Review Article

Management of diabetic kidney disease: Recent advances

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A B S T R A C T

Diabetic kidney disease, in present days, is being recognized as the commonest cause of end stage renal disease. Though there is no absolute therapy for diabetic kidney disease, decades of hard work has recognized some modifiable factors that can prevent its progression. This article is an attempt to review some recent advances in the understanding, diagnosis and management of diabetic kidney disease

Key words: Chronic kidney disease, anti hyperglycemic

INTRODUCTION

Advancement in understanding of a disease process, may sometime, outscores advancement in technology and pharmacology. Diabetes and diabetic kidney disease (DKD) are no exception to this rule. Emerging data from large interventional trials and outcome studies has helped us in designing better protocols for evaluation and management of DKD, a brief of which is being discussed here.

FIRST EVALUATION OF DKD

Chronic kidney disease (CKD) is not only present in ~40% patients with type 2 diabetes, but also in 18% of pre-diabetics. Efforts for early detection, staging and prevention of DKD should therefore begin right from the beginning. Recently, kidney disease outcomes quality initiative has recommended a combination of serum creatinine (and estimated glomerular filtration rate [eGFR]) and spot albumin: Creatinine ratio (ACR), both, for

predicting relative risk of DKD in a particular individual, since evaluation of either of them alone carries many inherent limitations.[1] The first observation of reduced eGFR should always be reconfirmed within 2 weeks to exclude acute and reversible renal injury.[2]

DIFFERENTIATING STABLE VERSUS PROGRESSIVE DKD

Contrary to normal belief, microalbuminuria in type 1 diabetes is not always a progressive disease and with improving glycemic control, has been observed to remain stationary (in 30-40%)[3] or may even revert back to normal (in up to 40% cases)[4] over 5-10 years of follow-up. Blanket advice for all cases with DKD is, therefore, not justifiable. Since there is a continuum of risk of cardiovascular disease with rising albuminuria and falling GFR, it is being advocated to differentiate individuals with progressive CKD (which is defined as a decline in GFR of >5 ml/min/1.73 m² within 1 year or >10 ml/min/1.73 m² within 5 years) against those with stable ones. It warrants GFR estimation to be repeated at least thrice over initial 3 months and annually thereafter and ACR at least twice in the first 3-6 months and annually thereafter. It's more important for young individuals with long life expectancy who may require serious interventions for a progressive disease rather than for elderly with > 70 years of age with stable eGFR of as

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low as 45-59 ml/min/1.73 m² (without any other evidence of kidney damage), which is considered to be benign and can just be supervised closely. Moreover, GFR estimation become less accurate when eGFR > 60 ml/min/1.73 m² and therefore less reliance should be paid on numerical value of eGFR >60 and a rise in serum creatinine level by >20% of the previous one should be taken as the criteria for deterioration in renal function.[2]

TARGETS OF MANAGEMENT OF DKD

Recently, it is being observed that "more is not always better" in terms of overall outcomes of patients where more and more drugs are being poured in to achieve tighter targets, with all patients. DKD results from an inter-play between hyperglycemia, hypertension and increased levels of angiotensin II in genetically susceptible individuals and each of them needs independent interventions. Intensive control of hyperglycemia has been shown to effectively prevent development of microalbuminuria and may also help in preventing macroalbuminuria, but evidence whether it reduces a decline in GFR is sparse. Since patients with DKD are at increased risk of hypoglycemia and since ADVANCE, ACCORD, VADT failed to show any additional benefits of more intensive glycemic control on creatinine-based estimates of GFR, glycated hemoglobin is still targeted at <7% and not <6.5 in these subsets of patients. One may opt for even less tighter targets for patients with DKD stage 3-5, during dialysis or for those with limited life expectancy.[1] One should strive to achieve a blood pressure (BP) of <130/80 mm Hg, preferably with inhibition of the renin-angiotensin-aldosterone system (RAAS) and a lower systolic BP target (110-130 mm Hg) should preferably be reserved for patients with persistent high-level macroalbuminuria (ACR > 500 mg/g).[2]

