Review Article

DIABETES AND ALTERNATIVE TREATMENT MODELS

ABSTRACT

Diabetes Mellitus is a collection of various conditions that have resulted in an increase in blood glucose levels. This article outlines the current classification of diabetes mellitus and compares the majority of the characteristics of both type 1 and 2 diabetes. Fasting and oral glucose resistance tests and legitimate biochemical demonstrative criteria when utilizing hemoglobin A1c (HbA1c) are moreover summarized. Rising rates of diabetes require focused on screening to distinguish diabetes and prediabetes in at-risk bunches. In order to prevent the development of diabetes in these random clusters and delay its progression, it is necessary to engage in early physical activity after that initial activity has occurred.

Concurring to the most recent information from The International Diabetes Federation (IDF) in 2021, the number of grown-up patients matured 20-79 a long time around the world is over 500 million and this number will increment to 800 million within the 2050s.

Diabetes is also a costly disease that consumes about 12% of healthcare costs globally. Considering the undesirable side effects and costs of known standard treatments; Today, the tendency and preference possibilities for alternative therapies (CAM) are increasing day by day. Herbal medicines, in other words, alternative treatments are the traditional methods used in the treatment of many diseases, which are mostly preferred especially within Eastern and Middle Eastern countries.

In this study, possible alternative treatment models and sources of active substances were presented, and the possibilities and studies for more effective treatment of diabetes were summarized and tried to be put forward.

Keywords: Diabetes, Alteratie Treatment, Type 1 and Type 2

INTRODUCTION

Diabetes mellitus is a metabolic disorder caused by a lack of insulin secretion or action, resulting in chronically high blood sugar levels [1].

Chronic hyperglycemia caused by insulin deficiency worsens carbohydrate, fat, and protein metabolism over time, resulting in long-term damage to tissues and organs such as the eyes, kidneys, nerves and blood vessels. Over time, complications such as neuropathy, nephropathy, retinopathy and heart problems develop [2].

Complications such as microvascular and macrovascular problems are long-term problems faced by type 1 DM patients. Type 2 DM patients develop arteriosclerosis in large blood

vessels due to hypertension, hyperlipidemia, and obesity. The long-term condition of type 2 DM is fatal due to renal failure and cardiovascular disease [3].

Diabetes can be divided into four different categories: Type 1 Diabetes, Type 2 Diabetes, gestational diabetes and specific diabetes caused by other factors. Type 2 Diabetes affects a large proportion of patients worldwide [4].

DM is a disease that is increasing not only in our country but also all over the world [5].

International Diabetes Federation (IDF) has reported that there are currently over 500 million adults aged 20 to 79 worldwide, with projections indicating that this number is projected to reach 800 million by 2050 [6].

The treatment of DM is very important due to the increasing morbidity and mortality rate associated with this disease. Even though insulin and antidiabetic medicines have many different mechanisms of action, this disease has not been brought under control yet, on the contrary, DM continues to increase rapidly in the world [7].

Approaches such as synthetic antidiabetic drugs, insulin injections, and habit changes can be used to control diabetes. Dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, glucosidase inhibitors and biguanides are commonly used synthetic antidiabetic agents. However, these drugs are not only very expensive, but also have many side effects.

Because DM is one of the leading health threats worldwide and increases drug costs, an alternative approach is needed to control this disease.

In this study, information about the definition of diabetes, diagnostic criteria, treatment principles, alternative treatment possibilities and treatment models for diabetes will be presented.

1. DIABETES MELLITUS DEFINITION

Type 2 Diabetes is an illness caused by high blood sugar levels. It can cause classic symptoms like high blood sugar, weight loss, vision problems and other health issues. It can also make you more likely to get infections, which can lead to a crash or coma. When your blood sugar is too high, your body doesn't make enough insulin to fight off the effects of the diabetes. This can lead to long-term problems with your body's tissues and organs, like your eyes, kidneys, nerve, heart and blood vessels [8].

2. CLASSİFİCATİON OF DİABETES

Insulin dependence is not a classification. Diabetes mellitus is divided into 4 types [9].

2.1 Type 1 Diabetes

Diabetes is a condition where your pancreas can't make insulin and it's also called Type 1 Diabetes. The primary cause of this condition is immune-mediated damage to beta cells in the body, often resulting in a complete lack of insulin. Latent autoimmuneadult-onsetdiabetes (LADA) is a type of autoimmune diabetes related toType 1 Diabetes, rather than a distinct subtype (adult-onsetdiabetes) characterized by a more gradual decline in insulin secretion.Autoantibodies related to diabetes play a big part in getting Type 1 Diabetes. It

looks like age, blood sugar levels, how many antigens you have and how sensitive you are all play a role in how your diabetes progresses [10].

