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Novel strategies for optimal end - Organ protection in diabetes

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ABSTRACT

Diabetes is increasing globally at a very high rate. Along with the growing prevalence of diabetes, there is an increase in the burden of the complications associated with diabetes. These complications not only affect the quality of life but reduce productivity, increase the economic burden and if not treated can lead to irreversible organ damage and even death. The progressive nature of diabetes adversely affects the efficacy of currently available hypoglycemic agents. The presence of comorbidities, desire to avoid common medication-related side effects and drug interactions further complicate the treatment process. There is still an unfilled therapeutic need for new pharmacological strategies that specifically target the complications of diabetes. Thus, new therapies that target the basic pathophysiology of diabetes complications and show organ-specific effects independent of glycemic control would be particularly helpful. The present review is an overview of promising, novel therapeutic strategies for optimal end-organ protection in diabetes.



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INTRODUCTION

Diabetes is an emerging epidemic that has an impact on almost every country, age group, and economy worldwide. As per the International Diabetes Federation report, in 2015, nearly 415 million people had diabetes worldwide, and this number is expected to rise to 640 million by 2040. Moreover, almost half of the patients with diabetes are not aware of their disease, thus more liable to develop complications (Papatheodorou K *et al.*, 2018).

The complication associated with diabetes lead to poor quality of life and increase in mortality (Lichtenauer UD *et al.*, 2003). The chronic vascular complications are the major contributor to the morbidity and mortality associated with diabetes

(Forbes JM *et al.*, 2017). The type 2 diabetes (T2D) is considered to be an independent risk factor for stroke and cardiovascular diseases (CVDs). The prospective studies have proven that diabetic patients have a 2- 4 times greater chances coronary artery disease (CAD) and myocardial infarction (MI).

Indeed, about 70% of death in T2D patients of age ≥ 65 years are reported to be due to CVD. Also, T2D patients with no history of CAD have an equal CV risk as patients with a history of the previous disease (Ma RC *et al.*, 2017). Without treatment, 20-40% of T2D patients with microalbuminuria progress to nephropathy after 20 years from the onset of disease and $\sim 20\%$ develop the end-stage renal disease (ESRD) (Aldukhayel, A. 2017). The CV and renal complications associated with T2D also a cause of the major economic burden. The coronary events, cerebrovascular events, heart failure, nephropathy, and the peripheral vascular disease accounts for nearly 60% of overall hospital admission among T2D patients in Asia (Ma RC. 2016).

However, controlling and managing diabetic complications is still a difficult area of therapy. The main hurdle in the treatment of T2D is limited treatment opportunities and scarcity of therapeutic agents that can delay the diabetic complications. Thus, this unmet need can be resolved by the

identification of novel therapeutic targets and development of new drugs (Patil PD *et al.*, 2017).

Potential Therapeutic Strategies for End organ Protection

The progressive nature of T2D limits the effectiveness of currently available glucose-lowering drugs (Bailey CJ *et al.*, 2016). Also, diabetes promotes organ damage, representing a substantial challenge for drug development (Hagiwara S *et al.*, 2014). The treatment process is further complicated by the desire to avoid medication-related side effects like hypoglycemia, weight gain, and drug interactions. These challenges have incited the development of new formulations and delivery methods for the current drugs alongside research into new therapeutic entities (Bailey CJ *et al.*, 2016). Developing a lone drug that is efficacious against all diabetes complications is not a rational goal. Thus, the interventions that target the basic pathophysiology of diabetic complications, along with drugs that have an organ-specific effect independent of glycemic control, can offer a better treatment strategy (Hagiwara S *et al.*, 2014). Some of the promising therapies developed or in development are as discussed below.

Incretin-based therapies

The incretin-based therapies include dipeptidyl peptidase (DPP)-4 inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1RA). These therapies are now extensively used for T2D management and have pleiotropic benefits like anti-inflammatory, antioxidant and antiatherogenic effects (Figure 1). Several clinical studies have been conducted to assess the effects of DPP-4 inhibitors and GLP-1RA on diabetic microvascular and macrovascular complications. Few are as summarized in Table 1 (Kawanami D *et al.*, 2016).

