https://doi.org/10.46389/rjd-2022-1250
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2022; volume 29, issue 4, pages 480-484

Review

Pathogenesis of type-2 diabetes mellitus and its complications – a narrative review

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Received: 28 June 2022 / Accepted: 4 October 2022

Abstract

Diabetes mellitus is the dynamic group of metabolic disorders whose progression leads to various complications. This review focuses on the dominance of type 2 diabetes among the diabetic population, risk factors, biomarkers, pathogenesis and therapeutic agents. It also explains the importance of drug therapy obtained from natural origin. In this review, we have presented an overview of the incidence of the glucose-induced release of insulin from β cells of the pancreas and its action on various tissues involved in the maintenance of blood glucose levels. Lifestyle modifications can be influential in preventing type 2 diabetes from further complications. In general, a sedentary lifestyle proved to be one of the crucial factors for the pathogenesis of type 2 diabetes. In addition, many biomarkers consort with type 2 diabetes and its complications. This review has shown a few important biomarkers to be examined at different stages of type 2 diabetes (prediabetes, newly diagnosed and known diabetes). Additionally, recent approaches to drug therapy that are conventional and traditional sources as an alternative therapy have been discussed.

Keywords: type 2 diabetes, antidiabetic drugs, biomarkers, peripheral neuropathy, cerebrovascular disease.

Introduction

Diabetes mellitus is a chronic disorder delineated by hyperglycemia and defective carbohydrate, lipid and protein metabolism caused by complete or partial insulin insufficiency. There are two major forms of diabetes, type-1 diabetes, formerly called insulin-dependent and type-2 diabetes, called insulin-independent type. Type 2 diabetes is the most predominant form of diabetes, which elucidates 92% of the diabetic population and is expected to increase to more than 400 million by 2030 [1]. Now, the global prevalence has been attributed to 9% among adults, which is rising more rapidly in developing economies [2]. In type 2 diabetes with chronic hyperglycemia, there is a significant risk of diabetes-related vascular complications. Microvascular complications comprise diabetic nephropathy, diabetic neuropathy and diabetic retinopathy, and macrovascular complication constitutes cardiovascular disease, peripheral vascular disease and cerebrovascular disease [3]. This review enlightens the prevalence, pathogenesis and progression of type 2 diabetes and its complications. It also reflects the importance of biomarkers associated with disease and the therapeutic need for control.

Additional studies have stated that a low-fiber diet with a high glycemic index correlates significantly with a higher risk of type 2 diabetes [4]. Epidemiological studies stipulate that major diabetes-protective factors involve plant food-based diets and moderate to high-intensity muscle work. Low calories with a protein-rich diet for meal replacement strongly improves metabolic control, decreases the amount of antidiabetic medication and lower body weight in type 2 diabetes on insulin treatment [5]. As lifestyle changes can subdue hyperglycemia, despite it, some antidiabetic drugs are required to control glycemic levels. Although, after using oral antidiabetic medications, several unfavorable

side effects, such as hypoglycemia, fluid retention, osteoporosis and heart failure, have occurred. This leads to limited clinical applications, which intended many researchers to suggest the necessity to develop new antidiabetic drugs with fewer side effects controlling hyperinsulinemia, hyperglycemia and hypertriglyceridemia [6].

Pathogenesis

Dysfunction in the feedback mechanism of insulin secretion and insulin action causes insulin resistance and malfunction of β-cells in type 2 diabetes, which results in elevated blood glucose levels. Therefore, insulin resistance increases glucose production in the liver and its declined uptake in muscles and adipose tissues at specified insulin levels (Figure 1). Moreover, deteriorated β-cells produce diminished insulin release, which is inadequate for maintaining normal blood glucose levels. This phenomenon of insulin resistance and β-cells dysfunction occurs at an early stage in the pathogenesis of type 2 diabetes [7]. There are also other factors convoluted in the pathogenesis of type 2 diabetes, such as environmental and genetic risk factors. Sedentary lifestyle factors such as overeating, lack of exercise, smoking, alcohol consumption, insufficient energy consumption and obesity are referred to as independent environmental factors. Abnormal levels of blood glucose and obesity are acquired by factors that include insufficient intake of dietary fiber, high fat intake, and more consumption of simple sugar and less complex carbohydrates [8].