2.2 Type 2 Diabetes

Diabetes mellitus, also known as Type 2 Diabetes, is a condition characterized by a relative lack of insulin, reduced insulin activity (insulin resistance), gradual decline in beta cell activity and impaired glucose-independent insulin secretion in the early stages of the disease. Functional impairments occur at varying rates long before diabetes occurs clinically alone or with a high risk of macrovascular consequences due to the metobolic syndrome.

There isresearch that suggestsclassifying Type 2 Diabetes into five clusters.These clusters are thought to differ in insulin resistance and beta cell functionand risk for diabetes-related complications [11]. Such a subclassification could be a basis for a new classification in the future and provide the classification or specification of diabetes treatment. Nonetheless, this requires extensive validation of results in other populations, therefore a subclassification has not yet recommended so far.

2.3 Gestational Diabetes (GDM)

Gestational diabetes is a glucose intolerance disorder first diagnosed during pregnancy. If it occurs before the 20th week of pregnancy, there is a high probability that she had diabetes mellitus before conception [8].

2.4 Other Specific Forms of Diabetes

These forms of diabetes include exocrine pancreatic diseases (e.g. pancreatitis, injuries, tumors, surgery, cystic fibrosis, hemochromatosis), endocrine organ diseases (e.g. acromegaly, Cushing's syndrome), pharmacochemical diseases (e.g.HAART for HIV/AIDS), genetic defects in insulin secretion (e.g. adult-onset diabetes) and insulin action (e.g. lipoatrophic diabetes), other genetic diseases (e.g. Down's disease, Klinefelter's disease, Turner's disease), infectious diseases (e.g. may include congenital rubella) and unusual forms of autoimmune-mediated diabetes (e.g. extreme bronchial disorder) [8].

3. DIABETES MELLITUS DIAGNOSIS

Diabetes is diagnosed using fasting blood glucose levels, OGTT (oral glucose tolerance test), or HbA1c (hemoglobin A1c). Hyperglycemia develops on a continuous basis. Fasting and postprandial disorders are classified into different time frames. As a result, the cut-off values used are not fully consistent in classifying patients with diabetes. All tests are subject to variation. Therefore, a repeat test or confirming a test result with another test is always required unless classic clinical symptoms are present [8].

3.1 Fasting Glucose and Oral Glucose Tolerance Test (OGTT)

The diagnosis is made by measuring multiple elevations in blood glucose levels on at least 2 different days, regardless of age and gender (Table 1). In clinical suspicion and conflicting results, the diagnosis is made by OGTT. Fasting glucose levels of < 100 mg/dl (<5.6 mmol/l) in venous plasma are considered "normal" under current conditions“.However, low values do not exclude the presence of impaired glucose metabolism or associated damage. The basis for the choice of breakpoints lies in the association between higher blood glucose values (2 hours after fasting and oral glucose exposure) and the resulting increased risk of harm [10].

Table 1. Standard diagnosis of diabetes and an increased risk of developing diabetes

	Diabetes Mellitus	Increased risk of diabetes (prediabetes)[a]
"random glucose" (venous or capillary)	≥200 mg/dL (11.1 mmol/L) for 2 days [b] or ≥200 mg/dL + classic symptoms [c]	–
Fasting glucose (venous plasma)	≥126 mg/dL (7.0 mmol/L) for 2 days [b]	≥100 mg/dL (5.6 mmol/L) but ≤125 mg/dL (6.9 mmol/L) (impaired fasting blood glucose)
2-hour glucose after 75 g OGTT (venous plasma)	≥200 mg/dL (11.1 mmol/L) for 2 days [b]	Glucose ≥140 mg/dL (7.8 mmol/L) but ≤199 mg/dL (11.0 mmol/L) (impaired glucose tolerance])
HbA1c	≥6.5% (48 mmol/mol) in 2 days [b]	≥ 5.7% (39 mmol/mol) but ≤ 6.4% (46 mmol/mol) [d]

a. It is possible to have an elevated risk of developing diabetes even when there is no evidence of glycemic insufficiency, and this risk can be identified through the use of risk tests.

b. If two different tests are positive, diabetes is diagnosed and the test can be stopped. If different tests give different results, you should repeat the test with increasing results.

c. HbA1c may be normal at the first signs of Type 1 Diabetes if hyperglycemia and classic symptoms are present.

d. Further diagnosis using fasting glucose or OGTT is required.

The prerequisites for glucose determination are:

- Exclusive use of quality-assured measurements or tests.
- Detection preferably in venous plasma (addition of lithium heparin or better EDTA + sodium fluoride). Serum samples should only be used if a glycolysis inhibitor has been added.
- No determination is made with blood glucose meters used for self-monitoring.
- "Fasting" means ≥ 8 hours without any caloric intake.
- During administration, it should be taken into account that the diagnosis is prone to possible errors due to intervening diseases (e.g. infections, dehydration, gastrointestinal diseases) or drugs (e.g. glucocorticoids).
- Criteria other than those listed in Table 1 are valid for the diagnosis of GDM.
- In cases of increased erythrocyte turnover/diseases (e.g. pregnancy, hemodialysis, blood transfusion, major blood loss, sickle cell anemia, thalassemia, hereditary spherocytosis), the HbA1c value may be falsely low in these cases [10].

