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Review Article

Diabetic nephropathy: Pathophysiology, Staging, Prevalence, and Management

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ABSTRACT

Diabetes mellitus (DM) has become a significant economic burden because of high healthcare costs for the treatment and its related complications. Chronic hyperglycemia, affect severely our organ systems mainly, cardiovascular, nervous, and renal system. These diabetic complications can progress into morbidity and mortality. Diabetic nephropathy (DN) is a major cause of end-stage renal disease (ESRD) which affects 20–30% diabetic patients, characterized by sustained reduction in end glomerular filtration rate (GFR)and persistently high urinary albumin-to-creatinine ratio. Elevated glucose levels, high blood pressure long duration of diabetes, obesity, and dyslipidemia can increase the progression of DN. The pathophysiology of DN is mainly due to result of interactions between metabolic and hemodynamic pathways, which are often disrupted in diabetes. Pharmacological approaches for DN mainly include regulation of BP, control of blood sugar level, use of hypolipidemic agents, quitting smoking, diet control, and use of vitamin D receptor agonists. Hence, strategies of treatment like BP control and dyslipidemia control etc. are required to decrease the burden of DN and prevent its progression to end stage renal disease (ESRD).

1. Introduction

Diabetes mellitus (DM) has become one of the potential epidemics in India. In India, more than 62 million individuals are currently diagnosed with diabetes.[1] According to the International Diabetes Federation Atlas (IDFA) 2015, about 69 million people in India and over 450 million people across the globe are suffering from diabetes. India, is hence infamously titled the "Diabetes capital of the world".[2] The World Health Organization (WHO) predicted that there will be 366 million adults with diabetes in 2030.[3]

Diabetes has become a significant economic burden because of high healthcare costs for the treatment and its related complications.[4] Unhealthy lifestyle including junk foods and lack of exercise and eventually obesity, increases the risk of the disease. Chronic hyperglycemia, will affect our cardiovascular, nervous, and renal system. These diabetic complications can progress into morbidity and mortality.[5–7] The age of individuals, duration of exposure to hyperglycemia and the time of diagnosis contributes to development of the chronic complications of diabetes.[8] Diabetic nephropathy (DN) is a major cause of end-stage renal disease (ESRD) which affects 20–30% diabetic patients. It can take many years to develop.[9] It affects approximately one-third of individuals with diabetes.[10] DN is a clinical syndrome characterized by sustained reduction in eGFR below 60 ml/min/1.73 m^2 and persistently high urinary albumin-to-creatinine ratio $\geq$30 mg/g along with presence of diabeticretinopathy.[11] Elevated glucose levels, high blood pressure long duration of diabetes, obesity, and dyslipidemia can increase the progression of DN.[12] The exact mechanisms of DN is not clearly understood. Uncontrolled glucose and blood pressure and unbalanced renin-angiotensin-aldosterone system (RAAS) could be the factors that make the patient enter into ESRD.[13]

To improve the quality of life and to reduce the progression of diabetic nephropathy early diagnosis and proper management is necessary.[14] The management of

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the contributing risk factors is essential for preventing the decline in renal function.[12] A decline in progression of disease has been observed in many countries because of the increased awareness by primary care physicians about chronic kidney disease (CKD), better control of hypertension and hyperglycemia and the implementation of protocols and clinical practice recommendations about the detection, prevention and treatment of CKD.[15]This paper provides a comprehensive review of the important aspects of diabetic nephropathy with added emphasis on its pathophysiology, prevalence, and management.

1.1. Pathophysiology:[16,17]

The pathophysiology and development of Diabetic Nephropathy (DN) are probably due to results of interactions between metabolic and hemodynamic pathways, which are often disrupted in diabetes, and are highlighted as below:

1.2. Hemodynamic Pathway

Increased angiotensin II levels and endothelin-1 (ET-1) cause efferent arteriolar vasoconstriction due to activation of the RAS. Elevated levels of angiotensin II leads to increased albuminuria and nephropathy.ET-1 is believed to activate receptors that directly increase glomerular permeability, hence aggravating albuminuria and leading to progression of DN.

