Diabetic nephropathy - current perspectives

Dr. R. Rajasekar

Sr. Consultant Physician & Diabetology
RR.Charitable and Educational Trust
Heart and Diabetes Therapy Centre, Kumbakonam

Abstract:

Diabetic nephropathy could even be a clinical syndrome characterized by persistent albuminuria. The risk for the event of diabetic nephropathy is low in a normo-albuminuric patient with diabetes, a duration of more than 30 years.But Patients who don't have proteinuria even for about 25 years have a risk of developing the overt renal disease of about approximately 1% annually.Apart from Albuminuria and Non-Albuminuria Diabetes renal disorder, Tubular biomarkers are reported as predictors of diabetes renal disorder. Hypertension, metabolic syndrome, and diabetes may play an important role in the pathogenesis of diabetic nephropathy. New guidelines say metformin is often continued right rightright down to an eGFR of 30 mL/min, adjusting the dose. A recent study says,Crosstalk exists between tubular epithelial cells and glomerular endothelial cells in diabetic renal disorder, and it plays a task.

What are the features of DM Nephropathy? Clinical- History of DM with one or more features-- A.Passing foamy urine, B.Proteinuria of any unexplored cause C.Diabetic retinopathy D.Malaise, fatigue, and pedal edema secondary to hypoalbuminemia viz nephrosis E.Any other disorders-Viz- peripheral vascular occlusive disease, hypertension, or arteria coronariadisease.Triad of Features.

1.Tenacious albuminuria of >300 mg/d or >200 μg/min, if confirmed on a least duration of twice 3 to six months apart 2.Progressive decline within the glomerular filtration rate (GFR) Vital sign--PROTENURIA 3.Nodular Glomerulosclerosis Proteinuria was first identified in DM within the late 18th century. It is These classic lesions of nodular glomerulosclerosis in Diabetes-related to proteinuria and hypertension. Kimmelstiel and Wilson vividly narrated it. During the year 1950s, the renal disorder was well identified as a typical complication of diabetes, with as many as 50% of patients with diabetes of quite 20 years having this complication.

DM-Nephropathy Presently, diabetic nephropathy is the leading cause of chronic renal disorder in the USA and other Western societies. it's also one among the foremost marked long-term complications in sight morbidity and mortality for diabetic patients. Diabetes is liable for about 30-40% of all end-stage renal disease (ESRD) cases.

Generally, diabetic nephropathy is recognized after a daily analysis of urine and screening for Microalbuminuria. Patients may have physical findings in patients with DM of a long duration. Good proof suggests that early therapy delays or prevents the onset of diabetic nephropathy or a diabetic renal disorder. This is well revealed in both type 1 and type 2 DM. ATYPICAL-DM NEPHROPATHY It is the dissociation of proteinuria from reduced kidney function, as an atypical presentation of diabetic nephropathy. Microalbuminuria isn't predictive of diabetic nephropathy. Yet a majority of the cases of diabetic nephropathy presents with proteinuria, which subsequently develops and becomes worse because the disease progresses and is nearly uniformly alright related to hypertension.

Pathophysiology There are three major histologic patterns that occur within the glomeruli of persons with diabetic nephropathy. First and foremost is a mesangial expansion that is directly induced by hyperglycemia, probably through increased matrix production or glycation of matrix proteins. Second change is the thickening of the

glomerular basement membrane (GBM) occurs. Third one is glomerular sclerosis. Intraglomerular hypertension causes lesions. it's induced either by dilatation of the afferent arteries or from ischemic injury initiated by hyaline narrowing of the vessels supplying the glomeruli. These three various histologic patterns seem to possess similar prognostic significance.

Diabetic Glomerulopathy The essential change in diabetic glomerulopathy is the augmentation of the extracellular matrix.A very early change is a morphologic abnormality in diabetic nephropathy is that the thickening of the Glomerular Basement Membrane and expansion of the mesangium.It is due to the accumulation of extracellular matrix.It is the hallmark of diabetic nephropathy.

Pathogenesis-DM Nephropathy Though Light microscopy and Immunofluorescence microscopy, though show histological changes, Electron microscopy reveals more detailed information of the structures involved; during a sophisticated state, the mesangial regions rather occupy an outsized portion of the tuft, with prominent matrix content.The basement membrane within the capillary walls viz the peripheral basement membrane is thicker than normal.

DM-Nephropathy-Severity The severity of diabetic glomerulopathy is assessed by the thickness of the peripheral basement membrane and mesangium and matrix expressed as a fraction of appropriate spaces, for e.g., the volume fraction of mesangium versus glomerulus, matrix versus mesangium, or matrix versus glomerulus.