3.2 HbA1c

The guidelines also added high HbA1c levels to the standard diagnostic criteria for diabetes [12]. Correspondingly, diabetes mellitus can be diagnosed by using HbA1c breakpoints ≥ 6.5% (Table 1). Basically, if your blood sugar level is higher than 6.5%, you're more likely to get diabetic retinopathy. Diabetes with an increase in HbA1c values between 5.7% and 6.4% can be assumed to be a risky condition, therefore an explanation is recommended in this situation by using fasting glucose and OGTT. When comparing HbA1c with Diabetes, a threshold value for microvascular or macrovascular outcomes has not yet been specified [13]. Even low HbA1c levels can increase your risk of diabetes. The advantages of measuring HbA1c values are high preanalytical stability and low log variance. Disadvantages are lower sensitivity between HbA1c and mean blood glucose values, higher costs (so not available worldwide) and lower correlation. The determination of HbA1c is an indirect measurement of average blood glucose values over several weeks and can deviate from actually measured glucose values due to influencing factors such as age, ethnicity and anemia/hemoglobinopathy [10].

4. EPİDEMİOLOGY AND PATHOPHYSİOLOGY OF TYPE 1 DİABETES

Type 1 Diabetes is a long-term condition that can develop at any age, but is most commonly diagnosed in children [14].Ladies are more likely to create autoimmune disorders than men, but Type 1 Diabetes tends to be marginally higher in boys than in grown-up men. Type 1 Diabetes can occur at any time of the year and depends on the time of year and the month you were born. However, some studies have found seasonal birth trends, with higher rates of vaginal birth among those born in the summer months compared with those born in the fall and winter. Autoimmunity (i.e. islet autoantibody formation) in Type 1 Diabetes has been observed to develop months or years before symptoms appear. Furthermore, seasonal synchronization is also observed. These results support the hypothesis that environmental factors initiate or modulate type 1 pathogenic mechanisms [15].

Type 1 Diabetes is the most common type of diabetes in the world [16]. In Finland, it affects around 60% of people aged 100,000 or over each year, while in Sardinia it affects around 40% of the population [17]. Despite this, Type 1 Diabetes is not very common in countries like China, India and Venezuela (0.1 cases in every 100,000 persons per year). Type 1 Diabetes is a disease that affects people all over the world and it's really complicated to figure out how it spreads. North America and In Europe, the incidence of Type 1 Diabetes varies greatly from region to region. For instance, the average distance between Estonia and Finland is under 120 km, but the rate of transmission is less than one-third of the rate in Finland [17].Type 1 Diabetes is the most common type of diabetes in the world and has been on the rise for decades. In Finland, Germany and Norway, there was an annual rise of 2.4, 2.6 and 3.3% respectively [18]. In recent years, there has been a decline in the incidence of Type 1 Diabetes in Sweden, despite the fact that it has been on the rise in many countries [19]. The magnitude of the increase was not uniform across all demographics. Within Europe, the largest increases were observed in children under the age of five [20]. It's not totally clear why the number of people with Type 1 Diabetes is increasing so quickly, but it's thought that it's mainly due to environmental factors. Genetics or having more kids from moms with Type 1 Diabetes can't explain why it's happening so fast [21]. In summary, we can say that today genetic predisposition does not seem to play as big a role as it used to in the development of Type 1 Diabetes [22].

The epidemiology of Type 1 Diabetes is said to be influenced by a variety of factors, including environmental factors, the diet of infants and adolescents and the components of vitamin D and the vitamin D pathway, with viruses being one of the most discussed topics [23].While there is growing interest in environmental-based models, such as the hygiene

hypothesis and gut microbiome, that explain the pathogenesis of Type 1 Diabetes, no single agent has been identified as having a direct effect on the disease [24].

Most studies of Type 1 Diabetes suggest that the disease is caused by autoimmune damage to insulin-producing beta cells in the pancreas. This hypothesis is supported by the presence of chronic inflammatory infiltrates in pancreatic islets during the onset of Type 1 Diabetes [25]. One theory is that in people with chronic diseases, the pancreas loses insulin-producing cells and the remaining beta cells are not replenished. This theory is explained below. Recent research shows that the majority of people with Type 1 Diabetes have very few beta cells. However, there is evidence that beta cells regenerate in infants, young children, adolescents and adults [26]. Most of our knowledge about the biology of Type 1 Diabetes comes from studies of pancreatic samples, serum and peripheral blood cells performed on patients with the disease. Studies of these components have shown that many functional defects in the bone marrow (including the thymus), immune system, red blood cells and beta cells interact to contribute to disease progression [27].