1.3. Metabolic Pathway

Glycolysis is the biochemical pathway in which cells break down glucose to generate energy. Increased glycolysis upregulates four specific entities: the polyol pathway, hexosamine pathway, production of advanced glycation end products (AGEs), and activation of protein kinase C (PKC) due to hyperglycemia.

1.4. The Polyol Pathway

Glucose is first converted to sorbitol then to fructose. The reduction of glucose to sorbitol results in decreased levels of intracellular NADPH which in turn results in decreased levels of GSH (glutathione). Decreased levels of GSH are believed to be associated with increased intracellular oxidative stress which in turn leads to increased cell stress and apoptosis. Finally, the end product of the polyol pathway, fructose, recently emerged as a potential nephrotoxin.

1.5. The Hexosamine Pathway

In the third step of glycolysis, fructose-6-phosphateis converted to glucosamine-6-phosphate by the enzyme glutamine: fructose-6-phosphate amidotransferase (GFAT). To increase the transcription of inflammatory cytokines tumor necrosis factor-α (TNF-α) and transforming growth factor-β1 (TGF-β1), glucosamine-6-phosphate is used as a substrate. Renal cell hypertrophy and increased mesangial matrix components, the two pathologic hallmarks of DN are in turn promoted by increased TGF-β1 levels.[16]

1.6. Advanced Glycation End Products (AGEs)

The elevated levels of glucose start forming covalent adducts with plasma proteins through a non-enzymatic process known as glycation.Glycation of proteins such as plasma proteins and collagen which is induced by high glucose levels leading to AGEs are the major causes of different diabetic complications. AGEs bindto proinflammatory receptors and then activate IL-1, IL-6 and TNF-α and increased generation of reactive oxygen species (ROS).

1.7. The PKC Pathway

Oxidants such as H_2O_2 and mitochondrial superoxide induced by increased glucose levels leads to activation of PKC. Multiple PKC isoforms that are changed by diabetes are responsible for the many abnormal vascular and cellular processes and deregulations, including endothelial dysfunction, vascular permeability, angiogenesis, cell growth and apoptosis, changes in vessel dilation, basement membrane thickening and extracellular matrix expansion, enzymatic activity alterations such as mitogen-activated protein kinase (MAPK), cytosolic phospholipase A2 (PLA2), Na^+–K^+–ATPase.

1.8. Staging of diabetic nephropathy

1.9. Pattern of diabetic nephropathy

1.10. Management of diabetic nephropathy in T2DM

The management of T2DM with DN can be achieved by following approaches:

1.11. Non pharmacological treatment:[30]

In addition to the use of oral antidiabetic medication, most patients will require insulin for control of diabetes at severe stages. Therefore, all patients should follow non pharmacological treatment option. These are medical nutrition interventions, change of lifestyles and bariatric surgery.

1.12. Medical nutrition therapy (MNT):[31]

Diets with low glucose level have also shown benefits in managing T_2DM and reducing complications.MNT controls blood glucose, hypertension, dyslipidemia and obesity.From various MNTs, the MD (Mediterranean diet) was associated with the largest reductions in HbA1c (-

Table 1: Staging of DN

Stages	DN Staging Tervaert et al. [18]	DN Staging Gheith et al [19]
Stage 1	Glomerular basement membrane thickening	From onset to 5 years, borderline GFR, no albuminaria, hypertension. But kidney size increased by 20% along with an increase in renal plasma flow
Stage 2	Mild or severe mesangial expansion	From 2 years after onset with basement membrane thickening and mesangial proliferation Normal GFR and no clinical symptoms
Stage 3	Nodular sclerosis	5-10 years after onset with or without hypertension, with glomerular damage and microalbuminaria (30-300mg/day)
Stage 4	Advanced diabetic glomeruloschlerosis that includes tubulointerstitial lesions and vascular lesions	Irreversible proteinuria, sustained hypertension and GFR below 60ml/min/1.73m^2
Stage 5	-	End stage kidney disease with GFR <15ml/mim/1.73m^2

