GAVIN PUBLISHERS

Journal of Urology and Renal Diseases

Ugur MC, J Urol Ren Dis 2017: J121.
DOI: 10.29011/2575-7903.000021

Review Article

Preventing Diabetic Nephropathy: Novel Therapies on the Horizon and Beyond

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Citation: Ugur MC, Taskiran E, Taskiran D, Akar H (2017) Preventing Diabetic Nephropathy: Novel Therapies on the Horizon and Beyond. J Urol Ren Dis 2017: J121. DOI: 10.29011/2575-7903.000021

Received Date: 06 January, 2017; **Accepted Date:** 23 January, 2017; **Published Date:** 30 January , 2017

Diabetes is one of the rapidly spreading illnesses universally [1]. Treatment is based on controlling blood glucose and blood pressure levels pharmacologically in a 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 opimal in patients with type 2 diabetes (T2DM) [3]. Increasing nutritional knowledge and experience provides a balanced approach to the care of T2DM [3]. Decreasing Hemoglobine A1c (HbA1c) can be provided similar to oral anti-diabetic drugs with patient education programs such as medical nutrition therapy (MNT). But patient compliance is very important for reaching to this target. In a study which determine diabetic patients in our clinic, 28.8% of patients performed regularly, 32.5% of unregularly and %32.5 of no perform was detected the MNT. Also, 18.1 of patients was detected not exercise in a week [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 results in less than 5 percent weight loss and it would not lead to useful results metabolically. When more than five percent weight loss 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, they 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].

When the macro and microvascular complications develop, problems related to diabetes are multiplied. Simply, diabetic microvascular complications contain nephropathy, retinopathy, and neuropathy. One of the goals of diabetes treatment is to prevent morbidity and mortality due to these complications. Renal and cardiovascular complications are the most problematic faces of T2DM. 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 cardiovascular events [9]. Insulin and glyburide was observed to be associated with a increased risk of major cardiovascular events. Lachin et al. examined differences among rosiglitazone, metformin and glyburide over 5 years [10]. The patients were examined with albumin/creatinine ratio, eGFR, and blood pressure. The albumin/creatinine ratio was found to be slowly increased 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 be slightly decreased with glyburide during the first 2 years, then increased slowly over time.

Strictly control of blood sugar and blood pressure at desired levels, prevent the formation and progression of microvascular complications. Reducing albuminuria effects of renin-angiotensin system inhibitors are greater than 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 death [11]. 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 has been shown in recently diagnosed T2DM with obesity [12]. Metformin lowers both mortality and morbidity in T2DM patients probably due to its cardioprotective property that is independent of its hypoglycaemic effect, and not produced by sulphonylureas or insülin [13]. Despite this positive cardiovascular effects in patients with T2DM, there is no evidence of nephropathy reducing effect of metformin. PPAR-γ agonists such as thiazolidinediones make insulin resistance better and contribute diabetes control in theory.

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, respectively 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 [14]. Potentially beneficial effects were reported on diabetic microvascular complications as a result of the inhibition of DPP4 in experimental studies [14].

Although early-clinical knowledge, support the protective role of DPP4 inhibitors in diabetic microangiopathy, there are inadequate information to claim that these class of drugs directly prevent or reduce microangiopathy independent from glucose control in humans [12]. Experimental plus early clinical knowledge propose that DPP4 inhibition, have the potential to interfere with the onset and progression of microangiopathy [14].

DPP4 inhibitors were found to set against vascular smooth muscle cell proliferation which alleviates neointimal hyperplasia in experimental and early clinical studies. 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 [15]. Zheng et al. demonstrates that increased plasma DPP4 activities are vigorously associated with type 2 diabetic nephropathy. They suggested these associations do not suggest causality [16].

Abdominal obesity, the 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 additionaly contribute to improved outcomes via their anti-inflammatory effects [17]. 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 look alike to have greater anti-inflammatory activity than sulphonylureas or glinides. Metformin and pioglitazone acts as AMP-activated protein kinase (AMPK) activator and peroxisome proliferator-activated receptor-gamma (PPARγ) agonists, respectively. Pioglitazones were associated with the most lowered tissue and serum inflammation. The effect of α-glucosidase inhibitors on inflammatory markers seems quite small. DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists seem more encouraging in this regard. These incretin-based therapies carry out pleiotropic effects. Sodium-glucose cotransporter type 2 (SGLT2) inhibitors have no clinical studies on this subject. Although SGLT2 inhibitors may have indirect effects due to reduced glucotoxicity, they do not seem to have a systemic anti-inflammatory activity. 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.

