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The Role of Proinflammatory Markers in TIDM and T2DM

Research project

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DECLARATION

I declare that the information of the research about **(**The Role of Proinflammatory Markers in TIDM and T2DM) is all my tiredness work and my hardworking. The information isn't presented like this before. This research can be a unique source of information for the science students in the future.

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Dedication

To My parents

My Supervisor

The rest of my family members for their encouragements,

love, care and support

I dedicate this, my modest effort

Acknowledgements

(In the name of Allah, most Gracious and most Merciful)

Thanks to Allah, for his infinite grace and for having made everything

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possible ways during my whole studies and gave me the possibility of a university education.

ABSTRACT

Diabetes mellitus (DM) is a metabolic disease characterized by high blood sugar levels due to either insufficient production of insulin by the body or cells that do not respond effectively to insulin. The classic symptoms include polyuria, polydipsia, and polyphagia. DM is traditionally classified into Type 1 DM, which requires insulin injections, Type 2 DM, which results from insulin resistance, and gestational diabetes, which occurs during pregnancy. Current pharmacotherapy for DM includes insulin and oral hypoglycemic agents, which aim to regulate blood glucose levels. However, these treatments have limitations and side effects. Herbal drugs have shown promise in the management of diabetes due to their beneficial properties. This review focuses on the immunophysiological aspects, complications, management goals, and both synthetic and herbal treatment options for diabetes.

Keywords: diabetes, type one diabetes, type two diabetes, gestational, epidemiology, pathology, physiology, diagnoses, risk factor, treatment.

INTRODUCTION

Diabetes mellitus (DM) is rapidly becoming one of the main health issues among humans in the 21st century and the number of patients is steadily increasing, globally, both in the developed and developing countries. It is a noninfectious chronic disease caused by the inability of the pancreas to effectively produce enough insulin or when the body in unable to properly use the insulin produced by it (Abdulaziz Al Dawish et al., 2016). There are four main types of diabetes mellitus: Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise. Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level(Kumar et al., 2020). additional clinically recognizable subtypes exist, such as monogenic diabetes (e.g.) Maturity-onset Diabetes of the Young [MODY] or neonatal diabetes), Maturity-onset diabetes of the young (MODY) is a group of monogenic disorders characterized by autosomal dominantly inherited non-insulin dependent form of diabetes classically presenting in adolescence or young adults before the age of 25 years. MODY is a rare cause of diabetes (1% of all cases) and is frequently misdiagnosed as Type 1 diabetes (T1DM) or Type 2 diabetes (T2DM) (Anık, 2015 #70). current global estimates indicate that this condition affects 415 million people and is set to escalate to 642 million by the year 2040.1 A further 193 million people with diabetes remain undiagnosed due to the often mild or asymptomatic nature of

this condition especially in type 2 DM (T2DM) (Atlas, 2015). The presence of DM shows increased risk of many complications such as cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, amputations etc. Drugs are used primarily to save life and alleviate symptoms. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Various types of hypoglycemic agents such as biguanides and sulfonylureas are also available for treatment of diabetes. Medicinal plants and their bioactive constituents can be used for treatment of DM throughout the world especially in countries where access to the conventional anti-DM agents is inadequate. Various experimental models are also available to screen antidiabetic activity of plant (Deshmukh et al., 2015b).

2. Literature Review

2.1 Definition of Diabetes Mellitus

Diabetes is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Oberoi and Kansra, 2020). With rising pervasiveness globally, diabetes is conceded as a major chronic pandemic disease that does not consider any ethnic background and monetary levels both in developing and developed economies and has also been designated with the status of 'public health priority' in the majority of the countries (Unnikrishnan et al., 2016). Individuals with diabetes are more susceptible to developing any of the associated complications, macrovascular or microvascular. As a consequence, people experience frequent and exhaustive confrontations with the healthcare systems. The treatment cost for diabetes and its associated complications exert an enormous economic burden both at the household and national levels (Kamath et al., 2019).The

main purpose is to know which type of immunity parameters effective and related to type one and type two diabetes, also to know which one is increasing and which one is decreasing to be identified.