Microvascular complications

Diabetic nephropathy is a heterogeneous disease involving progressive renal decline due to poor glomerular filtration rate (GFR) and albuminuria. The prediction factor for the subsequent progression of diabetic nephropathy depends on the rate of microalbuminuria (30–299 mg/day, moderately increased albuminuria), which pretends to be the earliest clinical manifestation of diabetic nephropathy. Besides protein intake, hyperglycemia, hypertension, dyslipidemia, GFR (125 and 140 mL/min/1.73 m^2) and smoking are modifiable risk factors of diabetic nephropathy [9]. Studies conducted in the northern region of India predicted the prevalence of microalbuminuria to be 26.6%. A follow-up study was also conducted among huge normoalbuminuric type 2 diabetes participants, of whom 44%

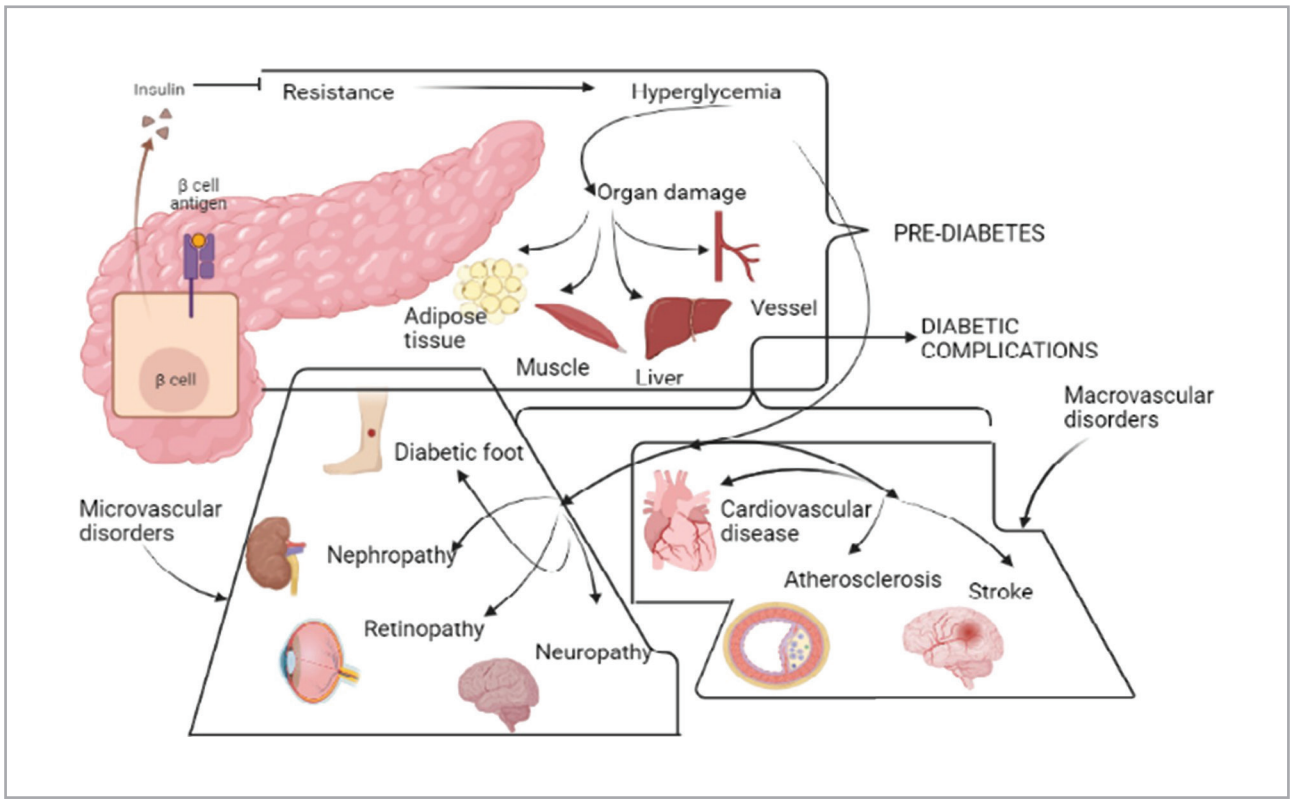

Figure 1: Diagrammatic illustration of the pathogenesis of type 2 diabetes: The figure illustrates the onset of prediabetes, diabetes and its complications.

seemed to develop frank proteinuria. Some population studies conducted in urban cities of South India have reported 41.5% of microalbuminuria to be present in type 2 diabetes. There seems to be a comparable similarity in the prevalence of microalbuminuria occurring in the South Indian rural population [10].