5. THE EPİDEMİOLOGY AND PATHOPHYSİOLOGY OF TYPE 2 DİABETES

The global prevalence of Type 2 Diabetes is on the rise at an unprecedented rate, driven by a combination of factors such as obesity, lack of physical activity and low-calorie diets. The International Diabetes Federation's (IDF) 2021 data indicates that the global adult population with diabetes aged 20 to 79 has surpassed 500 million and is projected to reach 800 million individuals by 2050 [6].

The incidence and prevalence of Type 2 Diabetes varies by country, with 80% of patients living in low- to middle-income countries. However, the global prevalence of diabetes has increased since 1980 and is increasing in all countries. Intensive lifestyle changes, medication or both may have prevented or reversed the onset of her Type 2 Diabetes [28].
People with Type 2 Diabetes are 15% more likely to die from all causes than people without diabetes and young people are twice as likely to die. A meta-analysis found that diabetes was associated with an increased risk of Coronary Artery Disease (CAD), Ischemic Stroke (IWS) and Vascular Disease (VDD) in 18 of 698,782 participants [29]. Diagnosis of Type 2 Diabetes can be delayed by up to 12 years if the patient has a history of complications such as retinopathy [28].

Type 2 Diabetes is a disease that is largely driven by genetics and environmental factors. It develops after exposure to an obesogenic environment, including genetic determinants, a sedentary lifestyle and excessive intake of sugar and fat. Common glucose genetic trait variants in Type 2 Diabetes have been identified in genome structure association studies (GSA). However, these common glucose genetic trait variants account for only about 10% of the overall trait variation in Type 2 Diabetes. This indicates that rare variants play a significant role [30]. Genotypic association between genotype and phenotype has been extensively studied in transcriptomic studies and has revealed that many genes involved in the onset of Type 2 Diabetes and obesity [31].

When it comes to diabetes, it's clear how important it is to change your environment and lifestyle, especially if you're overweight or white. Studies show that people with Type 2 Diabetes are more likely to die from any cause, especially if they are overweight or non-Hispanic. For this reason, his genetic risk score for Type 1 Diabetes was created, consisting of nine SNPs. It is designed to detect the difference between her Type 1 Diabetes and her Type 2 Diabetes in adults aged 20 to 40 years. Diagnosing Type 1 Diabetes based solely on clinical features and autoimmune markers is difficult [32].

A phenotype characterized by aggressive behavior has been observed in young individuals diagnosed with Juvenile-onset (Type 2) Diabetes (aged 15-30). This phenotype appears to be associated with an increased risk of cardiovascular mortality, macrovascular damage and neuropathic symptoms compared to patients with juvenile Type 1 Diabetes (Type 1) of the same age and duration [33]. People of different ethnicities can have different traits that can cause them to have a lot of risk factors for heart disease, like high blood pressure, insulin resistance and diabetes. But if you take care of those risk factors, it can help reduce your risk of heart disease. That's what three studies showed, looking at over 2,000 people with diabetes that wasn't related to heart disease [34].Type 2 Diabetes is a type of diabetes that affects the pancreas. It is characterized by hyperinsulinemia, insulin resistance and the loss of up to half of the body's cells at the time of diagnosis [35]. The rate of β-cell loss appears to be accelerated in younger patients (aged 10-17), which may be a contributing factor to the delayed onset of treatment failure in those diagnosed at an earlier age [36]. The pancreas is the primary organ system responsible for the development of Type 2 Diabetes. It is composed of alpha and beta cells and is supplemented by other organs such as the liver and skeletal muscle. Additionally, the brain, gastrointestinal tract, small intestine and fat tissue are also involved in the process. Incretins, changes in colonic and gastrointestinal tissue, immunodeficiency and inflammation have been identified as the main pathophysiological triggers of the disease [37].

6. DİABETİC COMPLİCATİONS

Complications of Type 2 and Type 1 Diabetes are the most common, but they are also the leading cause of death and mortality-related complications. Complications associated with chronic diabetes can be divided into microvascular and macrovascular categories, although microvascular complications are much more common [38]. Microvascular complications include nephropathy, retinopathy and neuropathy. Macrovascular complications include stroke, peripheral arterial disease (PAD) and cardiovascular disease. Diabetic Foot Syndrome is defined as foot ulcers associated with Peripheral Artery Disease (PAD), neuropathy and infection. This is one of the most common reasons for lower extremity amputation [39]. In summary, there are additional complications of diabetes that are not included in the above two categories, such as dental disease, decreased susceptibility to infections and obstetric complications related to gestational diabetes [38].