2.2 Classification of Diabetes Mellitus

Diabetes is a chronic metabolic disorder characterized by high blood glucose levels that result from absolute or relative insulin deficiency, in the context of beta-cell dysfunction, insulin resistance, or both. Though it's classically divided into an early-onset autoimmune form (type 1 diabetes or T1D) and a late-onset non-autoimmune form (T2D), additional clinically recognizable subtypes exist, such as monogenic diabetes (e.g.) Maturity-onset Diabetes of the Young [MODY] or neonatal diabetes), gestational diabetes, and possibly a late-onset autoimmune form (latent autoimmune diabetes in the adult or LADA). Indeed, the label of T2D is essentially applied to any diabetes that is not autoimmune or monogenic in nature, and it is increasingly recognized that it may represent a conglomerate of varied pathophysiological states. Regardless of this heterogeneity, all of these diabetes forms have a notable genetic component (Mahajan et al., 2018, Udler, 2019).

2.2.1 Type 1 Diabetes Mellitus

Type 1 diabetes is a chronic autoimmune disease characterized by insulin deficiency and resultant hyperglycemia. Knowledge of type 1 diabetes has rapidly increased over the past 25 years, resulting in a broad understanding about many aspects of the disease, including its genetics, epidemiology, immune and β-cell phenotypes, and disease burden. Interventions to preserve β cells have been tested, and several methods to improve clinical disease management have been assessed. However, wide gaps still exist in our understanding of type 1 diabetes and our ability to standardize clinical care and decrease disease-associated complications and

burden. This Seminar gives an overview of the current understanding of the disease and potential future directions for research and care (DiMeglio et al., 2018).

2.2.2 Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders worldwide and its development is primarily caused by a combination of two main factors: defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to insulin (Galicia-Garcia et al., 2020). Insulin release and action have to precisely meet the metabolic demand; hence, the molecular mechanisms involved in the synthesis and release of insulin, as well as the insulin response in tissues must be tightly regulated. Therefore, defects in any of the mechanisms involved can lead to a metabolic imbalance that leads to the pathogenesis of T2DM (Galicia-Garcia et al., 2020). Type 2 diabetes mellitus (T2DM) affects the 90–95% of the overall population of patients with diabetes mellitus, being an important health issue for more than 380 million people worldwide (Atlas, 2015).

2.2.3 Maturity Onset Diabetes of the Young (MODY)

Maturity-onset diabetes of the young (MODY) is characterized by autosomal dominant inheritance, onset before 25 years of age, absence of β-cell autoimmunity, and sustained pancreatic β-cell function. To date, mutations have been identified in at least 14 different genes, including six genes encoding proteins that, respectively, correspond to MODY subtypes 1–6: hepatocyte nuclear factor (HNF) 4α (HNF4α), glucokinase (GCK), HNF1α (HNF1α), pancreatic and duodenal homeobox 1 (PDX1), HNF1β (HNF1β), and neurogenic differentiation 1 (NEUROD1) (Urakami, 2019).

2.2.4 Gestational Diabetes Mellitus

Hyperglycemia that develops during pregnancy and resolves after birth has been recognized for over 50 years, but uniform worldwide consensus is lacking about threshold hyperglycemic levels that merit a diagnosis of 'gestational diabetes mellitus' (GDM) and thus treatment during pregnancy. GDM is currently the most common medical complication of pregnancy, and prevalence of undiagnosed hyperglycemia and even overt diabetes in young women is increasing. Maternal overweight and obesity, later age at childbearing, previous history of GDM, family history of type 2 diabetes mellitus and ethnicity are major GDM risk factors. Diagnosis is usually performed using an oral glucose tolerance test (OGTT), although a non-fasting, glucose challenge test (GCT) is used in some parts of the world to screen women for those requiring a full OGTT (McIntyre et al., 2019).

2.3 Epidemiology of Diabetes Mellitus

Diabetes mellitus is a disorder stemming from glucose dysregulation. Of those people with diabetes mellitus, 90% to 95% have type 2 diabetes mellitus, whereas 5% to 10% have type 1 diabetes mellitus (Virani et al., 2020). Diabetes is a serious and increasing global health burden. The number of people with diabetes increased from 108 million in 1980 to 422 million in 2014, in which 8.5% of adults ≥18 years had diabetes. It is expected that over 592 million people worldwide will have diabetes by 2035. Regarding death, 1.6 million deaths were directly caused by diabetes in 2016 (Reddy et al., 2018).