Diabetic retinopathy is a characterized disease associated with proliferative and non-proliferative diabetic retinopathy. It is mainly caused by complications of long-term diabetes. Some participants with retinopathy experience vision loss in the case of proliferative diabetic retinopathy (PDR), whereas non-proliferative diabetic retinopathy (NPDR) participants possess better vision. Vision loss is the most predominant cause of diabetic macular edema (DME), promoting a major healthcare challenge. NPDR is the early stage of diabetic retinopathy, wherein elevated vascular permeability and capillary occlusion are two important predictors in renal vasculature. At this point, retinal pathologies, including microaneurysms, hemorrhages and hard exudates, can be disclosed by fundus photography despite the asymptomatic condition of the participants [10, 11]. In 2017, a study called CURES Eye Study produced a report on the overall prevalence of diabetic retinopathy in Chennai to be 18% among 20.8% self-reported diabetic individuals' *vs*. 5% newly diagnosed diabetic individuals. Numerous studies are regulated to obtain the burden of diabetic retinopathy. The southern regions of Tamil Nadu, namely the Theni district, have provided a prevalence range of 12.2% diabetic retinopathy. Past studies have reported the global prevalence of diabetic retinopathy, which was predicted to be at lower rates among Indians compared to western countries [12].

Diabetic peripheral neuropathy (DPN) is a wide range of clinical diseases that could manifest as peripheral nervous system dysfunction. Peripheral limbs of participants with DPN typically exhibit varying degrees of numbness, tingling, and/or burning. It is indeed uncertain what specifically causes DPN. Sensory, motor and autonomic neuropathies are the characteristics of diabetic peripheral neuropathy. A disruption of the hexosamine, protein kinase C, and polymerase pathways, sorbitol accumulation, advanced glycosylation end products, and oxidative stress damage are the potential causes of peripheral nerve injury. Endothelial dysfunction and neurovascular damage with deficient repair mechanisms were also identified [13]. Most of the published studies are based on clinical aspects of diabetic neuropathy prevalence in India compared to population-based. The percentage of prevalence of DPN in urban cities around India has been depicted among newly diagnosed and known diabetic populations. Some others reported the prevalence of DPN to be 30.6% in rural Tamil Nadu, according to their Chunampet rural diabetes prevention project conducted in 2017 [14].

Macrovascular complications

The onsets of cardiovascular diseases (CVD) were related to the interplay of obesity, extreme obesity, insulin resistance and chronic inflammation. Several studies have continuously reported obesity as the major risk factor for CVD, which is recognized as a predominant criterion for heart failure, coronary artery disease and premature death [15]. CVD is more typical among participants with diabetes than those without diabetes. Compared with the European population, Indians tend to develop CVD a decade earlier in their midlife. The clinic-based studies have shown the prevalence of CVD among participants with diabetes to range from 11 to 28%, whereas not much evidence of population studies on CVD prevalence among diabetic participants is observed. Some studies have reflected the close association of CVD with and without diabetes could develop atherosclerosis in their early life [16].

Peripheral vascular disease (PVD) is primarily associated with atherosclerotic changes resulting in reduced cardiac output and end-organ ischemia. The breakthrough in atherosclerosis leads to macro and microvascular dysfunction. Hence, it commonly affects the abdominal aorta, iliac arteries, lower limbs, and sporadically the upper extremities. The worldwide prevalence of PVD is reported to occur among 200 million individuals, thus including the American population of 40 to 45 million [17]. The complications and mortality associated with PVD have been reported to increase since 2015 in developing countries and predicted increased proportion in developed nations. According to the clinic and population-based studies, the predominance of PVD in the Indian diabetic population is lower compared to the western diabetic population. This survey of PVD prevalence was reported to show ranges between 3.0 and 8.3% [18].