6.1 Microvascular Complications

Subclinical evidence of inflammation such as: elevated chronic reactive protein (CRP) is related to Type 2 Diabetes and metabolic syndrome [40]. Meprin plays a significant role in the onset and progression of diabetic nephropathy. This is due to the fact that it is an enzyme expressed by a tubule in the proximal part of the kidney [41]. In a paper called "Meprin Metalloproteinase Deficiency in Strychnine-Induced Type 1 Diabetic Mice," J. E. Bylander and colleagues found that mice with this disorder were more likely to die and have more severe problems with their kidneys. We conducted an experiment to investigate. The authors investigated the role of metalloproteins in the progression of diabetes (diabetes mellitus) using meprin-β knockout (KO) mice. In this study, mice with normal metalloprotein genes and severe diabetes showed reduced metalloprotein expression in their renal tissues. In other ways, diabetic mice with metalloprotein β knockout showed higher mortality and greater renal function loss than mice with a normal metalloprotein gene [42]. Mephrin can inhibit DN proliferation and this finding may not be limited to mice. This is an important finding with potential clinical relevance. Monofilament and vibration sensor testing is one of the most commonly used screening tools recommended by numerous clinical guidelines.

Additionally, these tests can be used to identify Diabetic Peripheral Neuropathy (DPN) and predict the likelihood of foot ulcers [43].

6.2 Macrovascular Complications

Diabetes can lead to a variety of complications and co-morbidities, one of which is Peripheral Arterial Disease (PAH). It's thought that about half of diabetics with foot ulcers also have PAH. Furthermore, PAH may be accompanied by chronic ischemia pain [44]. Pain can have a considerable influence on the quality of life for these individuals. In A. Tedeschi's study, they looked at how well and how much Tapentadol PR could be used in people with Severe Chronic Ichthyodontitis Pain (SCHP) and Type 2 Diabetes. This study used a numerical rating scale and questionnaire (DN4, SF-12) to examine how much pain painkillers can cause. Tapentadol PR acts not only as a μ-OPIOID receptor agonist but also as a norepinephrine reuptake inhibitor (NREI) in SCHP patients. This study showed that tapentol PR may help with chronic fish hygiene pain associated with her Type 2 Diabetes. It not only significantly reduced pain intensity but also reduced neuropathic symptoms and improved patients' quality of life [45].

6.3 Other Complications

Studies have shown that diabetic patients with severe hypoglycemic symptoms are more likely to develop cardiovascular disease [46]. Malkani et al. A retrospective study included patients with her type 1 or Type 2 Diabetes who were treated with insulin alone. The study looked at self-reported blood sugar and blood sugar A1c levels. The study found that although hypoglycemia is more common in patients with Type 1 Diabetes, only about 20% of patients with Type 2 Diabetes experience at least one episode of severe hypoglycemia. This study also found a positive correlation between glycemic variability and the frequency of hypoglycemia in patients with both types of diabetes [47]. Therefore, there is increasing evidence that the formation of advanced glycation end products (AGEs) may contribute to poor wound healing in diabetic patients [48]. Q. Wang and his colleagues focused on wound healing. They investigated the role of RAGE (senescence receptor)-expressing macrophages in impaired healing in diabetic mice. Our aim was to target AGE-rage signaling by locally applying anti-AGE antibodies specifically at the site of wound entry. A group of diabetic mice treated with anti-AGE antiretroviral antibodies showed accelerated wound healing compared to untreated mice. Furthermore, immunohistochemical staining showed improved phagocytic function of macrophages [49].These results are certainly promising and may be useful for clinical research on wound healing in diabetic patients.

7. MEDICAL TREATMENT OF DIABETES MELLITUS

Diabetes mellitus pathogenesis is one of the key determinants of the treatment of diabetes mellitus. A well-balanced diet, regular exercise and weight management are key components of almost all therapeutic programs for diabetes mellitus patients. Lifestyle modifications not only lead to a decrease in blood sugar levels, but also improve a variety of cardiovascular risk factors and facilitate weight loss. However, most patients are unable to lead a healthy lifestyle and become addicted to drugs for diabetes mellitus treatment.
Pharmacological treatment of DM is focused on controlling vascular blood glucose levels and reducing them to a normal level. The mechanism by which drugs lower blood sugar levels is as follows: stimulates the release of insulin into the islet beta cell of the pancreas; it also blocks the effects of hormones that raise blood sugar levels; increase the sensitivity of insulin receptor sites, glycogen hydrolysis inhibition in the liver; Promoting the uptake of glucose into tissues and organs [50].

At present, there are six primary categories of contemporary medications and two categories of injections used globally to regulate blood glucose levels [51]. The names of the tablets are biguanides (metformin), thiazolidinediones (glitazones), sulfonylureas, alpha-glucosidase inhibitors, meglitinides (glinides) and DPP-4 inhibitors. Two types of drugs can be given by injection: incretin mimics and insulin.

7.1 Insulin

Injections of insulin are the primary form of treatment for individuals with Type 1 Diabetes Mellitus who lack insulin. In T2DM where oral hypoglycemic medications are not effective enough to control glucose and high blood sugar (HbA1c), insulin can be used on its own or in conjunction with oral hypoglycemic drugs.

