

(D) Hexosamine Pathway . Fructose 6 phosphate is diverted into the hexosamine pathway increasing the concentrations of N-acetylglucosamine .This glucosamine modifies certain transcription factors such as Sp1 activity by post-translational O-linked glycosylation .In turn, Sp1 then leads to enhanced transcription of key mediators, such as TGF-B & plasminogen activator inhibitor 1.[5])

The detectable changes in the course of diabetic retinopathy are ;

(1) Glomerular lesions: Capillary basement membrane thickening occurs in virtually all cases of diabetic nephropathy. Careful morphometric studies demonstrate that this thickening begins as early as 2 years after the onset of type 1 diabetes and by 5 years amounts to about a 30% increase. Diffuse mesangial sclerosis consisting of diffuse increase in mesangial matrix as a result of proliferation of mesangial cells is observed. Nodular Glomerulosclerosis also known as intercapillary glomerulosclerosis or kimmelstiel-wilson disease take the form of spherical often laminated, nodules of matrix situated in the periphery of the glomerulus. It is a unique microscopic characteristic of diabetic nephropathy in which sclerosis of the glomeruli is accompanied by nodular deposits of hyaline.

(2) Reno vascular lesions: Renal atherosclerosis and arteriosclerosis affect both the afferent and efferent arterioles. Such efferent arteriosclerosis is rarely, if ever, encountered in individuals who do not have diabetes.

3) Renal Hypertrophy: Elevated plasma glucose levels cause hypertrophy by stimulating growth factors in the kidney including IGF-1, epidermal growth factor (EGF), PDGF, VEGF, TGF-beta & Ang II. Glucose as well as glucose derived AGE's & Ang II stimulate the production of TGF-beta in mesangial cells. TGF-beta stimulates protein synthesis (hypertrophy) but prevents cell proliferation & division by induction of cell cycle inhibitors. It is overexpressed in the glomeruli and the tubulointerstitium in DN.

4) Pyelonephritis: Is an acute or chronic inflammation of the kidneys that usually begins in the interstitial tissue and then spreads to affect the tubules. More common in diabetics than in the general population.

Protein may appear in the urine for 5 – 10 years before other symptoms develop. High blood pressure often accompanies diabetic nephropathy. Over time, the kidney's ability to function starts to decline. Diabetic nephropathy may eventually lead to the nephrotic syndrome (a group of symptoms characterized by excessive loss of

protein in the urine) and chronic renal failure. The disorder continues to progress towards end stage kidney disease, usually within 2 to 6 years after the appearance of proteinuria. Diabetic nephropathy is generally accompanied by other diabetic complications including retinopathy, neuropathy, and microangiopathy .[4],[5]

STAGING/ NATURAL HISTORY

This is based on the landmark work of Mogensen et al(1983) who identified 5 stages of DM nephropathy in type 1 DM patients.
STAGE 1 (hypertrophy and hyperfilteration).
STAGE 2 Asymptomatic stage that develops silently over 3-5yrs. Characterized by morphologic lesions without clinical signs.
STAGE 3 Incipient DM nephropathy that occurs after 5 yrs of disease. Characterized by abnormally raised urinary albumin excretion of between 20-200ug/min (microalbuminuria).
STAGE 4 Overt DM nephropathy occurring after 10-15yrs of disease. Characterized by persistent proteinuria > 0.5g/24 hrs.
STAGE 5 (ESRD).
Occurs about 5-10yrs from macroalbuminuria, 10-20yrs from onset of microalbuminuria . The GFR 0-10ml/min.
Albumin excretion starts decreasing.
Require renal replacement therapy.
Patient is frankly uraemic and in the US, about 25% of presentation is at this.[2],[14]

Natural History of Diabetic Nephropathy

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300 mg/d	Type 1 normal Type 2 normal hypertension	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>380 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

CLINICAL PRESENTATION

History:

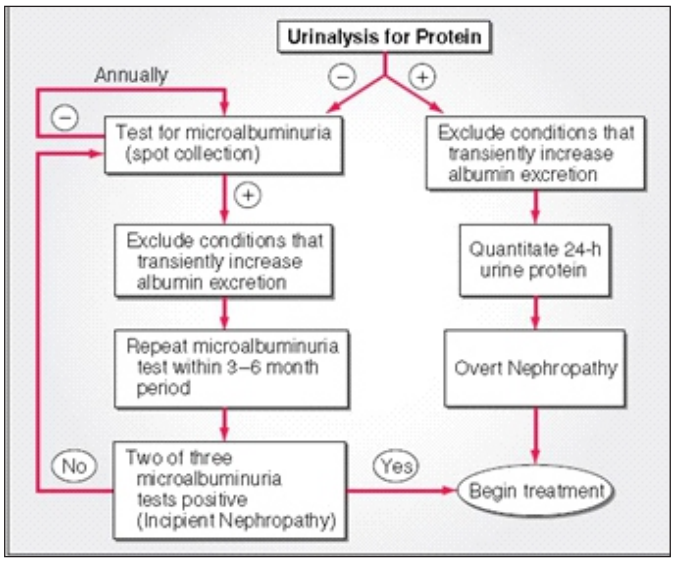
Diabetic nephropathy should be considered in patients who have diabetes mellitus and a history of one or more of the followings;
Passing of foamy urine.
Otherwise unexplained proteinuria.
Diabetic retinopathy.
Fatigue and foot edema secondary to hypoalbuminaemia.
Other associated disorders such as peripheral vascular occlusive diseases, hypertension, or coronary artery disease.