ANTI-HYPERGLYCEMIC THERAPIES

Use of metformin, the first line anti-hyperglycemic agent, is long been contraindicated in DKD since it undergoes renal excretion and is accumulated in DKD. Metformin clearance decreases by about 75% between GFR 60 and 30 ml/min and hence there is always an apprehension that it may accumulate, block gluconeogenesis and cause lactic acidosis in such circumstances. Contrary to this theoretical belief, metformin serum concentration in patients with GFR between 60 and 30 ml/min, has been found to be only two fold higher than those with normal renal functions, but still much lower (~3%) than when it is reported to produce lactic acidosis.[5] In patients with eGFR of 30-60 ml/min/1.73 m², who continued to consume metformin even in the presence of other risk factors for lactic acidosis, the later was still found to be rare.[6] In a

recent Cochrane review of 347 prospective comparative trials or observational cohort studies, use of metformin, when compared with other anti-hyperglycemic therapies, was not found to be associated with an increased risk of lactic acidosis.[7] In fact, when used in patients with eGFR of 30-60 ml/min/1.73 m² for over 2 years, use of metformin was associated with 36% lower mortality versus other glucose lowering agents. Similar reduced risks for all-cause mortality has also been observed in patients with an eGFR of 45-60 and >60 ml/min/1.73 m² as well. No benefit, but no harm either, has also been observed with metformin therapy in patients with an eGFR of 30-45 ml/min/1.73 m². Restricting metformin below GFR of 60 ml/min/1.73 m², is therefore, increasingly being considered as questionable. British National Formulary and the Japanese Society of Nephrology has recently proposed that metformin use may be re-evaluated only when GFR falls below 45 ml/min/1.73 m² and stopped only when less than 30 ml/min/1.73 m².[8,9]

Amongst second generation sulfonylureas, glipizide is the preferred compound since its metabolite is inactive, which when retained with falling GFR, does not cause hypoglycemia. Even then its doses should be reduced with DKD to prevent hypoglycemia. Glipizide and gliclazide can even be used during dialysis, keeping a watch on possible hypoglycemia. Amongst meglitinides, active metabolites of nateglinide (but not repaglinide) are retained in DKD. Repaglinide, therefore, is considered to be safer in DKD, until GFR falls <30 ml/min/1.73 m². Thiazolidinediones have shown to possess inherent albuminuria reducing properties and thus may be useful over other anti-hyperglycemic agents in DKD, but are best avoided due to fluid retention and possible fluid overload. Acarbose is only minimally absorbed, but serum concentrations of the drug and its metabolites increase significantly with falling kidney functions, which may cause possible hepatic damage. Miglitol has greater systemic absorption and undergoes renal excretion. Both should not be used in patients with GFR <30 ml/min/1.73 m².[1]

All dipeptidyl peptidase 4 (DPP-4) inhibitors except linagliptin needs dosage adjustment (~50%) with fall in GFR below 50 ml/min/1.73 m². Sitagliptin dose should further be halved (25%) when GFR falls below 25 ml/min/1.73 m². Linagliptin is unique amongst all DPP-4 inhibitors in having only <5% of its elimination through kidneys. It, therefore, does not show accumulation in DKD and has been found to be effective as well as safe, even in end-stage renal disease.[10] Exenatide has been reported to be associated with acute kidney injury or acceleration of DKD progression, if already present. It is therefore, not recommended for use with a GFR

<30 ml/min/1.73 m². Liraglutide is not metabolized through kidneys, yet is recommended not to be used with a GFR <60 ml/min/1.73 m².[1]

One-third of insulin degradation is carried out through kidneys and hence half-life of the insulin increases with impairment of kidney function. The common practice of avoidance of long acting insulin or reducing the dose of regular insulin is not being recommended unequivocally these days. This is because of the simultaneous impairment in insulin sensitivity with DKD.[1] Insulin lispro has been unique amongst all in having a blunting effect on postprandial hyperfiltration and albumin excretion, which may have its unique implications in DKD.[11]

ANTI-HYPERTENSIVE THERAPIES

RAAS inhibition has proven nephroprotective effects, but it is still not recommended in normotensive, normoalbuminuric diabetic individuals. To prevent or retard progression of albuminuria in DKD, angiotensin converting enzyme (ACE)-inhibitors (particularly in type 1 diabetes) or angiotensin receptor blockers (ARBs) (particularly in type 2 diabetes) are the first choice of therapy if either of microalbuminuria or hypertension is present.[1] The only indications for withdrawal of ACE-I/ARBs in DKD are a rise in serum potassium >6.0 mmol/L, fall in eGFR by >25% or a rise in serum creatinine by >30%, in the absence of dehydration or concomitant use of NSAIDs.[2] Cilazapril and benazepril are two novel ACE-I that possess additional nephroprotective properties of suppression of the expression of glomerular vascular endothelial growth factor, intracellular adhesion molecule and inhibition of P42/44 mitogen activated protein kinase (MAPK) pathway in experimental diabetic rats.[12]