Table 2: Pattern of diabetic nephropathy in some countries: [20–24]

Parameters	Iraq	Korea	East Uganda	Oman	India
Year	2016	2014	2017	2012	2017
Recruitment period	Jan -May 2013	2011		Sep 2010- June 2011	Sep 2014 -May 2015
Study design	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study
Age	25-54yrs	>30yrs	> 20yrs	>20yrs	>35yrs
Subjects	Men &Women-224	Men &Women-660	M: 315 F: 640	Men &Women- 699	M: 1620 F:1380
	16.1%	MU: 22% MAU: 4.6%	15.2%	M: 51.6% F:36.5 %	48.4%

Table 3: Pattern of diabetic nephropathy in India: [25–29]

Parameters	Karnataka	West Bengal	Gujarat	Kerala	Kashmir
Year	2018	2017	2018	2018	2016
Recruitment period	Jan – June 2017		Apr-Nov2016	Feb-June 2017	May-Oct 2015
Study design	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study
Age	>40 yrs	18 -60 yrs	>18yrs	40-70yrs	30-70yrs
Subjects	Men &Women-200	Men &Women-250	M-51 F-49	Men &Women-117	M-56 F-44
	NU: 71 % (142) MU : 29% (58)	TP: 85 (34%) MU: 69 (81 %) MAU: 16 (19%)	43%	45.3%	MU:44% MAU:6%

0.47%) and bodyweight (-1.84 kg on average).The MD is enriched with high amount of olive oil, vegetables, legumes, whole grains, fruits and nuts, a moderate amount of poultry and fish, a low amount of whole fat dairy products and red meat, and low to moderate amounts of wine.

1.13. Physical activity: [31]

The improvement in insulin sensitivity results from exercise lasts for 24 -72 hours (1-3 days). Diabetes patients should perform regular exercise with not more than 2 successive days without physical activity to balance the benefits of insulin sensitivity.

1.14. Bariatric surgery: [31]

The restriction in calorie intake achieved directly by surgical procedures and indirectly by self-adaptation to restrict post-prandial dumping syndrome, mal-absorption of nutrients, increase in beta cell mass and improvement in insulin production, and changes in the gut microbiome are some of the mechanisms that play important roles in control and remission of T2DM in patients undergoing bariatric surgical procedures.

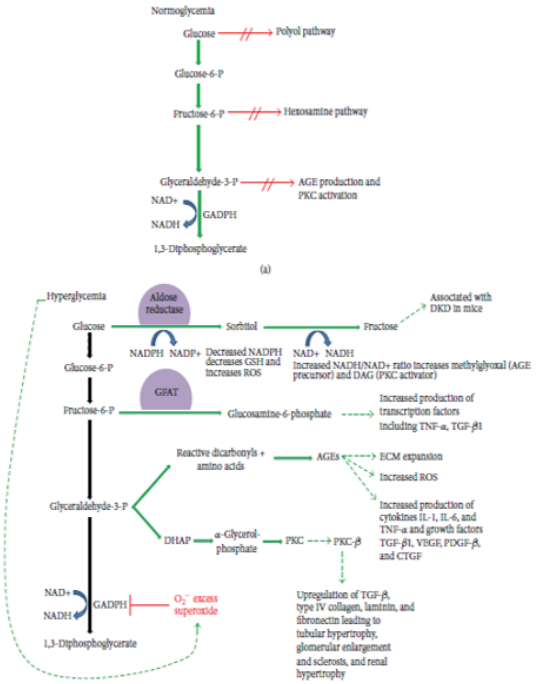

Fig. 1: (a) In normoglycemic conditions, glycolysis (i.e the breakdown of glucose to generate energy) proceeds in a well-defined manner without diverting its course into the multiple pathways involved in diabetic nephropathy. (b) However, in hyperglycemic conditions, elevated glucose levelspromote the activation of excess superoxides which hinders the enzyme GADPH which in turn restricts glycolysis from proceeding down its usual sequence.[16]

1.15. Sleep hygiene:[31]

Seven hours of uninterrupted sleep is vital for normal metabolic and hormonal regulations of the body. The sleep deprivation results in decreased production of brain glucose and there will be sequential hormonal dysregulation, and that can result in the development of diabetes.