Insulin is the limiting factor. It must be injected. This method has been shown to have positive effects on treatment. However, this method creates a compliance issue in patients who have needle phobia. Poor glycemic control is caused by this issue. Today, there are also devices available commercially that can be classified as insulin pumps. These are devices that are used to administer insulin directly to the skin. In addition, some devices can be used to inject insulin directly into the skin. These devices are called insulin pumps. The FDA classifies these devices as moderate-risk or high-risk devices. Clinical trials are being conducted to confirm the safety and effectiveness of these devices [52]. An alternative non-invasive route may be inhaled insulin or oral insulin. While the implementation of inhaled insulin has some challenges, improved pharmacokinetics and pharmacodynamics parameters can make this use case successful and facilitate insulin use. Another attractive option is oral insulin use. Currently, more research is needed in clinical trials before this formulation can be brought to market [53].

7.2 Biguanides

The most commonly prescribed antidiabetic drug is metformin. Metformin remains the best. Metformin improves insulin sensitivity, enhances glucose uptake through phosphorylation of GLUT-enriching factors and suppresses liver gluconeogenesis. Metformin helps with weight loss and exhibits moderate reductions in triglycerides and serum LDL cholesterol. Metformin inhibits mitochondrial complex 1 (MCC1) and the enzyme that produces it. Monotherapy drug. Metformin is most commonly prescribed to obese and overweight patients. It also activates one of the enzymes that stimulates the expression of liver gluconeogenic genes called AMP (activated protein kinase). All of this results in a decrease in both glucose and HbA1C. However, metformin does not affect β-cells. Muscle insulin sensitivity doesn't improve significantly in the absence of loss of weight. HbA1c gradually increases after the initial decline [54].

7.3 Sulfonylureas

Sulfonylureas are secretagogues that stimulate insulin secretion from the β-cell of the pancreas. It primarily targets ATP-sensitive potassium channels on the surface of beta cells and works only when there are residual pancreatic beta-cells present. Sulfonylureas don't provide long-term protection against β-cell damage and can speed up the rate of β-cell death. HbA1c increases after the initial drop in blood sugar levels. Hypoglycemia has been observed in many cases, especially with older-generation drugs. It can lower blood sugar levels by nearly 20%. It also lowers HbA1C levels by about 1-2%. Weight gain is an undesirable side effect of sulfonylurea [55].

7.4 Thiazolidinediones

Thiazolidinediones (TZDs) are receptors that are activated by peroxisomal proliferator-activated receptors gamma. These receptors are responsible for increasing insulin sensitivity in fat cells, the heart and the liver. They are responsible for controlling insulin secretion by interacting with the β-cells. It is used as an insulin resistance treatment for T2DM with long-term effects (up to 5 years). One of the most common side effects is weight gain. The higher the body weight, the more successful the reduction in HbA1c and the better the function of the β-cells and the insulin sensitivity. TZD has been shown to reduce carotid artery thickness in patients with T2DM. Previously, the FDA prohibited the use of rosiglitazone due to its high incidence of cardiovascular events. However, the ban has been lifted in recent years. Pioglitazones contraindications in Patients with Class III to IV Heart Failure. It is well tolerated in elderly patients and people with kidney insufficiency. However, it is important to note that it should not be indicated in Elderly Patients with Congenital Heart Failure as it is linked to breakage in females [56].

7.5 Dipeptidyl Peptidase-4 (DPP4) Inhibitors

Dipeptidyl peptidase 4 (DPP4) inhibitors (also known as gliptins) are a new class of drugs that work by blocking the enzyme. Blocking this enzyme delays the inactivation of incretin-related hormones, such as GLP-1 and GIP (gastric insulin polypeptide), which play a physiological role in glucose regulation. GLP-1 stimulates insulin synthesis in pancreatic β cells, whereas GLP-1 reduces glucagon secretion in pancreatic α cells. These interactions improve glycemic control in T2DM patients. These drugs have few side effects, low risk of hypoglycemia and do not cause weight gain [57].

7.6 Glucagon-Like Peptide 1 (GLP-1) Analogues

The majority of Glucose-dependent insulin (GLP-1) analogues are incretin based therapies that enhance glucose-independent insulin secretion, reduce glucagon secretion and suppress glucose production in the liver. HbA1c can decrease for up to 3 years. These drugs are less well tolerated than DPP4 inhibitors. However, they provide more effective weight loss and promote weight loss. Corrects endothelial dysfunction, prolongs gastric emptying, improves lipid profile, and lowers blood pressure. Many studies have shown that incretin-based treatments improve sleep, inflammation (reduced levels of reactive proteins) and diseases of the central nervous system, liver and cardiovascular system [58].