A combination of ACE-I and ARB has earlier been suggested for persistent hyperalbuminuria over 500 mg/g of creatinine with well-controlled BP on ACE-I/ARB monotherapy.[1] However, demonstration of the risk of hyperkalemia or deterioration in renal functions in ONTARGET trial has put this policy on hold.[13] Similarly, after initial observations of further reduction in albuminuria, combination of ACE-I/ARB with direct renin inhibitor aliskiren has also been contraindicated after ATTITUDE trial results, which showed an increased risk of renal impairment, hypotension, hyperkalemia and stroke in patients with DKD.[1]

If albuminuria persists along with uncontrolled BP on ACE-I/ARB monotherapy, non-dihydropyridine calcium channel blockers (diltiazem or verapamil) could be a better choice over combination of ACE-I and ARB. The combination of trandolapril with verapamil, has been shown its efficacy in this regard.[12] Dihydroxypyridine derivatives like amlodipine, should only be used in DKD in the presence of concurrent RAAS inhibition since taken alone, it has been shown to worsen albuminuria.[1]

Diuretics are the preferred add on agent after ACE-I or ARB in the management of hypertension with DKD if proteinuria is not the issue.[1] Aldosterone receptor antagonists (such as spironolactone) possess independent renoprotective effects. Eplerenone, a novel aldosterone receptor antagonist has been shown to improve GFR and inhibit glomerulosclerosis in OLETF rats. Moreover, the combined treatment of eplerenone with enalapril markedly decreased the renal expression of transforming growth factor-beta (TGF-b), type IV collagen and plasminogen activator inhibitor-1 in OLTEF rats. FAD286, an aldosterone synthase inhibitor has been shown to downregulate the renal expression of NFkB, interleukin-6 mRNA, TGF-b messenger ribonucleic acid (mRNA), fibronectin and type IV collagen and reduce the occurrence of albuminuria in diabetic rats with nephropathy.[12]

LIPID LOWERING THERAPY

Lowering low-density lipoprotein cholesterol (LDL-C) with statin-based therapies in DKD has been shown to reduce risk of major atherosclerotic events (but not all-cause mortality). Statin should, therefore, be used for cardiac prevention in patients with DKD stages 1-4 or after renal transplantation who have LDL-C > 100 mg/dL. Atorvastatin may be used in its full therapeutic doses (10-80 mg/dL) up until DKD stage 5. Simvastatin require doses reduction (5-20 mg/dL) in DKD stages 4 and 5, whereas rosuvastatin dose should be halved (up to 20 mg/d) in DKD stage 3 and to its quarter (up to 10 mg/dL) in DKD stage 4 and 5. Doses of all should be reduced to their quarter after renal transplantation.[1] Results of AURORA trial have found no survival benefits of initiation of statin therapy in patients on maintenance hemodialysis and actually observed an increased risk of hemorrhagic stroke, therefore, initiation of statin therapy during hemodialysis is not recommended.[14] Since there is always a concern about myopathy with higher doses of statins, especially in patients with DKD, concurrent use of ezetimibe is also advisable to achieve equivalent LDL-C reduction with lower doses of statins.[15] Even though, antiplatelet therapy (low dose aspirin) carries a minor risk of gastrointestinal hemorrhage, it should always be continued for secondary prevention with DKD.[2]

On the Horizon

TGF-b, a fibrogenic cytokine plays a key role in the development of DKD and anti-TGF-b2 IgG4, circular antisense TGF-b oligodeoxynucleotides (ODNs) or soluble human TGF-b type II receptor has been shown to produce renoprotective effect in animal models.[16]

Advanced glycation end products (AGEs) are involved in the induction of glomerular extra-cellular matrix accumulation and glomerular hypertrophy by upregulating the expression of type IV collagen and TGF-b in diabetic mice. In addition, AGEs stimulate collagen mRNA expression by activating protein kinase C (PKC) and upregulating TGF-b1 in cultured human mesangial cells. Inhibition of renal formation of AGEs through AGE inhibitors such as OPB-9195, ALT-946, ALT-711, aminoguanidine, TM2002 and LR-90 as well as combination of AGE inhibitor with ACE inhibitor (aminoguanidine with perindopril) has been shown to offer renoprotection by reducing the occurrence of albuminuria in diabetic hypertensive rats.[17]