2.3.1 Epidemiology of Type 1 Diabetes mellitus

The incidence of type 1 diabetes increases with age up to a peak around 10–14 years, but the disease can occur at any age (Weng et al., 2018). The incidence tends to be higher in boys than in girls in high– incidence countries, with the opposite

pattern seen in low–incidence countries (Group, 2006). After puberty, males tend to have increasingly higher incidence of developing type 1 diabetes than females, even in low–incidence countries such as China.5 Most standardized long-term incidence data focus on children younger than 15 years, with incidence ranging from 1 to 3 per 100 000 per year in China and other Asian and South American countries (Weng et al., 2018, Group, 2006) .

2.3.2 Epidemiology of T2DM

Globally, the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death. About 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM). Asia is a major area of the rapidly emerging T2DM global epidemic, with China and India the top two epicenters (Zheng et al., 2018).

2.4 History of Diabetes mellitus

Diabetes mellitus is a group of metabolic diseases involving carbohydrate, lipid, and protein metabolism. It is characterized by persistent hyperglycemia which results from defects in insulin secretion, or action or both. Diabetes mellitus has been known since antiquity. Descriptions have been found in the Egyptian papyri, in ancient Indian and Chinese medical literature, as well as, in the work of ancient Greek and Arab physicians. In the 2nd century AD Aristaeus of Cappadocia provided the first accurate description of diabetes, coining the term diabetes, while in 17th century Thomas Willis added the term mellitus to the disease, in an attempt to describe the extremely sweet taste of the urine. The important work of the 19th century French physiologist Claude Bernard, on the glycogenic action of the liver, paved the way for further progress in the study of the disease. In 1889, Oskar Makowski and Joseph von Mering performed their famous experiment of removing

the pancreas from a dog and producing severe and fatal diabetes. In 1921, Frederick Banting and Charles Best extended Makowski's and Miring's experiment. They isolated insulin from pancreatic islets and administrated to patients suffering from type 1 diabetes, saving thus the lives of millions and inaugurating a new era in diabetes treatment (Karamanou et al., 2016).

2.5 Pathology of Diabetes mellitus

It is now generally agreed that the underlying characteristic common to all forms of diabetes is the dysfunction or destruction of pancreatic β-cells. Many mechanisms can lead to a decline in function or the complete destruction of β-cells (these cells are not replaced, as the human pancreas seems incapable of renewing β-cells after the age of 30 years). These mechanisms include genetic predisposition and abnormalities, epigenetic processes, insulin resistance, auto-immunity, concurrent illnesses, inflammation, and environmental factors. Differentiating β-cell dysfunction and decreased β-cell mass could have important implications for therapeutic approaches to maintaining or improving glucose tolerance (Organization, 2019). Understanding β-cell status can help define subtypes of diabetes, and guide treatment (Skyler et al., 2017). The presence of DM shows increased risk of many complications such as cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, amputations etc (Dutta and Deshmukh, 2015).

2.5.1 Pathophysiology of Type 1 Diabetes mellitus

The pathogenesis of type 1 diabetes results from a complex interaction between the pancreatic β-cell and innate and adaptive immune systems. Cognate interactions between T cells and B cells occur that can lead to islet-targeting autoantibody formation (Wong, 2014) (FIG. 1). However, the triggering event is

unknown, but the appearance of the first islet-targeting autoantibody reflects autoantigen presentation by dendritic cells and the subsequent responses of autoantigen-specific CD4+ and CD8+ T cells.