DM Nephropathy Versus Chronic insufficiency The glomeruli and kidneys are either typically normal or increased in size at the onset, thus distinguishing diabetic nephropathy from most other forms of chronic insufficiency, where the dimensions of the kidney are reduced except in polycystic renal disorder and renal amyloidosis.

Overt DM Nephropathy/HT Apart from renal hemodynamic changes, patients with overt diabetic nephropathy, i.e., .dipstick-positive proteinuria and decreasing glomerular filtration rate, generally do develop systemic hypertension. Hypertension also can be an adverse event alongside progressive renal diseases and appear exclusively so in diabetic nephropathy. The deleterious effects of hypertension are likely directed at the vasculature and microvasculature.

HT-Association Evidence suggests that hypertension-related to obesity, metabolic syndrome, and diabetes may play a crucial role within the pathogenesis of diabetic nephropathy. Central obesity, metabolic syndrome, and diabetes cause increased vital signs.

Central Obesity Central obesity induces hypertension initially by increasing renal tubular reabsorption of sodium. Further, it creates a hypertensive shift of renal-pressure natriuresis through multiple mechanisms, including activation of two systems, namely the sympathetic nervous system and renin-angiotensin-aldosterone system, and cause physical compression of the kidneys. Hypertension, in association with it, increases intraglomerular capillary pressure, and thus the metabolic abnormalities like dyslipidemia and hyperglycemia are likely to interact to hasten renal injury.

DM Nephropathy Features almost like obesity-associated glomerular hyperfiltration renal vasodilation, increase within the glomerular filtration rate, and intraglomerular capillary pressure, and increased vital sign are also features of diabetic nephropathy. Increased systolic vital sign further intensifies the disease progression to proteinuria and a decline within the glomerular filtration rate, resulting in end-stage renal disorder.

Etiology-DM-Nephropathy Etiology The actual explanation for diabetic nephropathy is unknown, but various hypothesized mechanisms are hyperglycemia, namely hyperfiltration and renal injury, advanced glycation products, and activation of cytokines. Many explorers now concur that diabetes is an autoimmune disease, with overhanging pathophysiologies contributing to both type 1 and sort two diabetes and up thus far,the research emphasizes the pivotal role of

natural immunity (toll-like receptors) and regulatory T- cells (Treg)

Mechanism –Hyperglycemia Glycemic control envisages the balance between the intake of diet and gluconeogenesis and tissue uptake or utilization through storage as glycogen or fat and oxidation. This balance is regulated by the production of insulin from the β cells of the pancreas. Serum glucose is regulated by insulin through its actions on the liver, striated muscle, and fat tissue. In Insulin resistant state, insulin cannot suppress hepatic gluconeogenesis, thus leads to hyperglycemia. Simultaneously, insulin resistance by insulin-sensitive tissues, i.e., fat and striated muscle, results in increased lipolysis and reduction in glucose disposal, causing hyperlipidemia additionally to hyperglycemia. CYTOKINES Evidence shows that when there's insulin resistance, the pancreas is forced to extend its insulin output, which stresses the β cells, eventually leading to β-cell exhaustion. The high blood sugar levels and high levels of saturated fatty acids create an inflammatory medium, leading to activation of the innate system,which results in activation of the nuclear transcription factors-kappa B (NF-ϰB), and release of inflammatory mediators,including interleukin (IL)–1β and tumor necrosis factor (TNF)–α, promoting systemic insulin resistance and β-cell damage as a result of autoimmune insulitis. Hyperglycemia and high serum levels of free fatty acids and IL-1 cause glucotoxicity, lipotoxicity, and IL-1 toxicity, leading to apoptotic β-cell death. TGF-B/VEGF Hyperglycemia also increases the expression of remodeling growth factor-β (TGF-β) within the glomeruli and of matrix proteins, specifically stimulated by this cytokine. TGF-β and vascular endothelial protein (VEGF) may contribute to cellular hypertrophy and enhanced collagen synthesis, thus inducing the vascular changes seen in persons with diabetic nephropathy. Hyperglycemia also induces protein kinase C, which can contribute to renal disease and other vascular complications of diabetes.

Familial/Genetic Familial or probably even genetic factors also play a task. The ethnic population, especially African Americans, persons of Hispanic origin, and American Indians, are predisposed to renal disease as a complication of diabetes. Genetic predisposition to diabetes, like, thrifty genotype hypothesis.

Role of Polymorphism there's any evidence in the role of Polymorphism within the gene for angiotensin-converting enzyme (ACE) in either predisposing to nephropathy or enhances its course. Anyhow, definitive genetic markers are yet to be identified. Recently, the role of epigenetic modification within the pathogenesis of diabetic nephropathy is additionally highlighted.