Cerebrovascular disease is characterized by the stream of diseases, conditions and disorders that affects the blood vessels and blood supply to the brain. The problems associated with blood flow are stenosis, thrombosis, hemorrhage, embolism and stroke. The important mechanism of cerebrovascular disease in

https://doi.org/10.46389/rjd-2022-1250

participants with type 2 diabetes is reported to be atherosclerosis as an essence of inflammatory response. Some studies have shown its preponderance with type 2 diabetes to be 20 to 40% possessing cerebral blood vessel diseases. Studies have depicted that individuals with diabetes are at a higher risk of stroke than those without diabetes. In addition, this review suggests that cerebrovascular disease was predicted to be 0.9% among 3010 diabetic participants involved in the clinic-based study in South India [9]. As a follow-up study, they also reported that among 50 participants involved, 16% of the participants possessing diabetes, of which 37% had relatively showing stenosis [19].

Biomarkers

According to the definition of WHO, diagnosis of diabetes with a single random blood sugar over 200 mg/dl (11.1 mmol/l) and the use of a 75 g oral glucose challenge test (OGTT) is supposed to diagnose those in "the ambiguous range" (postprandial blood glucose 140–199 mg/dl) [20]. Various biomarkers are associated with the progression and pathogenesis of type 2 diabetes; those include genetic, biochemical and inflammatory markers. Enzymes and genes associated with type 2 diabetes are observed to have direct involvement in decreasing insulin secretion, inflammation and oxidative stress leading to β-cell dysfunction. Biomarkers can be classified as traditional, novel and inflammatory. Traditional biomarkers include HbA_{1c}, Fructosamine (FA), glycated albumin (GA), and 1,5-anhydroglucitol (1,5 AG). Adiponectin, fetuin-A (FetA), α-hydroxybutyrate (α-HB), triglycerides, HDL, ceramide, ferritin and transferring, acyl-carnitine, microRNA are the novel biomarkers that were identified a decade earlier. Furthermore, there are groups of inflammatory markers, namely white blood cells (WBC), c-reactive protein (CRP), interleukin-6 (IL-6), interleukin-18 (IL-18), fibrinogen, plasminogen activator inhibitor 1 (PAI-1) and IL-1 receptor antagonist (IL-1RA) [21].

Therapeutic approaches for type 2 diabetes

Due to the complicated pathogenicity of diabetes, the essence of controlling and treating diabetes is integrated with the participants' condition to make self-conductance which includes diet modification, suitable exercise, close monitoring of blood glucose levels, mood analysis and drug treatment in combination. Antidiabetic drugs are commonly prescribed for drug treatment consisting of insulin, insulin analogs and oral antidiabetic drugs, which include insulin sensitizers, insulin secretagogues and glucose regulators and gene therapy [22]. Metformin is an insulin sensitizer that is the first drug of choice to manage type 2 diabetes. Apart from this, thiazolidinediones (glitazones) were newly provoked promising drugs due to their safety issues [23]. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have a highly commanded approach by clinical guidelines as second-line of drug therapy accompanying metformin intolerance, as SGLT-2 inhibitor is manifested to be effective in glycemia and HbA_{1c} reduction. All the above-mentioned conventional drugs, including sulfonylureas, dipeptidyl peptidase4 inhibitor and glucagon-like peptide-1, are there, but side effects still exist.

Furthermore, researchers have continuously reported on the enormous plant extracts with antidiabetic effects, which can be used as a potential therapeutic agent for type 2 diabetes with minimal side effects [24]. The balanced composition of phenols, alkaloids, terpenoids and flavonoids present in plant extracts have been reported to exert antidiabetic potential. All these components can also be obtained from dietary sources such as certain fruits, vegetables and nuts [25].

Conclusion

This overview of the pathogenesis of type 2 diabetes is aimed to provide researchers with a complete understanding of metabolic control in glycemic conditions. It has also high lightened the importance of pathogenesis, risk factors and therapeutic approach to type 2 diabetes. Moreover, it paves the way for future researchers to analyze the role of marker enzymes associated with type 2 diabetes at different intervals of diseased conditions. Hence, the authors conclude that even though conventional drug therapies are the gold standard for tight control of glycemia, the predominance of plant extracts possessing antidiabetic properties have the inclined potential to manage-side effects associated with type 2 diabetes. The molecular mechanism associated with the effect of dietary components on oxidative stress in type 2 diabetes is still unclear.

Conflict of interest

The authors declare no conflict of interest.

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https://doi.org/10.46389/rjd-2022-1250