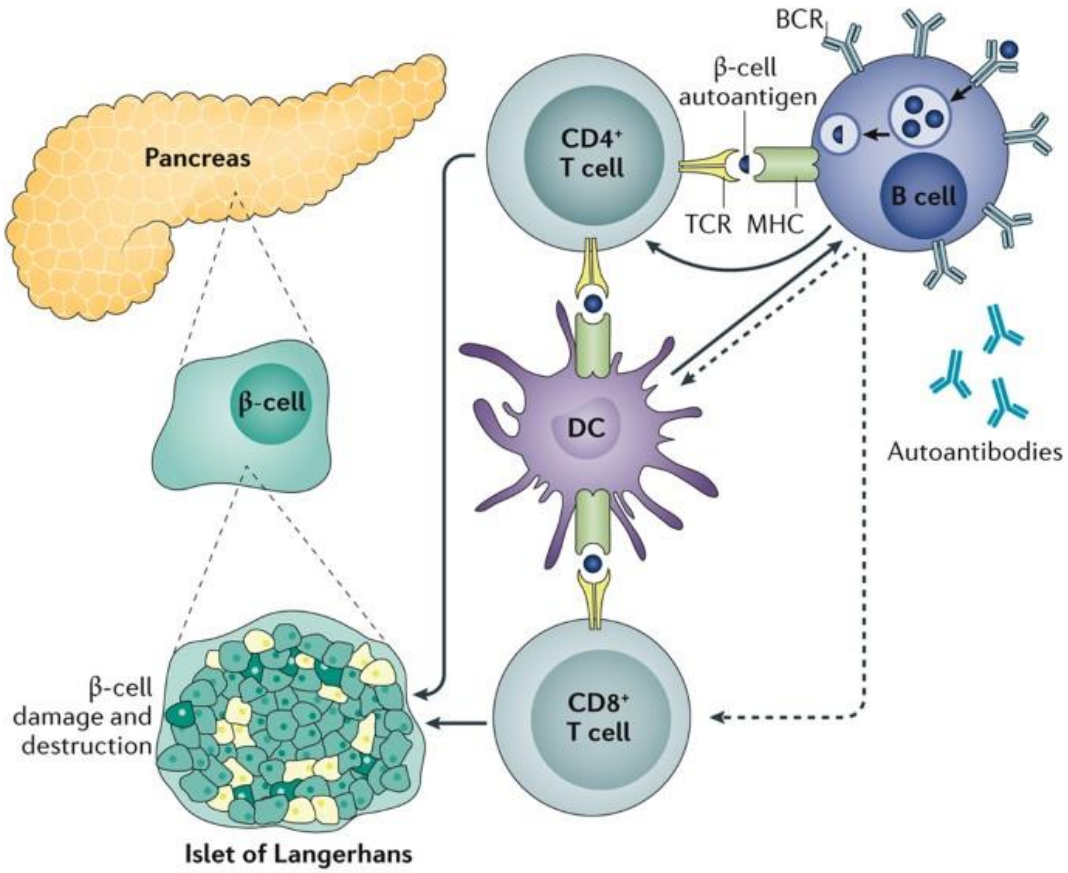

Figure1: Pathophysiology of T1DM. Type 1 diabetes mellitus (T1DM) is an immune mediated disease. Activated B cells interact with CD4+ and CD8+ T cells, as well as dendritic cells (DCs). Antigen presentation by B cells and DCs drives the activation of β-cell-specific T cells. In addition, the exposure of B cells to β-cell autoantigens lead to the production of islet-targeting autoantibodies, which serve as biomarkers of asymptomatic disease. Dashed arrows indicate the potential interactions between B cells and CD8+ T cells and between B cells and DCs. BCR, B cell receptor; TCR, T cell receptor (Katsarou et al., 2017).

2.5.2 Pathophysiology of Type 2 Diabetes Mellitus

T2DM is a multifactorial disease involving the influence of multiple genes along with obesity, insulin resistance, and environmental factors (Himanshu et al., 2020). In T2DM, insulin resistance contributes to increased glucose production in the liver and decreased glucose uptake in muscle and adipose tissues at a set insulin level. Additionally, dysfunctional β-cells also result in reduced insulin secretion which is not enough for maintaining normal glucose levels (Asmat et al., 2016). In this type of diabetes, multiple genetic defects, and certain environmental factors especially obesity are responsible for beta cell defects and peripheral tissue insulin resistance respectively (Abdulaziz Al Dawish et al., 2016). In type 2 diabetes (T2DM), the body can produce insulin. However, the insulin level may not be sufficient, the body may not respond to insulin, or the body may not use insulin efficiently, resulting in insulin resistance(Khin et al., 2023) (Figure 2). T2DM is usually diagnosed in middle-aged individuals, and its prevalence increases with age. Similar to T1DM, genetic and lifestyle factors influence the onset of T2DM. T2DM is usually identified by a defective secretion of insulin resulting from a progressive loss of β-cell mass and/or overproduction of insulin for a long period (Inaishi and Saisho, 2020, Hunter and Stein, 2017, Khin et al., 2023). Eventually, T2DM patients experience diabetes-induced complications, including retinopathy, nephropathy, and neuropathy. Recent evidence has suggested that β-cell dysfunction is the main pathogenic mechanism of diabetes and is crucial for T2DM development (Khin et al., 2023). In patients with T2DM, a decrease in β-cell mass was observed with duration of the disease and considered as a consequence of diabetes with impaired insulin secretion(Khin et al., 2023). Moreover, decreased β-cell mass leads to the imbalance of α-cell/β-cell ratio which is essential for the maintenance of blood glucose homeostasis (Hunter and Stein, 2017, Khin et al., 2023). In some studies, it