1.16. Pharmacological treatment:[31]

Pharmacological interventions of diabetic nephropathy include control of BP, control of blood sugar, use of hypolipidemic agents, quitting smoking, diet control, and use of vitamin D receptor agonists.

1.17. Glycemic control

The American Diabetes Association advocates that glycemic targets should be adjusted to age, comorbidities, and life expectancy of individual patients. Similarly, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend maintaining a target HbA1c of about 7.0% to prevent or delay progression of the microvascular complications of diabetes. However, patients with diabetes and CKD who are at risk of developing hypoglycemia should not be treated to an HbA1c target of< 7.0%.[11]

1.18. BP Control

For management of hypertension, the Eighth Joint National Committee (JNC-8) approved initiation of pharmacologic treatment at a BP 140/90 mmHg, with treatment goals less than these levels. Initial antihypertensive treatment, in the general hypertensive population, including those with diabetes, may include a thiazide-type diuretic, a calcium channel blocker, an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB). Irrespective of diabetes status, the same BP targets are recommended for all patients with CKD. The KDIGO guidelines recommend use of an ACE inhibitor or an ARB and a BP goal 130/80 mmHg in all patients with CKD and albuminuria irrespective of diabetes status. There is distinct evidence that renin-angiotensin system blockade with either an ACE inhibitor or an ARB reduces the progression of DKD in patients with macroalbuminuria. Combination therapy on the other hand (an ACE inhibitor and an ARB administered together) increases the risk of serious side effects, primarily hyperkalemia and AKI, and offers no clinical benefit.[11]

2. Dyslipidemia

2.1. Hypolipidemic treatment

Statins are the first line therapy for all patients with DN. Although they have a significant impact on the risk of atherosclerotic cardiovascular disease in CKD patients, their effect, if any, on CKD progression is minimal. Statins did not significantly impact either stroke or all-cause mortality in diabetic adults with CKD when compared to placebo. Fenofibrate treatment helped convert microalbuminuria to normoalbuminuria in DN patients compared to placebo.[31] Combination therapy (simvastatin plus fenofibrate) had a high impact on the suppression of the development of both microalbuminuria and overt proteinuria in patients with type 2 diabetes, compared to simvastatin alone. This implies that fenofibrate has protective effects against DN. Simvastatin-ezetimibe combination therapy had significant impact on the reduction in LDL-C and also reduced atherosclerosis-related events by 17% in comparison to patients who received a placebo. The ezetimibe and simvastatin combination did not show a decline in renal function.[35]

3. Conclusion

This review provides a brief understanding of the various pathways involved in the pathophysiology of diabetic

Table 4: Currently available medication with dosage for glycemic control: [32,33]

