
Review

Prevention of Diabetic Kidney Disease in the Light of Current Literature

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Abstract

Diabetes is a rapidly growing problem of the community health. The resulting morbidity and mortality are responsible for the complications of diabetes. Nephropathy caused by diabetes often causes serious morbidity and mortality. In this review, we discuss the current approaches to prevent diabetic nephropathy based on the available literature evidence.

Keywords: nephropathy, novel approaches, diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is one of the rapidly spreading illnesses universally [1]. When the macro- and microvascular complications develop, problems related to diabetes are multiplied. Simply, diabetic microvascular complications contain nephropathy, retinopathy, and neuropathy. Renal and cardiovascular complications are the most problematic faces of T2DM. One of the goals of diabetes treatment is to prevent morbidity and mortality due to these complications.

Lifestyle Modifications

Treatment is based on controlling blood glucose and blood pressure levels pharmacologically in an ailment that is firmly related to lifestyle components such as bad diet habits, stationary and sedentary life [2]. One of the most important element of diabetes care should compose dietary interventions [1]. Nutrition information helps keep blood sugar levels optimal in patients with T2DM [3]. Increasing nutritional knowledge and experience provides a balanced approach to the care of T2DM [3]. Decreasing hemoglobin A1c (HbA1c) can be presented along with the oral anti-diabetic drugs with patient education programs such as medical nutrition therapy (MNT). Individualized MNT was found effective in decreasing HbA1c level in patients diagnosed with pre-

diabetes [4]. Regular movement prevents disease progression in subjects with impaired glucose tolerance [5]. The majority of people with T2DM are individuals with weight management problems, and weight loss is an approach which is preferable. Most of the weight-loss initiatives in overweight or obese adults with T2DM result in less than 5 percent weight loss and it would not lead to useful results metabolically. When more than five percent weight loss it can provide positive effects on glycemic control and blood pressure. Achieving this level of weight loss needs concentrated attempts such as energy limitation and tidy physical activity. Losing weight in many diabetics with weight problems is not a realistic approach to primary treatment of meticulous glycemic control. Nutrition therapy for individuals with T2DM should urge a healthy eating behavior, decreased energy intake, orderly and steady physical activity [6]. T2DM develops as a result of a decrease in the sensitivity of insulin receptors. Largely, these diabetic patients have uncontrolled blood sugar levels, obesity and cardiovascular disease. Metabolic correction such as proper diet and scientific supplementation has been suggested as a suitable approach to improve clinical parameters [7]. In addition, attempts as precise metabolic, blood pressure and lipid management is aimed to slow down the loss of renal function. Therefore, to develop new methods to improve the complications of T2DM has become a priority for research. Despite the rapid progress of information on the molecular mechanisms of these complications, effective new treatments are still missing [8]. Despite recent scientific innovations, diabetic nephropathy continues to be a therapeutic problem. Diabetes management, targets a retarded progression of renal function loss by rigorous blood sugar, blood pressure and lipid control. At the same time, diabetes treatment is necessary to be individualised. Meticulous, tight glycemic control reduces microvascular complications in patients with diabetes. On the other hand, meticulous glycemic control has a limited effect on the macrovascular complications or it may lead to increased risk of major

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cardiovascular events [9]. By the way, smoking is a risk factor for the progression of diabetic nephropathy in patients with type 1 diabetes [10]. So, one of the most important initiatives that can be done at this point may be to quit smoking.

Conventional treatments and renal and cardiovascular complications

Insulin and glyburide were observed to be associated with an increased risk of major cardiovascular events. Lachin *et al.* examined differences among rosiglitazone, metformin and glyburide over 5 years [11]. Albumin/creatinine ratio, eGFR, and blood pressure were examined in the patients. The albumin/creatinine ratio was found to slowly increase with metformin. Metformin was found as ineffective in lowering albuminuria and in microvascular protection in the short and long term, respectively. The albumin/creatinine ratio was found to slightly decrease with glyburide during the first 2 years, then increased slowly over time.

Strict control of blood sugar and blood pressure at desired levels prevent the formation and progression of microvascular complications. Albuminuria reducing effects of renin-angiotensin system inhibitors are greater than those of calcium channel blockers. In the ADVANCE study, a combined touch of blood pressure reducing and meticulous glucose control by gliclazide resulted in significant reductions in major renal events and all-cause mortality [12]. During 4.3 years of follow-up, risks of macrovascular and microvascular events, renal events, and death were assessed yearly in this study.

There was no report about the possible role of alpha-glucosidase inhibitors on the progression of diabetic nephropathy. Positive effects of metformin have been shown in the recently diagnosed T2DM with obesity [13]. Metformin lowers both mortality and morbidity in T2DM patients probably due to its cardioprotective property that is independent of its hypoglycemic effect, and not produced by sulphonylureas or insulin [14]. Despite this positive cardiovascular effects in patients with T2DM, there is no evidence of nephropathy reducing effect of metformin.