has been described that glucotoxicity and lip toxicity are considered the major causes of defects in β-cell mass, eventually leading to β-cell apoptosis through various intracellular mediators (Khin et al., 2023). However, since the β-cell turnover is very slow (Khin et al., 2023). other priority factors contributing to the loss of β-cell function and cell death should be explored. In this review, we present the major risk factors and underlying molecular mechanisms of β-cell dysfunction and death in T2DM, based on current evidence.

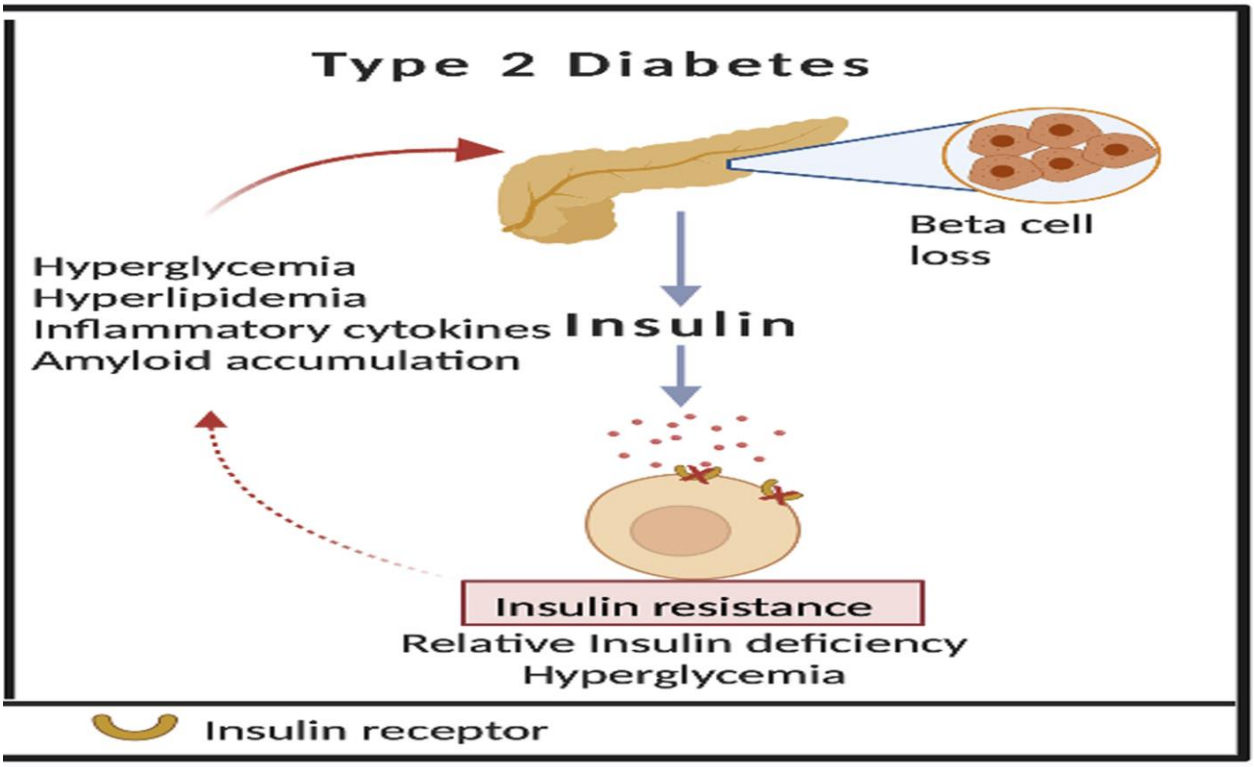

Figure2: in type 2 diabetes, pancreatic β-cells are damaged by hyperglycemia, hyperlipidemia, cytokines, and amyloids. Although pancreatic β-cells produce insulin, the insulin level is insufficient to compensate for insulin resistance, resulting in a relative insulin deficiency, leading to hyperglycemia (Khin et al., 2023).