Protein kinase C through activating MAPK increases the expression of fibronectin in mesangial cells and damages the glomeruli of kidney. Inhibitor of PKC, ruboxistaurin (LY333531), alone or with perindopril can reduce albuminuria and glomerulosclerosis in hypertensive rats with DKD.[12,18]

Renin upregulates the gene expression of TGF-b in mesangial cells of the rat kidney via activation of extra-cellular regulated kinase 1/2 pathways.[19] Treatment with aliskiren, a novel renin inhibitor was noted to attenuate the progression of DKD in animal studies, but on the contrary was found to be harmful in human studies.[1]

Rho/Rho-kinase pathway is involved in upregulation of TGF-b, CTGF and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the diabetic kidney. Fasudil, a selective Rho-kinase inhibitor, has been found to attenuate the development of DKD by inhibiting the renal upregulation of TGF-b, TGF and NADPH oxidase in rats.[20]

References

1. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850-86.
2. NICE guidelines 73, September 2008.
3. de Boer IH, Rue TC, Cleary PA, Lachin JM, Molitch ME, Steffes MW, et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: An analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med 2011;171:412-20.
4. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285-93.
5. Frid A, Sterner GN, Löndahl M, Wiklander C, Cato A, Vinge E, et al. Novel assay of metformin levels in patients with type 2 diabetes and varying levels of renal function: Clinical recommendations. Diabetes Care 2010;33:1291-3.
6. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: Reconsideration of traditional contraindications. Eur J Intern Med 2002;13:428.
7. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010:CD002967.
8. British National Formulary. Available from: http://www.bnf.org. [Last accessed on 2011 Nov 15].
9. Japanese Society of Nephrology Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012. Tokyo, Japan: Tokyo Igakusya; 2012. (In Japanese).
10. Newman J, McGill JB, Patel S. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment. Poster: 821, 47th European Association for the Study of Diabetes Annual Meeting, Lisbon, Portugal, 12-16 September, 2011.
11. Ruggenenti P, Flores C, Aros C, Ene-Iordache B, Trevisan R, Ottomano C, et al. Renal and metabolic effects of insulin lispro in type 2 diabetic subjects with overt nephropathy. Diabetes Care 2003;26:502-9.
12. Balakumar P, Arora MK, Ganti SS, Reddy J, Singh M. Recent advances in pharmacotherapy for diabetic nephropathy: Current perspectives and future directions. Pharmacol Res 2009;60:24-32.
13. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. Lancet 2008;372:547-53.
14. Holdaas H, Holme I, Schmieder RE, Jardine AG, Zannad F, Norby GE, et al. Rosuvastatin in diabetic hemodialysis patients. J Am Soc Nephrol 2011;22:1335-41.
15. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): A randomised placebo-controlled trial. Lancet 2011;377:2181-92.
16. Benigni A, Zoja C, Campana M, Corna D, Sangalli F, Rottoli D, et al. Beneficial effect of TGFbeta antagonism in treating diabetic nephropathy depends on when treatment is started. Nephron Exp Nephrol 2006;104:e158-68.
17. Izuhara Y, Nangaku M, Takizawa S, Takahashi S, Shao J, Oishi H, et al. A novel class of advanced glycation inhibitors ameliorates renal and cardiovascular damage in experimental rat models. Nephrol Dial Transplant 2008;23:497-509.
18. Kelly DJ, Buck D, Cox AJ, Zhang Y, Gilbert RE. Effects on protein kinase C-beta inhibition on glomerular vascular endothelial growth factor expression and endothelial cells in advanced experimental diabetic nephropathy. Am J Physiol Renal Physiol 2007;293:F565-74.
19. Huang Y, Noble NA, Zhang J, Xu C, Border WA. Renin-stimulated TGF-beta1 expression is regulated by a mitogen-activated protein kinase in mesangial cells. Kidney Int 2007;72:45-52.
20. Kikuchi Y, Yamada M, Imakiire T, Kushiyama T, Higashi K, Hyodo N, et al. A Rho-kinase inhibitor, fasudil, prevents development of diabetes and nephropathy in insulin-resistant diabetic rats. J Endocrinol 2007;192:595-603.