7.7 Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors

Inhibitors of SGLT2, or Gliflozin, slow down the flow of sodium and make it easier for the kidneys to get rid of glucose. They do this by blocking glucose from being reabsorbed in the lower tubules of the kidneys, which lowers the amount of glucose in the blood. This class of pharmacological agents includes canagliflozin, dapagliflozin and empagliflozin. Because they work independently of insulin, they can be used by patients at all stages of diabetes. These drugs have the potential to enhance the functioning of β-cells, enhance insulin responsiveness and reduce glucotoxicity due to glucosuria, among other effects. It has been observed to reduce HbA1c levels by a range of 0.5% to 1%, as well as to reduce body weight and blood pressure. Adverse reactions have been identified, with urinary tract infections being the most common, particularly in women, as well as genital Mycotic Infections and symptoms associated with volume reduction [59].

7.8 Combination of Multiple Treatments

Combination therapy for single-drug dose reduction also provides quicker and more effective blood sugar control. Combination therapy is typically initiated when monotherapy fails to

control blood glucose levels and various oral antidiabetic agents and exogenous insulin can be used in combination to reduce insulin doses. Combination therapy improves glycemic control when insulin is used in combination with metformin or TZD. Basal insulin when used in combination with GLP- 1 receptor agonists, reduces high blood sugar (HbA1c) levels along with weight loss. In addition, they can be used in conjunction with inhibitors of DPP4 to enhance glycemic regulation and weight loss without exacerbating hypoglycaemia [60].

Studies have shown that low-dose metformin, when used in combination with TZD class drugs (rosiglitazone and pioglitazone), is effective in preventing the progression of diabetes in prediabetic patients [61].

8. ALTERNATİVE THERAPİES (CAM)

CAM (Complementary And Alternative Treatments) The tendency to alternative treatments and natural methods is increasing rapidly because they are economically cheaper, patients and their relatives can reach them more easily, they are thought to be more reliable and similar reasons. CAM stands for complementary and alternative medicine. CAM is a term used to describe medications and practices that aren't part of traditional medical care but are offered as an alternative treatment. Alternative medicine refers to the practices that aim to obtain the curative effects of the drug instead of the drug used in standard treatment, but that are not biologically appropriate and cannot be tried or tested. CAM, integrated medicine, integrative medicine and holistic medicine are all part of the same system. What makes alternative medicine different from experimental medicine is that it uses science to test real treatments through ethical clinical trials and prove their effectiveness or not. Traditional practices can be called "alternative" if they're used outside of their proper context without proper scientific explanations and evidence [62].

Complementary medicine refers to treatments that are utilized in addition to traditional medical care but are not classified as traditional medical care. Alternative medicine, on the other hand, is a form of treatment that is used instead of traditional medical care [63].
In response to growing public and patient interest in complementary and alternative medicine methods, the U.S. government established the National Center for Complementary and Alternative Medicine (NCCAM) in 1998. NCCAM is responsible for conducting research, making recommendations on CAM techniques and providing guidance. They are;
1. Traditional Alternative Medicine: Acupuncture, homeopathy and oriental practices (also known as natural therapy, chinese or oriental medicine) are also part of this field.

2. Body Therapies: The use of touch in medicine dates back to the earliest days of medicine. The concept of tactile healing is derived from the principle that a condition or injury in a particular area of the body will have an impact on all the other areas. Manual intervention allows the body to fully focus on healing the area where the injury or disease occurred, while allowing other areas to return to optimal health. Chiropractic, osteopathic, massage, body movement therapies, Tai Chi, and Yoga are just a few examples.

3. Dietary and Herbal Approach: There are many different dietary and herbal approaches to nourish the body. Dietary and herbal approaches include: Nutritional supplements; herbal medicine; nutrition/diet apps

4. Application of external energy: It is generally accepted that external energy from physical objects or other sources directly affects a person's well-being. Examples of external energy therapies include electromagnetic therapies such as Reiki and Qigong

5. Mind-Based Therapies: Meditation, biofeedback, and hypnosis are some of the therapies that can help you improve your mental and emotional health. Both modern and traditional medicine recognize the mind-body connection and research shows that people with good mental and emotional health tend to be more successful.

6. Types of Sense-Based Therapy: It is widely accepted that the human senses, such as touch, vision, hearing, scent and taste, have a significant influence on one's overall health. For instance, Art, Dance and Music are examples of therapies that involve the senses, as well as Visualization and Auxiliary Images [64].

It is very popular in the Far East. It's accepted as a way of living a healthy life, rather than preventing the onset of disease, intervening when symptoms appear or curing diseases. Herbal treatments have become increasingly popular since the late 20th century. This is largely because they are more affordable, easier to access and less likely to cause side effects or toxic effects. Some of the herbs used in herbal treatment are Temple tree, Garlic, Green tea, Licorice Cloves Ginger, Different fruits juice Cinnamon [65,66].

9. NATURAL PRODUCTS USED İN ALTERNATİVE TREATMENT OF DİABETES

Diabetes is on the rise because of poor diet and obesity and it's only going to get worse in the next few years. Since there is no substitute for insulin in Type 1 Diabetes and the oral anti-diabetic drugs used in Type 2 Diabetes cause severe liver and kidney toxicity, the search for new drugs is intensifying. In addition, it appears that plants are an important source of new antidiabetic drugs.