Role of B-complex vitamin -Folic Acid – in DM NEPHROPATHY A study by Bherwani et al. suggested an association between decreased serum vitamin folic acid levels and diabetic nephropathy. EPIDEMIOLOGY Even way back in the 1950s, the renal disorder has been recognized as a typical complication of DM (DM), with as many as 50% of patients with DM of quite 20 years' duration having this complication. RISK OF DEVELOPMENT DM-NEPHROPATHY the danger for the event of diabetic nephropathy is low during a normoalbuminuric patient with diabetes' duration of greater than 30 years. Patients who haven't any proteinuria after 20-25 years have a risk of developing the overt renal disease of only approximately 1% once a year. Epidemiology differs among European countries, especially in Germany; renal replacement therapy is more so than in the USA. In China, in Patients with T2DM, the high propensity of non-diabetic renal disease (NDRD) like Membranous nephropathy, immunoglobulin A (IgA) nephropathy, and focal segmental glomerulosclerosis.

Gender'and age occurrence: Both males and females are equally affected. Diabetes of 10 to 20 years duration develop DN, not so of less than ten years duration. Above the age of 60 years, ESRD can occur. The high frequency of DN in populations, socioeconomic factors play a role-

factors like diet, poor control of hyperglycemia, hypertension, and obesity.

Prognosis Diabetic nephropathy accounts for significant morbidity and mortality. Proteinuria could even be a predictor of morbidity and mortality. The overall prevalence of Microalbuminuria and macroalbuminuria in both sorts of diabetes is about 30-35%. Microalbuminuria independently predicts cardiovascular morbidity. Microalbuminuria and macroalbuminuria increase mortality from any cause in DM. Microalbuminuria is additionally related to increased risk of coronary and peripheral vascular disease and death from disorder within the general non-diabetic population.

Proteinuria & Mortality Patients, if not develop proteinuria, have a lesser incidence of mortality while patients with proteinuria have multiple-40-times higher risk in mortality. Bell-shaped relationship exists between duration of diabetes /age and relative mortality, with maximal relative mortality within the age interval of about 34 to 38 years.Type 1 DM Patients and proteinuria show a well-defined bell-shaped relationship between diabetes duration versus age and relative mortality.

Metformin in Renal Disease What are these recommendations regarding metformin use in renal disease? FDA recently changed the guidelines regarding the suitable prescription of metformin in response to a citizen's petition. Thus the new labeling guidance is that metformin is often continued right rightrightright down to an eGFR of 30 mL/min. The rationale that this guidance changed is that it's been observed in many, many large observational studies and far from thousands of patients that there are extremely few adverse outcomes in patients on metformin until the creatinine clearance really is below 30.

Metformin Dose Adjustment: What do I do? What do many of us neutralize practice? Many of us feel that it's prudent to reduce the dose of metformin when the creatinine clearance drops to 45, so between 30 and 45, the dose is often reduced from 1000 mg twice each day, perhaps to 500 mg twice each day, and truly in patients who have unstable renal function who are in peril for acute kidney injury, who are in peril for infection or have rapid changes in their clinical status, caution is warranted, perhaps increased monitoring or even discontinuation of metformin. Apart from folks that basically are in a very steady-state, with an eGFR within the quite 35 to 40 range, not only is it safe to continue metformin, it's getting to be safer to continue metformin than it's to select an alternate glucose-lowering medication ESRD ESRD, contributes about 59 to 66% of deaths in patients with type 1 DM and nephropathy. during a prospective study in Germany, the 5-year survival rate was 10% within the elderly population with type 2 DM, and it was 40% within the younger population with type 1 DM. The cumulative incidence of ESRD in patients with proteinuria and Type 1 DM is 50%. Ten years after the onset of proteinuria, whereas in Type 2 DM patients, it's 3-11% in 10 years after the onset of proteinuria in European patients.

Medications- Are there any medications apart from ACE Inhibitors or angiotensin receptor blockers that may help to ameliorate diabetic nephropathy? Physiology of SGLT2 inhibitors could even be beneficial for the kidney as an additive effect to angiotensin receptor blockers and ACE inhibitors. One of the good things about SGLT2 inhibitors is that they decrease intraglomerular pressure and reduce, actually cause afferent arteriolar vasoconstriction. As a result, they're really protecting the glomerulus against the hyperfiltration that's seen in diabetic renal disorder, and as people probably know, a blockade of the renin-angiotensin system results in dilation of the efferent arteriole, which also decreases the pressure within the macula densa.So, there's an opportunity that combining these two drugs together could lead to decreased pressure across the glomerulus and be very protective in restoring

normal physiology in people with diabetic renal disorder.