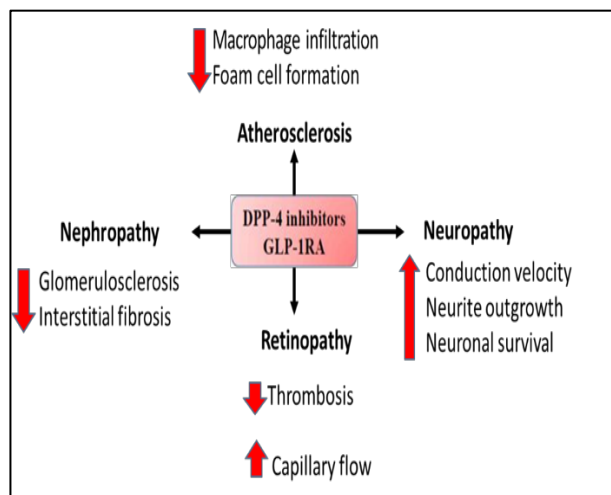


Figure 1: Pleiotropic effects of incretin-based therapies

Sodium-glucose cotransporter 2 inhibitors

The sodium glucose cotransporter-2 (SGLT-2) inhibitors are the most recent class of drug to get approval for T2D management. The SGLT-2 proteins found in the proximal convoluted tubule of the kidney help in reabsorbing ~ 90% of the glucose filtered by the kidney. Independent of glycemic control the SGLT-2 inhibitors also provide significant protection against the progression of CV and renal disease (Miller BR *et al.* 2014; Dekkers CCJ *et al.* 2018). The studies have reported that due to inhibition of renal glucose reabsorption SGLT-2 inhibitors reduce blood pressure, alleviate glucotoxicity and produce hemodynamic effects that lead to improvement in CV and renal outcomes in T2D patients (Figure 2) (DeFronzo RA *et al.*, 2017).

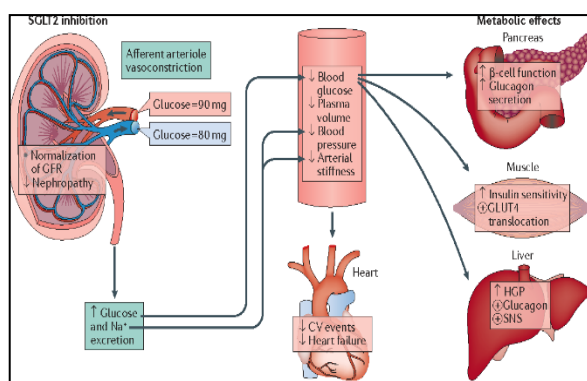


Figure 2: Beneficial effects of SGLT2 inhibition on glucose homeostasis and the CV and renal systems. HGP, hepatic glucose production; GLUT4, glucose transporter 4; SNS, sympathetic nervous system.

Empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin are the four SGLT2 inhibitors currently approved for the treatment of T2D. After several large SGLT2 inhibitor CV outcome trials which showed neutral results, two studies designed with empagliflozin (EMPA-REG: Empagliflozin cardiovascular outcomes and mortality in T2D) and canagliflozin (CANVAS: Canagliflozin cardiovascular assessment study), respectively, reported favourable CV effects independent of glycemic control (Zelniker, TA *et al.*, 2018).

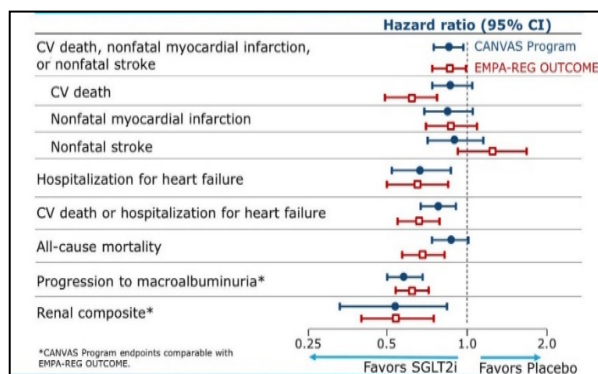


Figure 3: Comparison of key results of the EMPA-REG Outcome and CANVAS Trial

Table 1: Summary of clinical studies conducted to assess the effect of incretin-based therapies

Complication	Drug	Doses	Patients	Duration	Conclusion
CV outcome	Liraglutide	1.8 mg/day	T2D patients \geq 50 years of age with at least one CV condition or \geq 60 years of age with at least one CV risk factor ($n = 9340$)	3.8 years	The decrease in CV death, nonfatal MI, or nonfatal stroke
Nephropathy	Sitagliptin	50 mg/day	T2D patients ($n = 36$)	6 months	Decrease in Albuminuria
	Saxagliptin	2.5 or 5 mg/day	T2D patients ($n = 16492$)	2 years	
	Linagliptin	5 mg/day	T2D patients ($n = 217$)	6 months	
	Liraglutide	1.8 mg/day	T2D patients ($n = 9340$)	3.8 years	Reduction in renal and retinal microvascular events

Table 2: Summary of key RAAS Inhibition Trials

Trial	Patients	Treatment groups	Conclusion
VA NEPRON-D	T2D with proteinuria	Losartan and lisinopril vs losartan and placebo	Due to acute kidney injury events and hyperkalemia with losartan and lisinopril combination the trial was stopped early
ROADMAP	T2D w/o microalbuminuria	Olmesartan vs placebo	The onset of microalbuminuria was delayed by olmesartan
IRMA-2	T2D with microalbuminuria	Irbesartan 150 mg vs irbesartan 300 mg vs placebo	Development of overt proteinuria was reduced by irbesartan
IDNT	T2D with proteinuria and reduced renal function	Irbesartan vs amlodipine vs placebo	Risk for doubling of serum creatinine, ESRD, or death was reduced by irbesartan
RENAAL	T2D with proteinuria and reduced kidney function	Losartan vs placebo	Risk for doubling of serum creatinine, ESRD, or death was reduced by losartan
ONTARGET	Patients with CV risk	Ramipril vs telmisartan vs telmisartan and ramipril	No CV benefit was seen in any treatment group; proteinuria reduction was seen only with telmisartan and ramipril combination therapy