Physical Examination:

Generally, diabetic nephropathy is considered after a routine urinalysis and screening for microalbuminuria in the setting of diabetes. Patients may have physical findings associated with long-standing diabetes mellitus, such as;
Hypertension.
Peripheral vascular occlusive disease.
Evidence of diabetic neuropathy in the form of decreased fine sensations and diminished tendon reflexes.
Evidence of fourth heart sound during cardiac auscultation.
Non healing skin ulcers/osteomyelitis.
Almost all patients with nephropathy and type 1 DM demonstrate signs of diabetic microvascular disease, such as retinopathy and neuropathy.[2]

SCREENING AND DIAGNOSIS

Screening for DN must be initiated at the time of diagnosis in patients with Type 2 DM.
For patients with Type 1 DM, the 1st screening has been recommended at 5 years after diagnosis.
However, the prevalence of microalbuminuria before 5 yrs in this group can reach 18%, especially in patients with poor glycaemic and lipid control, and high normal blood pressure levels.
Furthermore, puberty is an independent risk factor for Microalbuminuria.
Therefore, in Type 1 DM, screening for Microalbuminuria might be performed 1 year after diabetes diagnosis, especially in patients with poor metabolic control and after the onset of puberty.
If Microalbuminuria is absent, the screening must be repeated annually for both Type 1 and 2 diabetic patients.
The first step in the screening and diagnosis of DN is to measure albumin in a spot urine sample, collected either as the first urine in the morning or at random.
This method is accurate, easy to perform, and recommended by ADA guidelines.
24hour and timed urine collections are cumbersome and prone to errors related to collecting samples or recording of time.



Screening for microalbuminuria. (Adapted from RA DeFronzo, in Therapy for Diabetes Mellitus and Related Disorders, American Diabetes Association, Alexandria, VA, 1998)

DIABETIC NEPHROPATHY STAGES: CUTOFF VALUES OF URINE ALBUMIN FOR DIAGNOSIS AND MAIN CLINICAL CHARACTERISTICS

Stages	Albuminuria cutoff values (ref. 14)	Clinical characteristics (ref. no.)
Microalbuminuria	20–199 μg/min	Abnormal nocturnal decrease of blood pressure and increased blood pressure levels (163)
	30–299 mg/24 h	Increased triglycerides, total and LDL cholesterol, and saturated fatty acids (164, 165)
	30–299 mg/g*	Increased frequency of metabolic syndrome components (166)
		Endothelial dysfunction (167)
		Association with diabetic retinopathy, amputation, and cardiovascular disease (168)
		Increased cardiovascular mortality (2, 169)
		Stable GFR (82)
Macroalbuminuria†	≥200 μg/min	Hypertension (99)
	≥300 mg/24 h	Increased triglycerides and total and LDL cholesterol (170)
	>300 mg/g*	Asymptomatic myocardial ischemia (171, 172)
		Progressive GFR decline (83, 84)

*Spot urine sample. †Measurement of total proteinuria (≥500 mg/24 h or ≥430 mg/l in a spot urine sample) can also be used to define this stage.

Nephropathy is often diagnosed with urinalysis. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (>_ 30mg/day or 20ug/min) of albumin in the urine, referred to as microalbuminuria, and patients with this condition are referred to as having incipient nephropathy. Without specific interventions, 80% of subjects with type 1 diabetes who develop sustained microalbuminuria have their urinary albumin excretion increase at a

rate of approximately 10% - 20% per year to the stage of overt nephropathy or clinical albuminuria(›_ 300mg/24h or ›_ 200ug/min) over a period of 10-15 years, with hypertension also developing along the way. Once overt nephropathy occurs, without specific interventions, the glomerular filtration rate(GFR) gradually falls over a period of several years at a rate that is highly variable from individual to individual(2—20 ml/min/year). ESRD develops in 50% of type 1 diabetic individual with overt nephropathy within 10 years and in 75% by 20 years.

INVESTIGATIONS

Other investigations that should be carried out include :

Full Blood Count, Electrolyte Urea and Creatinine, Calcium, Phosphate and Uric Acid, Renal Ultra Sound , Doppler Studies, Fasting Lipid Profile, Urine Microscopy and Culture, Electrocardiography, Echocardiography, Chest x-ray, Renal Biopsy.

MANAGEMENT

Depends on the stage of DN or level of GFR patient is presenting with. Often requires a multidisciplinary therapeutic approach involving the nephrologist, diabetologist, dieticians, interventional cardiologist, special renal & diabetic nurse specialists, etc.