Creatinine Bump: We often do see a creatinine bump within the use of angiotensin receptor blockade or within the use of SGLT2 inhibitors, which could even be a physiologic increase in creatinine that's associated with decreased GFR, but what that basically represents is sort of a functional improvement within the pressure across the glomerulus. It is very hard to inform whether that represents true acute kidney injury or actually the intended goal of therapy. Thus, it's vital to carefully monitor patients on the dual blockade, but that over the long run, when used properly, this has been seen in clinical trials to possess benefits on the diabetic renal disorder and offers very exciting benefits.

Guidelines-The guidelines are for lowering the dose of insulin in patients with deteriorating renal function. We are cornered because it's quite difficult to manage insulin in patients with progressive renal failure. There are many things at play. As renal disorder progresses, insulin resistance also increases, and insulin clearance decreases. So it's rather difficult to assess whether one must increase or decrease the insulin. In addition, there is often a time within the course of people's illness where there's many other compelling requirements, multimorbidity, chronic illness, sometimes erratic dietary intake, and infact, we've to watch carefully in patients on complex insulin regimens and to be very dynamic in adjusting them.

Creatinine/Hypoglycemia: Even a small increase in creatinine dramatically raises the danger of hypoglycemia because the kidney is liable for about 30% of gluconeogenesis. Monitoring the patient, asking the patient to undertake to have careful self-monitoring, and ensuring the patient to understand how to adjust his or her own insulin in anticipation of changes in diet and activity is that the foremost vital strategy.

New Biomarkers-Are there any new markers beside the microalbumin/creatinine ratio to spot and track renal disease in patients with diabetes? There are literally many other markers of acute kidney injury and various stages of renal disease. But in clinical practice, we still believe the creatinine, particularly the creatinine clearance or glomerular filtration rate, urine microalbumin to creatinine ratio, are extremely important markers.

New Bio-Markers apart from Albuminuria, Tubular biomarkers are reported as predictors of Diabetic renal disorder. They are cystatin C, kidney injury molecule-1microglobuin, N-acetyl-Beta-D-glucosaminidase, and lever-type fatty-acid binding protein. Several studies show that these markers aren't only more sensitive but are much earlier predictors of diabetic nephropathy than Microalbuminuria. Although their advantages over Microalbuminuria are evidence-based, the majority still got to be validated for diagnostic purposes. Traditional studies have shown that podocyte injury plays a crucial role during this process. Recently, it's been found that glomerulotubular balance and tubuloglomerular feedback (TGF) could even be involved in the progression of DKD. Injury to tubular epithelial cells (TECs) is the key link in DKD. Additionally, injury to glomerular endothelial cells (GECs) plays a key role within the primary occurrence and development of DKD. However, TECs and GECs are on the brink of every other in anatomical position and will crosstalk with each other, which can affect the event of DKD, which is the foremost explanation for DKD. Improving the injury to TECs and GECs and maintaining normal Crosstalk between them may become a replacement strategy for the prevention and treatment of DKD in the long run. Further research efforts should be aimed towards demonstrating that prevention of progression of the Crosstalk between TECs and GECs is feasible and results in improved outcomes.

ANGPLT2

(Angiopoietin-like protein 2)

and Urine and Serum ZAG: ANGPTL2 could even be a biomarker that has direct involvement in podocyte dysfunction and is

independent of the progression of DKD stages. ANGPTL2 is found to increase albumin permeability via the translocation of zonula occludens-1 from the membrane to the cytosol by activating focal adhesion kinase. The vital early marker is Microalbuminuria to detect diabetic nephropathy (DN). But it is not a sufficiently accurate predictor of DN risk. Thus, new biomarkers that can help to predict DN risk earlier and the possibility of preventing the occurrence of the end-stage renal disorder are being investigated. Urine and Serum ZAG (Zinc alpha two glycoproteins) could be useful as early biomarkers for the detection of DN in T2DM patients, detectable before Microalbuminuria.

Neprilysin Inhibitors in CKD- Despite these negative findings, neprilysin inhibition may yet to play a role in patients with proteinuric kidney disease. While the majority of patients enrolled were presumed to possess diabetic kidney disease, i.e., proteinuria was 310 mg/d,a Prolonged duration of treatment is required to determine a difference in eGFR. So we'll try neprilysin inhibitors as they're related to renal protection.