Abdominal obesity, metabolic syndrome, type 2 diabetes, cardiovascular disease and microvascular diabetic complications are all closely connected with chronic low grade inflammation. Likewise, glucose-lowering agents could additionally contribute to improved outcomes via their anti-inflammatory effects [15]. Since both agents are considered as insulin-sparing or insulin sensitizers, most of the studies have used metformin and pioglitazone for this purpose. Both agents seem to have greater anti-inflammatory activity than sulphonylureas or glinides. Metformin and pioglitazone act as AMP-activated protein kinase (AMPK) activator and peroxisome proliferator-activated receptor-gamma (PPAR γ) agonists, respectively. Pioglitazones were associated

with very low tissue and serum inflammation. The effect of α -glucosidase inhibitors on inflammatory markers seems quite small. PPAR- γ agonists such as thiazolidinediones make insulin resistance better and contribute to diabetes control in theory.

Externally supplied insulin may also have anti-inflammatory effects. It is necessary to differentiate anti-inflammatory effects due to meticulous glucose control from anti-inflammatory class effect.

The classic nomenclature "diabetic nephropathy" has altered to "diabetic chronic kidney disease" (DCKD) [16]. In the diabetic environment, both metabolic and hemodynamic disequilibriums, principally such as activation of the renin-angiotensin system, create a chain of events. Tubular epithelial cells, podocytes, and mesangial cells can fabricate profibrotic cytokines which contribute to increasing proteinuria during the formation and progression of DCKD [17]. The benefits of intensive glycemic control in type 1 and 2 DM were delaying the commencement and progression of DCKD and decreasing the cardiovascular event rates [17,18]. There is no detailed information specific to renal protective properties of insulin therapy other than the benefits arising from rigorous blood glucose control [17]. On the other hand, as a more advanced technology insulin pump therapy was found to be associated with lesser cardiovascular mortality than multiple insulin injection in type 1 diabetes mellitus [19].

New pharmacological strategies and renal and cardiovascular complications

Dipeptidyl peptidase-4 inhibitors (DPP4-I) reduce blood glucose levels by preserving glucagon-like peptide-1 (GLP-1) from enzymatic breakdown, thereby repairing insulin release induced by food. Since DPP-4 inhibitors have some non-incretin substrates, such as cytokines, chemokines, and neurohormones, there may be some desired and unanticipated vascular effects due to stabilization of these substrates by DPP4-I.

As a result of experimental studies, inhibition of DPP4 is thought to improve inflammation, endothelial function, blood pressure, and lipid metabolism [20]. Potentially beneficial effects were reported on diabetic microvascular complications as a result of the inhibition of DPP4 in experimental studies [21]. Although early clinical knowledge support the protective role of DPP4 inhibitors in diabetic microangiopathy, there is inadequate information claiming that this class of drugs directly prevents or reduces microangiopathy independent of glucose control in humans [21]. Experimental plus early clinical knowledge propose that DPP4 inhibition has the potential to interfere with the onset and progression of microangiopathy [21,22]. DPP4 inhibitors were found to set against vascular smooth muscle cell proliferation which alleviates neointimal hyperplasia in experimental and early clinical studies [21]. Although

experimental and early clinical studies propose that DPP4-I can provide protective effects on vasculature, results of placebo-controlled phase IV trials have yet shown no decline in cardiovascular outcomes [21]. Zheng *et al.* demonstrated that increased plasma DPP4 activities were vigorously associated with type 2 diabetic nephropathy. They suggested these associations do not suggest causality [15]. DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists seem more encouraging in terms of their anti-inflammatory effects [15]. These incretin-based therapies carry out pleiotropic effects. Inhibitors of sodium-glucose cotransporters type 2 (SGLT2) recommend a new route for the handling of T2DM [23]. These promising drugs diminish hyperglycemia by increasing urinary glucose excretion. Ensuing decline in glucotoxicity rehabilitates beta-cell sensitivity to glucose and tissue insulin sensitivity. So, SGLT2 inhibitors meaningful and permanently lower glycated hemoglobin, with the least hypoglycemia risk. The amelioration of glucose control is similar or even slightly better than metformin, sulfonylureas or sitagliptin, with the add-on value by providing meaningful reductions in body weight and blood pressure. Inhibition of SGLT2 by dapagliflozin has moderate and marked effects on uric acid elimination and reduces plasma uric acid levels. Although the inhibition of SGLT2 increases uric acid excretion, the osmotic effect of glucose significantly dilutes the urine, increases the urine flow rate and reduces the likelihood of nidus formation [24]. Inhibitors of sodium-glucose transporter-2 (SGLT-2) may have a "potentially nephroprotective" effect by a number of mechanisms such as restoring the tubuloglomerular feedback mechanism and reducing glomerular hyperfiltration, reducing hyperglycemic inflammation and fibrotic markers, and limiting renal injury. Attention has been suggested in frail geriatric patients and patients with chronic kidney disease. It shows an increased risk of genital fungal infections. Concern about an unforeseen risk of euglycemic ketoacidosis has been lately reported. As an interesting finding, a striking reduction in cardiovascular mortality was reported with empagliflozin which is an example of a SGLT2 inhibitor. Canagliflozin usage in elderly patients and in patients with renal impairment was found to be associated with a decreased efficiency and an increased risk of unwanted effects such as hypotension, further deterioration of renal function, hyperkalemia, hypoglycemia, genital fungal infections, and elevation in the low-density lipoprotein levels [25]. There are no clinical studies about anti-inflammatory effects of sodium-glucose cotransporter type 2 (SGLT2) inhibitors. Although SGLT2 inhibitors may have indirect effects due to reduced glucotoxicity, they do not seem to have a systemic anti-inflammatory activity. Tight blood pressure and glucose control is evenly important. Renin-angiotensin-aldosterone system (RAAS) inhibitor medications only partially protect against the