Principles of management include;

Good Glycaemic control.

Treatment of Hypertension.

Renin- Angiotensin-Aldosterone System blockade.

Treatment of Dyslipidemia.

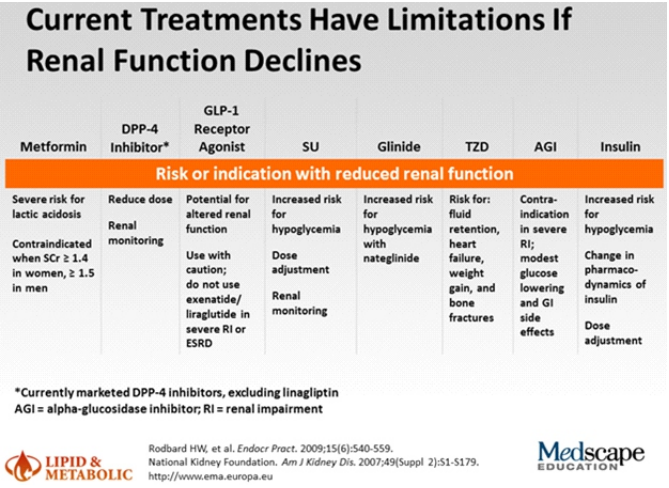
Lifestyle modification (Management / Management of Risk factors).

Management of complications.

Renal Replacement Therapy.

Glycemic Control. The National Kidney Foundations KDOQI guideline recommends lowering of HbA1c levels to 7.0% for both type 1 & 2 diabetes. In persons with either type 1 or 2 DM hyperglycemia has been shown to be a major determinant of the progression of diabetic nephropathy. The evidence is best reported for type 1 diabetes mellitus. The American Diabetes Association recommends that treatment aim at achieving target pre-prandial glucose of 80-120 mg/dL (whole blood) or 90-130mg/dL (plasma); bedtime glucose of 100-140 mg/dL (whole blood) or 110-150 mg/dL (plasma), and HbA1c<7%.

Target blood sugar levels can be achieved using oral hypoglycaemic agents, insulin, or a combination of both. The Diabetes Control and Complications Trial (DCCT) compared conventional (mean achieved glycosylated hemoglobin [HbA1c,] 9.1%) with intensive treatment (mean achieved HbA1c, 7.3%) in 1,441.[5]



Blood Pressure Control. Both systolic and diastolic hypertension markedly accelerate the progression of DN, and aggressive anti-hypertensive management has been shown to decrease the rate of fall of glomerular filtration rate, increase the median life expectancy, and reduce the need for dialysis and transplantation. The primary goal of therapy for non pregnant patients with diabetes aged ›18 years is to reduce blood pressure below 130/80 mmHg for patients with proteinuria ‹1 g/day, and ‹125/75 mmHg for patients who have ›1 g/day of proteinuria[10].

Mogensen showed that anti-hypertensive treatment attenuates the rate of decline in renal function in patients who have Type 1 DM, hypertension, and proteinuria.

Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor blockers(ARBs) reduce the risk of the development or progression of overt nephropathy.

Classic Beta-blockers have adverse metabolic effects & are therefore undesirable in diabetes, but this is no longer true for the modern beta-blockers : carvedilol & nebivolol.

Treatment Of Dyslipidemia. Dyslipidaemia is a major issue in DM and CRF patients and contributes to morbidity and mortality. Use of statins has been demonstrated to significantly reduce cardiovascular morbidity and mortality DM patients. Current guidelines recommend a goal for LDL-Cholesterol of below 100mg/dl (2.57mmol/l) for diabetic patients in general & below 70mg/dl for diabetic patients with Cardiovascular disease. (National Cholesterol Education Program Adult Treatment panel III guidelines).

Lifestyle Modification. For all diabetics, this lowers the risk of cardiovascular events :

Obese type II DM patients will need to lose weight.

Cessation of cigarette smoking.

Dietary Restriction of salt and saturated fat.

Exercise as appropriate.

Renal Replacement Therapy. The renal replacement modalities available for patients with ESRD from diabetes include peritoneal dialysis, hemodialysis, and renal transplantation.

Renal Transplantation. Renal transplantation is associated with better survival, improved quality of life, and a higher degree of rehabilitation compared to dialysis. Recurrence of DN can occur in the allograft which could be as a result of poor glycaemic control and /or insulin deficiency.

COMPLICATIONS

Cardiovascular events.

Renal Tubular Acidosis type IV.

Contrast Nephropathy.

Anemia (Treatment with Erythropoietin is useful).

Complications of treatment : Hypoglycemia, dialysis & Renal Transplantation complications.

PREVENTIONS

Prevention can be primary , secondary or tertiary.

These involve;

Optimal blood glucose control.

Control of hypertension.

Avoidance of potentially nephrotoxic substances such as herbals, NSAIDS, aminoglycosides, etc.

Early detection and optimal management of diabetes, especially in the setting of family history of diabetes.

Annual screening of diabetics for microalbuminuria .

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