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Recent therapeutic targets for the prevention and management of diabetic complications

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Abstract

Diabetes and associated complications represent major global public health issues which are associated with impaired quality of life and premature death. Although some diabetic complications have decreased in the developed world, the majority are still prevalent, with an increasing trend in the developing world. Currently used therapies are mainly 'gluco-centric', focusing on the optimization of glycemic control to prevent, delay or manage diabetes-associated complications- other common comorbidities, such as dyslipidemia and hypertension are often underestimated. Although a number of novel therapeutic approaches have been reported recently, some of them have not received comparable attention in relation to either further studies or potential clinical implementation. This editorial briefly discusses some recent therapeutic approaches to the prevention and management of diabetes and its associated complications, as well as potential directions for future research and development in this area.

Key Words: Diabetic complications; Oxidative stress; Phytochemicals; Zinc; Silent information regulator 1; FOXO; Micro RNA

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Core Tip: 'Glucocentric' approaches are currently being used for the management of diabetes and its associated complications. This articles highlighted some recent therapeutic approaches for the management of diabetes and its associated complications such as the management of oxidative stress by using antioxidative phytochemicals, molecular cell signaling pathways *via* Silent information regulator 1 and FOXOs and micro RNAs.

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INTRODUCTION

Diabetes and associated complications are major global causes of premature mortality. A minimum of 50% of people who have type 2 diabetes face premature death from diabetes-associated cardiovascular diseases and some 10% from renal failure with a total of 3.8 million deaths per annum[1]. According to a recent review, the rates of myocardial infarction, stroke and limb amputation have decreased among people with diabetes with a concomitant decline in mortality. The majority of these data are, however, sourced from high income countries, when other diabetic complications such as nephropathy, retinopathy and cancers are well represented[2]. It has been reported that the prevalence of diabetic complications are much higher in low and middle-income countries with a range of 12%-16% for microvascular and 2%-6% for macrovascular complications[3].

Diabetes-associated microvascular complications occur frequently in individuals with diabetes, both their prevalence and severity are inversely proportional to the efficacy of management of hyperglycemia. At least 50% of diabetic patients have one or more diabetic complications in their lifetime and many have multiple complications. Microvascular complications such as, diabetic nephropathy, retinopathy, neuropathy and diabetic foot disease represent a major causes of morbidity, impaired quality of life and mortality and are more common than macrovascular complications, such as diabetic cardiomyopathy and peripheral vascular diseases[4]. While improved management of hyperglycemia represents a major approach to prevent or delay diabetic complications, currently available therapies are not consistent in maintaining optimum glycemic control, their efficacy in glucose lowering exhibits a substantial interindividual variation and their long-term use is associated with adverse effects[5]. Additional major challenges with currently available therapies include, but not limited to, optimizing the dose to control the blood glucose, blood pressure and lipids as well as self-management of diabetes and lifestyle[6]. Hence, there is a need for newer or alternative therapies not only for better glycemic control, but also for the management of blood pressure and blood lipids with an ultimate goal for the prevention of diabetes associated micro- and macro-vascular complications. The outcomes of recent, large cardiovascular prevention trials, initially mandated for regulatory purposes, have provided major insights into the need for a broader, rather than simply 'glucocentric', approach to therapy of type 2 diabetes. Both GLP-1 receptor agonist and SGLT-2 inhibitors are now used widely with the recognition that their beneficial effects include cardiovascular and renal protection[7]. A number of novel therapeutic approaches are currently being evaluated with the potential to improve the prevention and management of diabetic complications, some of which are highlighted below.

Oxidative stress is a major culprit for the induction of diabetic complications[8], since it causes endothelial dysfunction both in small and large vessels, not only by increasing the production of oxidative free radicals and advanced glycation end products, but also by the concomitant reduction of physiological antioxidative status. Over expression of the antioxidative enzyme, superoxide dismutase (SOD) in transgenic diabetic mice has been shown to prevent diabetic micro and macrovascular complications[9]. Accordingly, over expression of antioxidative enzymes, such SOD and catalase, may represent a therapeutic approach to the reduction of diabetic complications, however, the level of over expression also needs to be optimized in order to avoid additional complications[10].

Polyphenols, flavonoids, phenolic acids and zinc have recently been shown to have potent beneficial effects in relation to hyperglycemia, diabetes and its associated complications. Curcumin, the major bioactive compound of turmeric and its analogues, has anti-inflammatory, antioxidant, anti-tumor and epigenetics modulatory effects with potential efficacy against diabetic complications[11,12]. Depletion of zinc in diabetes increases oxidative stress while zinc supplementation has been shown to have a hypoglycemic, antioxidant effect and alleviates some diabetes-associated complications[13]. Resveratrol, a key bioactive compound derived from red grapes, has been shown to have number of benefits including on glycemic control and the management of diabetic complications[14]. Furthermore, nanotechnology or nano-formulations of polyphenols, flavonoids and phenolic acids has the potential to enhance solubility, and intestinal absorption, as well as bioavailability and, therapeutic efficacy in diabetes and its associated complications[15].

Silent information regulator 1 (SIRT1), a member of the sirtuins family when the sirtuins are NAD⁺ dependent histone deacetylase. Apart from activating LKB1 mediated AMPK followed by PGC α , PPAR α , eNOS pathways and inhibiting mTOR and NOX or NADPH oxidase pathways[16]; SIRT1, has been reported to regulate the activity of other proteins, such as forkhead box protein of class O or FOXO, which regulates oxidative stress resistance, insulin signaling and metabolism along with its other activities as a transcription factor[17]. Of the many FOXOs, FOXO1 is widely expressed in muscle, liver and pancreas and protects pancreatic β -cells from oxidative stress by increasing the expression of antioxidant genes[18]. On the other hand, there is evidence that FOXO3 can prevent atherosclerosis *via* inhibiting smooth

muscle cell proliferation and activation[19]. FOXO1 and FOXO3 are also involved in many other mechanisms of relevance to glucose metabolism, as well as diabetic complications. Hence, SIRT1 and FOXO1 and FOXO3 may also represent therapeutic targets for the management of diabetic complications.

Like many other molecular pathways, epigenetic factors, including histone modifications, DNA methylations and non-coding RNAs play a major role in the pathogenesis of diabetes and its complications[20]. Among many non-coding RNAs, some micro-RNAs have been shown to have a pivotal role in the management of diabetes and diabetic complications, particularly in relation to the diagnosis and prognosis of prevalent microvascular complications *e.g.* diabetic neuropathy. A number of microRNAs are involved in the signaling pathways of diabetic complications, which can be targeted for the early diagnosis and development of therapeutics for diabetic microvascular complications, particularly for diabetic neuropathy and diabetic foot disease[21].

CONCLUSION

In conclusion, although many other therapeutic targets are being investigated for the improved management of diabetes and its associated complications, the approach of reducing oxidative stress or increasing antioxidant status using antioxidant phytochemicals or bioactive compounds and mineral such as zinc; molecular metabolic pathways such as SIRT1 and FOXOs and micro RNAs represent important and novel approaches to the diagnosis, prevention and improved management of diabetic complications. We look forward to the outcomes of these ongoing studies, which will be facilitated by an effective collaboration between basic scientists, clinicians and pharma and, hopefully, their prompt translation to clinical practice.

FOOTNOTES

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