development and progression of diabetic nephropathy. In contrast, RAAS inhibitors seem to fail as primary prevention therapy in type 1 diabetes [26]. Examples for hopeful targets for neurohormonal activation (inhibition of alternative components of RAAS and neprilysin), tubuloglomerular feedback mechanisms (sodium glucose cotransporter 2 inhibitors and incretin-based therapy) and renal tissue inflammation and fibrosis. DPP4 activity was demonstrated as a predictor for the onset of inflammation and microalbuminuria in Chinese patients without diabetes and it was suggested that this finding might have important implications in understanding the proinflammatory role of DPP4 in microalbuminuria pathogenesis [27]. There was a limited number of reports on the assessment of different antihypertensive agents in preventing nephropathy among type 1 hypertensive diabetics. Many studies display the profit of an ACEI or ARB in preventing or delaying the onset of nephropathy in patients with type 2 diabetes and hypertension [28]. Antiproteinuric effects of RAS combination therapy do not seem to augment the prevention of renal disease progression. Combined use of the RAS inhibiting agents was found to be associated with an increased rate of serious adverse events [29].

Discussion

The common point of microvascular complications is glucose-induced damage. Factors that lead to the progression of diabetic complications may be the formation of oxidative stress, inflammation and advanced glycation end products. Carotenoids (such as lutein, zeaxanthin, lycopene, and astaxanthin) as part of the antioxidant system may contribute to attenuate free radical injury, and reduce inflammation, and they may be used as part of an approach to inhibit the complications associated with diabetes [30]. Recent molecules, such as bardoxolone methyl, pentoxifylline, inhibitors of protein kinase C (PKC), sulodexide, pirfenidone, endothelin receptor antagonists, vitamin D supplements, and phosphate binders have been associated with controversial consequences or significant side effects [29]. GLP-1R agonists have impact over glucose control that may have an indirect role in nephroprotection. GLP-1R agonists induce fullness and reduce body weight. Body weight was not affected by DPP-4 inhibitors. DPP4 inhibitors improve renal microvascular complications to a lesser extent than GLP-1R agonists [31]. Incretin-based therapies may have positive effects on renal hemodynamic, metabolic and inflammatory parameters involved in the pathogenesis of diabetic nephropathy [31]. Both incretin-based drugs have been reported to inhibit renal tubular sodium reabsorption in experimental models and in humans, as well as to reduce glomerular pressure and albuminuria [31]. DPP4 inhibitor linagliptin was found to be associated with a significant reduction

in clinically relevant kidney disease end-points in patients with type 2 DM in a large-scale study [32]. Both the angiotensin converting enzyme and dipeptidyl peptidase-4 are the main enzymes involved in the degradation of bradykinin and substance P, theoretically increasing the risk of angioedema (AO), especially due to the accumulation of vasoactive kinins, when both are pharmacologically inhibited. It has been reported that the use of concurrent ACEI and DPP-4 inhibitor may be associated with a five-fold increase in the risk of AO when compared with ACEI alone. Patients with a known predisposition for angioedema should be carefully considered and monitored when treating [33].

Conclusions

The available early information on the potential cardiorenoprotective role of SGLT2 inhibition in patients with diabetes are supportive. Strong enough trials with renal outcomes are needed to assess the renal protective effects of antihyperglycemic drugs, especially in the cases of dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors. Since glucose, blood pressure and lipid levels are paramount parameters of vascular load, new approaches are needed to adjust these factors vigorously together in T2DM. There is still a long way to go in the field of DN research.

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