ROADMAP: Randomized Olmesartan and Diabetes Microalbuminuria Prevention; IDNT: Irbesartan Diabetic Nephropathy Trial; IRMA-2: Effect of Irbesartan in the Development of Diabetic Nephropathy in Patients With T2D; RENAAL: Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; ONTARGET: Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint; VA-NEPHRON-D: Veterans Affairs Nephropathy in Diabetes; W/o : Without.

Both EMPA-REG and CANVAS demonstrated a reduction in major adverse CV events like MI, stroke and CV death. The improvement in renal outcome was also reported in both the trials (Figure 3). Further, CANVAS also included patients with no prior CV events, thus indicating the beneficial effects of

canagliflozin in primary prevention of CV events as well (Rastogi A *et al.*, 2017; Ryder RE *et al.*, 2017).

Renin-Angiotensin-Aldosterone System Inhibitors

The tight blood pressure and glycemic control with renin-angiotensin-aldosterone system (RAAS)

blockade make it a cornerstone of the management strategies for diabetic nephropathy. The available evidence also firmly supports the use of RAAS-inhibitors in the treatment of diabetic nephropathy (Table 2). Despite the fact that RAAS blockade with more than one agent may be effective in reducing proteinuria, the adverse-event profile such as hyperkalemia, acute kidney injury, increased CV events and no benefit in preventing ESRD, prohibit its general use for the treatment of diabetic nephropathy (Kim, Y *et al.*, 2017; Umanath K *et al.*, 2018).

Agents Targeting Inflammation and Oxidative Stress

Oxidative stress and inflammation are closely interlinked and play a significant role in the development of diabetic complications. Therefore, therapies that can target both oxidative stress and inflammation may help to improve the outcome of the disease (Pickering RJ *et al.*, 2018). The anti-inflammatory therapies relevant to the management of diabetic complications include statins, antibiotics like doxycycline and peroxisome proliferator-activated receptor agonists (Hagiwara S *et al.*, 2014). Recently, studies have demonstrated that targeting interleukin-1 β signalling pathway with canakinumab significantly reduced recurrent CV events, particularly in diabetic patients as compared to placebo. Thus, showing that targeting inflammation is not only important for classical anti-inflammatory disorders but also relevant for chronic conditions. Unlike the effect of targeting inflammation, large clinical trials have failed to show the CV benefits of antioxidants. However, antioxidants have shown some benefits in diabetic nephropathy, e.g. selenium reported to prevent oxidative stress marker of diabetic nephropathy. Similarly, L-carnitine supplement has shown to reduce oxidative stress, improved glycemic control and renal function (Pickering RJ *et al.*, 2018).

Agents Targeting the AGEs / RAGE Axis

AGEs together with its receptor (RAGE) plays a crucial role in the onset of microvascular and macrovascular complications of diabetes. Thus, therapeutic strategies that target AGE-RAGE axis are of great interest in the management of T2D. The most widely studied pharmacological interventions acting on AGE-RAGE axis are dicarbonyl scavengers (aminoguanidine or pimagidine) and AGE cross-link breaker (alagebrium) (Cheng HS *et al.*, 2017).

The ACTION I (A Clinical Trial in Overt Nephropathy of Type 1 Diabetes) trial failed to establish beneficial effects of aminoguanidine on diabetic nephropathy. Another similar trial, ACTION II, intended to study the effects of aminoguanidine on

diabetic renal complications, was terminated early due to safety issues and low efficacy of the drug. As for the AGE cross-link breaker, alagebrium, trials have yielded mixed results on its efficacy. Treatment with alagebrium (200-210 mg) could reduce arterial and left ventricular stiffness, but failed to confer a beneficial effect on overall CV health. Two smaller and single-arm studies showed that the beneficial effects of alagebrium on CV function were more prominent at much higher dosage (420 mg). Unlike aminoguanidine, there are no reported serious adverse effects with alagebrium (Cheng HS *et al.*, 2017).

CONCLUSION

The growing epidemic of diabetes has become one of the biggest challenges to mankind. Furthermore, the prevalence of diabetes and its complication is predicted to rise. The complications associated with diabetes not only leads to increased morbidity, and mortality, but also poses an economic threat to the countries, especially the developing ones. Even after years and years of research into the pathogenesis of diabetic complications, the pathological pathways that initiate disease remains to be fully decoded. Hence, the need of the hour is to search for novel therapies that can prevent and/or treat diabetic complications. Even though one cannot prevent diabetes, but can certainly stabilize the disease. Thus, we should continue to treat the major risk factors with the currently available therapies, and not ignore new pathways that could help to develop novel and innovative therapies.

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