Clustering of DM The Five unique subgroups supported severity and underlying disease mechanism analysis -- reported by Emma Ahlqvist of Sweden, Cluster 1: Severe type I diabetes (SAID) Cluster 2: Severe insulin-deficient diabetes (SIDD) Cluster 3: Severe insulin-resistant diabetes (SIRD) Cluster 4: Mild obesity-related diabetes (MOD) Cluster 5: Mild age-related diabetes (MARD). Cluster 3 has the highest degrees of insulin resistance and also revealed a marked risk for diabetic kidney disease than the other groups. Those of the insulin-deficient cluster(Cluster-2) had the absolute best risk for diabetic retinopathy.

Cigarette Smoking and DM: Cigarette smoking as a risk factor for diabetics: a scientific review and meta-analysis of prospective cohort studies. The present study highlighted that smoking was an independent risk factor for DN, especially in patients with T1DM. The Familiarity of Rapid Renal Decline in Diabetes: An estimated GFR (eGFR) from serum creatinine measurements got from more than 15,000 patients with diabetes at the University of Utah Health Sciences Center and entrenched their renal function trajectories.

FAMILIALITY OF RAPID RENAL DECLINE IN DIABETES: Familial analysis revealed that fast renal decline documents in such families and is said to be an increased risk among first-degree relatives. Further study of these families is important to understand the magnitude of the influence of shared familial factors, including environmental and genetic factors, on the rapid renal decline in diabetes.

eGFR Formula. : My mnemonics. 2C 2A 2M.

2.C.CK - Cockcroft-Gault formula.

Chronic kidney disease epidemiology collaboration equation formula

2A-Age Related Formula - Schwartz formula-For Children

Prabhat's formula-Above 30yrs.

2M. MDRD-Modification of diet in renal disease formula

Mayo Quadratic Clinic formula.

Conclusion

Although Microalbuminuria remains a legitimate test for early identification of diabetic nephropathy (DN), it isn't an accurate predictor of DN risk. Thus, new biomarkers' role in predicting DN risk at an early stage and possibly can prevent the occurrence of end-stage kidney diseaseis under investigation.

References

1. Tejas P. Desai. Do Neprilysin Inhibitors Have a Role in Patients With CKD? - Medscape - Dec 14, 2018.
2. Frodsham SG, Yu Z, Lyons AM, Agarwal A, Pezzolesi MH, Dong L, Srinivas TR, Ying J, Greene T, Raphael KL, Smith KR, Pezzolesi MG. The Familiality of Rapid Renal Decline in Diabetes. Diabetes. 2019 Feb;68(2):420-429. doi: 10.2337/db18-0838. Epub 2018 Nov 13. PMID: 30425064; PMCID: PMC6341306.
3. Chen SJ, Lv LL, Liu BC, Tang RN. Crosstalk between tubular epithelial cells and glomerular endothelial cells in diabetic kidney disease. Cell Prolif. 2020 Mar;53(3):

e12763. doi: 10.1111/cpr.12763. Epub 2020 Jan 11. PMID: 31925859; PMCID: PMC7106959.

4. Ref:international Journal of Nephrology and Kidney Failure-19 March. 2018.
5. Ishii T, Furuya F, Takahashi K, Shikata M, Takamura T, Kobayashi H, Miyazaki A, Morinaga J, Terada K, Oike Y, Kanda E, Kitamura K. Angiopoietin-Like Protein 2 Promotes the Progression of Diabetic Kidney Disease. J Clin Endocrinol Metab. 2019 Jan 1;104(1):172-180. doi: 10.1210/jc.2017-02705. PMID: 30137449.
6. Liao D, Ma L, Liu J, Fu P. Cigarette smoking as a risk factor for diabetic nephropathy: A systematic review and meta-analysis of prospective cohort studies. PLoS One. 2019 Feb 4;14(2):e0210213. doi: 10.1371/journal.pone.0210213. PMID: 30716100; PMCID: PMC6361430.
7. Elsheikh M, Elhefnawy KA, Emad G, Ismail M, Borai M. Zinc alpha 2 glycoprotein as an early biomarker of diabetic nephropathy in patients with type 2 diabetes mellitus. J Bras Nefrol. 2019 Oct-Dec;41(4):509-517. doi: 10.1590/2175-8239-JBN-2018-0200. Erratum in: J Bras Nefrol. 2019 Oct-Dec;41(4):587. PMID: 30897192; PMCID: PMC6979576.
8. Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spégel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark Å, Lahti K, Forsén T, Tuomi T, Rosengren AH, Groop L. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018 May;6(5):361-369. doi: 10.1016/S2213-8587(18)30051-2. Epub 2018 Mar 5. PMID: 29503172.