Inhibitors of sodium-glucose cotransporters type 2 (SGLT2) recommend a new route for the handling of T2DM [18]. These promising drugs diminish hyperglycemia by lowering the renal glucose threshold and increasing urinary glucose excretion. Ensuing decline in glucotoxicity rehabilitates beta-cell sensitivity to glucose and tissue insulin sensitivity. So, SGLT2 inhibitors meaningful and permenantly lower glycated hemoglobin, with a least hypoglycemia risk. The amelioration of glucose control is similar or even lightly better than metformin, sulfonylureas or sitagliptin, with the add-on value by providing meaningful reductions in body weight and blood pressure. Attention has been suggested in frail geriatric patients and patients having 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 inhibitors. 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, hyperpotassemia, hypoglycemia, genital fungal infections, and elevation in the low-density lipoprotein levels [19].

The classic nomenclature “diabetic nephropathy” has altered to “diabetic chronic kidney disease” (DCKD) [20]. In the diabetic

environment, both metabolic and hemodynamic disequilibriums, principally such as activation of the renin-angiotensin system, creates 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 [21]. The benefits of intensive glycemic control in type 1 and type 2 DM were delaying the commencement and progression of DCKD and decreasing the cardiovascular event rates [22]. There are no detailed information specific to renal protective properties of insulin therapy other than the benefits arising from rigorous blood glucose control [21]. 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 [23].

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 [24]. 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 for understanding the proinflammatory role of DPP4 in microalbuminuria pathogenesis [25]. There were 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 [26]. 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 [27].

The common point of microvascular complications is glucose-induced damage. Factors that lead to the progression of diabetic complications possibly is 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 reducing inflammation, and they may be used as part of an approach to inhibit the complications associated with diabetes [28]. 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 [28].

By the way, smoking is a risk factor for the progression of diabetic nephropathy in patients with type 1 diabetes [29]. So, one of the most important initiatives that can be done at this point may be to quit smoking.

There are limited number of studies analyzing the effectiveness of glinides on albuminuria or in other words on the progression of diabetic nephropathy [21].

Despite the likely profits of pioglitazone in delaying the progression of DCKD, it is considerable to determine whether the benefits outweighs the risks as heart failure and minimal increase in bladder cancer [21,30,31].

GLP-1R agonists have impacts over glucose control that may be of indirect role for nephroprotection. GLP-1R agonists reduce body weight and induce fullness. Body weight was not affected by DPP-4 inhibitors. DPP4 inhibitors improve renal microvascular complications to a lesser extent than GLP-1R agonists [32]. Incretin-based therapies may have positive effects on renal haemodynamic, metabolic and inflammatory parameters involved in the pathogenesis of diabetic nephropathy [32]. 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 [33].

The available early information on the potential renoprotective role for SGLT2 inhibition in patients with diabetes are supportive. Strong enough trials with renal outcomes are needed to assess the renal protective effects of antihyperglycaemic 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.

References

1. Hołyńska A, Kucharska A, Sińska B, Panczyk M (2015) [The level of nutrition knowledge versus dietary habits of diabetes patients treated with insulin]. Pol Merkur Lekarski 39: 292-296.
2. Simpson KA, Mavros Y, Kay S, Meiklejohn J, de Vos N, et al (2015) Graded Resistance Exercise And Type 2 Diabetes in Older adults (The GREAT2DO study): Methods and baseline cohort characteristics of a randomized controlled trial. Trials 16: 512.
3. Breen C, Ryan M, Gibney MJ, O'Shea D (2015) Diabetes-related nutrition knowledge and dietary intake among adults with type 2 diabetes. Br J Nutr 114: 439-447.
4. Erdem S. Bayrak B. Ugur MC, Orman M, Akar H (2016) Adaptation to

lifestyle changes in patients with type 2 diabetes mellitus FNG & Bilim Tıp Dergisi 2: 243-246.