2.6 Risk Factor for Diabetes Mellitus

Globally, the prevalence of DM has increased and therefore has grown in severity as a public health problem. Multiple risk factors are involved in the actual onset of the disease. Genetics, atmosphere, loss of very first phase associated with insulin launch, sedentary way of life, lack of physical exercise, smoking, alcoholic beverages, dyslipidemia, reduced β-cell sensitivity, hyperinsulinemia, improved glucagon activity are the primary risk elements for prediabetes and DM (Knott et al., 2015, Chen et al., 2015, Akter et al., 2017). These factors appear to play a significant role in insulin resistance or insulin no functionality resulting in disease advancement. Based on WHO (2011), approximately 90% of patients develop T2DM, mostly related to excess body weight. Obstructive sleep apnea and sleep disorder that are seen among overweight adult individuals are a common risk factor for insulin resistance and glucose sensitivity which collectively progresses to prediabetes and then T2DM. The diet containing low fiber but a high glycemic index (GI) is thought to be positively related to the onset for diabetes (Akter et al., 2017, Sears and Perry, 2015). Some classes of drugs (i.e., antipsychotics, diuretics, immune suppressants, betablockers) also can induce diabetes (Alam et al., 2021). Immunoglobin E (Ige) and chemise interact with other risk factors and both put a positive impact on the release of protease from mast cells and act as significant risk factors for prediabetes (Li et al., 2015). ROS and reactive nitrogen species (RNS) which increase the oxidative stress level in the body also induce the development of vascular diseases and diabetes. Increased iron in blood makes an environment for the Fenton reaction and Haber–Weiss reaction. which decreases the ability of antioxidants and detoxifying enzymes Low expression of catalase and superoxide dismutase 2 (SOD2) makes pancreatic β-cells sensitive to oxidative stress and decreased

expression of a transcription factor responsible for low insulin production (Alam et al., 2021).

2.6.1 Risk Factor for Type 1 Diabetes

Environmental factors also play an important role in the pathogenesis of T1DM. Strong evidence for this derives from the study of monozygotic twins, where occurrence of the disease in both siblings varies around 50% and never reaches 100%. The environmental factors involved include viruses (rubella, coxsackievirus B or enteroviruses), toxins and nutrients (cow's milk, cereals). The precise effect of these factors remains unclear, but it is important to be identified, since these factors can be modified and possibly lead to prevention or treatment interventions(Paschou et al., 2018). Other risk factors for type 1 diabetics include obesity, hypertension, inflammation, resistance to insulin, hypovitaminosis D, and dyslipidemia (Gheith et al., 2016).

Table 1 Contributing factors in type 1 diabetes mellitus.

A. Genetic factors
1. HLA
2. Insulin-VNTR
3. CTLA-4
4. Other genetic associations (PTPN22, AIRE, FoxP3, STAT3, IFIH1, HIP14, ERBB3)
B. Epigenetic factors
C. Environmental factors
1. Viruses (rubella, enteroviruses)
2. Diet (cow's milk, cereals, omega-3 fatty acids, vitamin D)
3. Gut microbiota
D. Immunologic factors
1. Immune tolerance (central, peripheral, Tregs)
2. Cellular immunity
3. Humoral immunity (GAD65, IA-2, IAA, ZnT8)

2.6.2 Risk Factor for Type 2 Diabetes Mellitus

T2DM risk factors include a complex combination of genetic, metabolic and environmental factors that interact with one another contributing to its prevalence. Although individual predisposition to T2DM due to non-modifiable risk factors (ethnicity and family history/genetic predisposition) has a strong genetic basis, evidence from epidemiological studies suggests that many cases of T2DM can be prevented by improving the main modifiable risk factors (obesity, low physical activity and an unhealthy diet) (Galicia-Garcia et al., 2020). Genetic predisposition plays an important part in the risk of developing T2DM. Over the past decade, several T2DM genome-wide association studies have shown the complex polygenic nature of T2DM in which most of these loci increase T2DM risk through primary effects on insulin secretion, and a minority act through reducing insulin action (Dimas et al., 2014, Flannick and Florez, 2016). Obesity (body-mass index [BMI]≥30 kg/m2) is the strongest risk factor for T2DM (Bellou et al., 2018).