S.No	Medications	Recommended dosing with impaired GFR
1.	Metformin	eGFR is ≥45–59 ml/min/1.73 m^2- use with caution. eGFR is ≥30–44 ml/min/1.73 m^2 - again use caution with dosing (≤1000 mg daily or using a 50 % reduction), avoid newly initiating metformin in patients with this level of CKD. eGFR< 30 ml/min/1.73 m^2 – avoid use
2.	Sulphonyl ureas	risk of hypoglycaemia hence with eGFR< 60 ml/min/1.73 m^2 - Glyburide should be avoided, Glimepiride should be used with caution, glipizide is generally considered the sulfonylurea of choice in this population and no dose adjustment needed.
3.	Thiazolidinediones (TZDs)	Nearly completely metabolized by the liver hence no dose adjustment needed but still avoided in DKD due to side effects such as refractory fluid retention (leading to heart failure) and increased fracture risk.
4.	Glinides	increased risk of hypoglycemia due to decreased renal clearance, eGFR < 60 ml/min/1.73 m^2 - nateglinide should not be used, repaglinide Is safe(eGFR< 30 ml/min/1.73 m^2 – exercise caution and start at the lowest dose i.e 0.5 mg)
5.	Alpha-glucosidase inhibitors Acarbose Miglitol	Avoid if eGFR <30 Avoid if eGFR< 25
6.	DPP-4 inhibitors Sitagliptin	100 mg daily if eGFR >50 50 mg daily if eGFR 30–50 25 mg daily if eGFR 50
	Saxagliptin	5 mg daily if eGFR >50 2.5 mg daily if eGFR ≤50
	Linagliptin	No dose adjustment required
	Alogliptin	25 mg daily if e GFR >60 12.5 mg daily if e GFR 30–60 6.25 mg daily if e GFR <30
7.	SGLT2 inhibitors Canagliflozin	No dose adjustment required if e GFR ≥60 100 mg daily if e GFR 45–59 Avoid use if e GFR <45
	Dapagliflozin	Avoid use if e GFR <60
	Empagliflozin	No dose adjustment required if e GFR ≥45 Avoid use if e GFR<45

Table 5: Drug regimen and their deleterious effects in hypertension patients with DKD: [34]

Drugs and their combinations in established DKD	Current information
ACE inhibitor + ARB	increased risk of hyperkalemia and acute kidney injury, no benefit on
Direct renin inhibitor (aliskiren) + an ACE inhibitor	higher renal and cardiovascular event
MR blockers (spironolactone) + ACE inhibitor/ ARB.	Greater reductions in BP and albuminuria but risk of hyperkalemia (highest risk for hyperkalemia have an eGFR < 45 mL/min and a baseline serum potassium level of 4.5 mEq/L) and hence to be used with frequent monitoring.
Potassium binding agents such as patiromer and ZS-9	Reduce the risk of hyperkalemia, may allow for future investigation of the various RAAS combinations.
Calcium channel blockers (CCBs), e.g diltiazem and verapamil	May be used as first-line therapy in patients intolerant of ACE inhibitors and ARBs or as second-line agents in combination with an ACE inhibitor or ARB, may reduce higher-level albuminuria without an RAAS blocker.
Amlodipine and nifedipine	effective antihypertensive agents but do not reduce proteinuria and cause dose-dependent peripheral edema as a side effect, should only be used in conjunction with an RAAS blocker because they do provide benefit in this setting and side effects can be reduced.
CCBs+ ACE inhibitor or ARB	They help to reduce blood pressure while preserving kidney function in people with diabetes.
Thiazide or thiazide-like diuretics (e.g., chlorthalidone and indapamide)	To be used with ACE inhibitors/ ARBs/ CCBs, any of which may be used to initiate BP-lowering therapy, have the most significant BP-lowering effect in advanced CKD (eGFR >30 mL/min/1.73 m2). Multiple side effects present but their use with management of these side effects does not adversely affect outcomes.
Thiazide diuretics +ACE inhibitor or ARB	Lowers risk of hyperkalemia, and patient's pill burden.
Long-acting loop diuretics (e.g., torsemide)	Effective at an eGFR < 30 mL/min/1.73 m2 and helpful in volume management.
	mortality and cardiovascular events

nephropathy. Sustained reduction in eGFR below 60 ml/min per1.73 $m^2$and persistently high urinary albumin-to-creatinine ratio $\geq$30 mg/g along with clinical features, such as diabetes duration and presence of diabetic retinopathy are the characteristics used to clinically identify DN. Hence, other strategies of treatment like BP control and dyslipidemia control etc. are still required to decrease the burden of DKD and prevent its progression to end stage renal disease (ESRD). Glucose control in diabetes patients should be individualized according to the patient's alert of hypoglycemia, underlying CKD or cardiovascular disease status, and age.

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None.

5. Conflict of Interest

None.

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