5. Rossen J, Yngve A, Hagströmer M, Brismar K, Ainsworth BE, et al (2015) Physical activity promotion in the primary care setting in pre- and type 2 diabetes - the Sophia step study, an RCT. BMC Public Health 15: 647.
6. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ (2015) Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet 115: 1447-1463.
7. Miranda-Massari JR, Gonzalez MJ, Fernando AS, Cidre C, Paz IM, et al (2015) Metabolic Correction as a tool to improve diabetes type 2 management. Bol Asoc Med P R 107: 54-59.
8. Pryor R and Cabreiro F (2015) Repurposing metformin: an old drug with new tricks in its binding pockets. Biochem J 471: 307-322.
9. Bell DS, Patil HR, O'Keefe JH2 (2013) Divergent effects of various diabetes drugs on cardiovascular prognosis. Rev Cardiovasc Med 14: 107-122.
10. Lachin JM, Viberti G, Zinman B, Haffner SM, Aftring RP, et al (2011) and ADOPT Study Group. Renal function in type 2 diabetes with rosiglitazone, metformin, and glyburide monotherapy. Clin J Am Soc Nephrol 6: 1032-1040.
11. Zoungas S, de Galan BE, Ninomiya T, Grobbee D, Hamet P, et al (2009) Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. Diabetes Care 32: 2068-2074.
12. Buhse S, Mühlhauser I, Lenz M (2016) The 'Old' Anti-Diabetic Agents: A Systematic Inventory. Endocr Dev 31: 28-42.
13. UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352: 854-865.
14. Avogaro A and Fadini GP (2014) The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications . Diabetes Care 37: 2884-2894.
15. Fadini GP, Albiero M, Avogaro A (2015) Direct effects of DPP-4 inhibition on the vasculature. Reconciling basic evidence with lack of clinical evidence. Vascul Pharmacol 73: 1-3.
16. Zheng T, Liu Y, Qin S, Liu H, Zhang X, et al (2016) Diab Vasc Increased plasma dipeptidyl peptidase-4 activities are associated with high prevalence of diabetic nephropathy in Chinese patients with newly diagnosed type 2 diabetes: A cross-sectional study. Dis Res 13: 127-136.
17. Scheen AJ, Esser N, Paquot N (2015) Antidiabetic agents: Potential anti-inflammatory activity beyond glucose control. Diabetes Metab 41: 183-194.
18. Scheen AJ (2015) SGLT2 inhibition: efficacy and safety in type 2 diabetes treatment. Expert Opin Drug Saf 14: 1879-1904.
19. Toderika Y and Ferguson N (2014) Canagliflozin: a new class of antidiabetic agent targeting the sodium-glucose cotransporter. Cardiol Rev 22: 97-104.
20. Martínez-Castelao A, Navarro-González JF, Górriz JL, de Alvaro F (2015) The Concept and the Epidemiology of Diabetic Nephropathy Have Changed in Recent YearsJ Clin Med 4: 1207-1216.
21. Górriz JL, Nieto J, Navarro-González JF, Molina P, Martínez-Castelao A, et al (2015) Nephroprotection by Hypoglycemic Agents: Do We Have Supporting Data?. J Clin Med 4: 1866-1889.
22. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353: 2643-2653.
23. Steineck I, Cederholm J, Eliasson B, Rawshani A, Eeg-Olofsson K, et al (2015) Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study. BMJ 350:h3234.
24. Lytvyn Y, Bjornstad P, Pun N, Cherney DZ (2016) New and old agents in the management of diabetic nephropathy. Curr Opin Nephrol Hypertens 25:232-239.
25. Zheng T, Baskota A, Gao Y, Tian H, Yang F (2015) Increased plasma dipeptidyl peptidase 4 activities predict new-onset microalbuminuria in association with its proinflammatory effects in Chinese without diabetes: a four-year prospective study. Nephrol Dial Transplant 30: 460-466.
26. Isaacs AN and Vincent AJ (2016) Antihypertensive therapy for the prevention of nephropathy in diabetic hypertensive patients. Clin Pharm Ther 41: 111-115.
27. Dounousi E, Duni A, Leivaditis K, Vaios V, Eleftheriadis T, et al (2015) Improvements in the Management of Diabetic Nephropathy. Rev Diabet Stud 12:119-133.
28. Murillo AG and Fernandez ML (2016) Potential of Dietary Non-Provitamin A Carotenoids in the Prevention and Treatment of Diabetic Microvascular Complications. Adv Nutr 7: 14-24.
29. Feodoroff M, Harjutsalo V, Forsblom C, Thorn L, Wadén J, et al (2015) Smoking and progression of diabetic nephropathy in patients with type 1 diabetes. Acta Diabetol 53: 525-533.
30. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE (2007) Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 298: 1180-1188.
31. Lewis JD, Habel LA, Quesenberry CP, Strom BL, Peng T, et al (2015) Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes. JAMA 314: 265-277.
32. Muskiet MH, Smits MM, Morsink LM, Diamant M (2014) The gut-renal axis: do incretin-based agents confer renoprotection in diabetes? Nat Rev Nephrol 10: 88-103.
33. Cooper ME, Perkovic V, McGill JB, Groop PH, Wanner C, et al (2015) Kidney Disease End Points in a Pooled Analysis of Individual Patient-Level Data From a Large Clinical Trials Program of the Dipeptidyl Peptidase 4 Inhibitor Linagliptin in Type 2 Diabetes. Am J Kidney Dis 66: 441-449.