2.7 Diagnosis of Diabetes Mellitus

The diagnosis of diabetes in an asymptomatic subject should never be made on the basis of a single abnormal blood glucose value. If a diagnosis of diabetes is made, the clinician must feel confident that the diagnosis is fully established since the consequences for the individual are considerable and lifelong. The diagnosis of diabetes mellites include, urine sugar, blood sugar, glucose tolerance test, renal threshold of glucose, diminished glucose tolerance, increased glucose tolerance, renal glycosuria, extended glucose tolerance curve, cortisone stressed glucose tolerance test, intravenous glucose tolerance test, oral glucose tolerance test (Singh et al., 2016).

2.8 Treatment of Diabetes Mellitus

2.8.1 Insulin and Oral Hypoglycemic Drugs

Treatment options for hyperglycemia are varied and its initiation depends on the underlying pathology and presentation of the patient (Alam et al., 2014).Insulin therapy should aim to mimic nature, which is remarkably successful both in limiting postprandial hyperglycemia and preventing hypoglycemia between meals. Site of administration of insulin injection is equally important for better and safe action of insulin and can be given by intramuscular or intravenous route (Deshmukh et al., 2015a).and treatment for type two diabetes its Sulphonyl urea's such as glipalamide, glipizide and biguanides such as metformin, phenformin are oral hypoglycemic drug. Metformin reduces hepatic glucose output, enhances peripheral tissue sensitivity, and stimulates GLP-1 secretion. Sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic ß-cells (Chatterjee et al., 2017).

2.8.2 Herbal Treatment of Diabetes

traditional medicines have been used for a long time and play an important role as alternative medicines. Moreover, during the past few years, some of the new bioactive drugs isolated from plants showed antidiabetic activity with more efficacy than oral hypoglycemic agents used in clinical therapy. Traditional medicine performed a good clinical practice and is showing a bright future in the therapy of diabetes mellitus (Tran et al., 2020). Herbal drugs are proved to be a better choice over synthetic drugs because of less side effects and adverse effects. Herbal formulations are easily available without prescription (Verma et al., 2018) In the last few decades eco-friendly, bio-friendly, cost effective and relatively safe, plant-based medicines have moved from the fringe to the main stream with the increased research

in the field of traditional medicine. There are several literature reviews by different authors about anti-diabetic herbal agents, but the most informative is the review by Atta-art-Rahman who has documented more than 300 plant species accepted for their hypoglycemia properties. This review has classified the plants according to their botanical name, country of origin; parts used and nature of active agents. One such plant is Momordica Charentais (Family: Cucurbitaceae). WHO has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called the botanical garden of the world (Tran et al., 2020).

Different antidiabetic mechanisms of herbs are included into one of following groups:

1. Blocking calcium channels of pancreas beta cells
2. Stimulation of cAMP and inhibition of renal glucose uptake.
3. Exciting insulin secretion and inhibiting mechanisms involved into decreased insulin secretion.
4. Decreasing insulin resistance.
5. Providing essential elements to beta cells including calcium, zinc, magnesium and copper.
6. Improving regeneration of beta cells.
7. Increasing number and size of cells within pancreas islands.
8. Stimulating glycogenesis and hepatic glycolysis.
9. Inhibiting activity of α- and β-galactosidase.
10. Cortisol reducing activities.
11. Inhibiting α-amylase activity.
12. Prevention of oxidative stress.

Also wide range of medicinal herbs has been studied to treat diabetes, such as (ginger, barberry, fenugreek, walnut, green tea, thyme, peanuts, Tribulus terrestrosin, pomegranate, ginseng, olive, aloe vera, nettle, sumac, cannabis) (Khazaei et al., 2018).

CONCLUSIONS

Diabetes mellitus is the epidemic of the century and without effective diagnostic methods at an early stage, diabetes will continue to rise. This review focuses on the types of diabetes and the effective diagnostic methods and criteria to be used for diagnosis of diabetes and prediabetes. Evidently, diabetes is a complex disease with a large pool of genes that are involved in its development. The precise identification of the genetic bases of diabetes potentially provides an essential tool to improve diagnoses, therapy (more towards individualized patient targeted therapy) and better effective genetic counseling. Furthermore, our advanced knowledge of the association between medical genetics and the chronic complications of diabetes, will provide an additional advantage to delay or eradicate these complications that impose an immense pressure on patient's quality of life and the significantly rising cost of health-care services.

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