9.1 Natural Remedies for Type 2 Diabetes

Weight loss and lifestyle modifications are effective treatments for Type 2 Diabetes. However, patients' acceptance and adherence to this treatment are low. In the clinic, many synthetic drugs are used with anti-diabetes effects. However, taking these drugs can lead to adverse effects such as weight gain, fluid deficiency, hypoglycemia and heart failure. Herbal medicines and their ingredients have been shown to have antidiabetic effects and are also less toxic and have fewer side effects.

9.1.1 Flavonoidler

Many flavonoids are found in fruits and vegetables, as well as herbs and other plant-based foods. Some flavonoids are anti-cancer and anti-toxigenic, while others are anti-hepatoprotective and anti-inflammatory, as well as antiviral. In recent decades, some flavonoid species have been shown to have anti-diabetes properties (Table 2) [67].

Quercetin: Quercetin is a substance with a wide range of biological effects due to its anti-inflammatory and antioxidant properties. Its antidiabetic effects were thoroughly tested using STZ on diabetic rats. Quercetin improved hyperglycemia, hypercholesterolemia and hypertriglyceridemia in these rats. The main mechanism of action in the treatment of hyperglycemia is inhibition of free radicals and oxidative stress in T2DM mice. It has been shown to reduce hepatic inflammation, lipoprotein accumulation and glucose homeostasis in hyperglycemic conditions by stimulating glucose-glucose transporter type 4 (GLT4) [68].

Rutin: Rutin is an amino acid found in a variety of plants and foods. It is a type of polyphenol flavonoid. Recent studies have confirmed the pharmacological benefits of rutin in T2DM treatment. In T2DM animal models, rutin reduced fasting and non-fasting blood glucose

levels. Studies have also shown that rutin reduces, serum low-density lipoproteins (LDL) and high-density lipoproteins (HDL) and increases levels in various diabetes models [69].

Naringin: Naringin, also known as naringin flavanone, is a glycoside found in tomatoes and grapefruit. Some studies suggest that naringin exerts a strong inhibitory effect on serum DPP-4 (dipeptidyl peptidase-4) levels and reduces the incidence of random blood glucose. It also increases liver glycogen levels and decreases liver gluconeogenesis, thereby preventing the development of hyperglycemia [70].

Baicalein: By increasing the survival of islet β-cells in diabetic mice, baicalein improves hyperglycemia and glucose tolerance, as well as blood insulin levels. Studies have demonstrated that baicalein has anti-diabetic properties by altering the GSK3β, Akt and PI3K pathways, thereby decreasing oxidative nitrosative stress and the inflammation process [71].

Hesperidin: The active ingredient in Hesperidin, which is extracted from large quantities of Citrus aurantium, is effective against diabetes.

The inhibition of oxidative metabolism and inflammation by hesperidin has been demonstrated to be efficacious in the reduction of hyperglycaemia in T2DM-infected rats [72].

9.1.2 Polyphenols

Polyphenols are also called polyhydroxyyphenols. They are commonly consumed in the form of cocoa, tea and coffee. They are also found in grains and vegetables. Polyphenols are used to prevent and treat a wide range of illnesses. They help keep your body from getting too stressed out and inflamed and they can help prevent fibrosis and other health issues that come with being overweight. Extracted polyphenols of Antirhea borebonica act on adipocytes to protect them from inflammation and oxidative damage. As a result, they play a significant role in diabetes development and prevention (Table 2) [73].

9.1.3 Terpenoids

Terpenoids from plants have been used in traditional medicine for a long time. Abscisic acid can help your body release insulin and regulate glucose uptake through GLUT 4 in vitro. It's also been shown to help with glucose tolerance in rats with insulin resistance or insulin deficiency, as well as in people with diabetes (Table 2) [74].

9.1.4 Alkaloids

Alkaloids also have anti-malaria, anti-hyperglycemia, anti-asthma, anti-cancer and anti-bacterial properties. Many alkaloids have been used in both traditional and modern medicine to discover new drugs (Table 2) [75].

9.1.5 Saponins

Saponins are a group of steroids and triterpenoid glycosides found in many plant species with a variety of biological functions. Saponins are commonly used in cosmetic and pharmaceutical products (Table 2) [76].

9.1.6 Quinones

Quinones are a type of drug that can be used to make anti-bacterial, cancer-fighting, and malaria-fighting medicines. Radix et Rhizoma Rhei contains different types of quinones, some of which have very important anti-T2DM properties (Table 2) [77].

9.1.7 Other components

In addition to the aforementioned natural products, a variety of other bioactive substances, such as proteins, polysaccharides, amino acids and other natural substances, possess biological properties antithetical to T2DM. For example, cinnamaldehyde, a naturally occurring flavoring and odorant that is commonly consumed daily, has been shown to reduce insulin resistance, increase glycogen synthesis and improve islet dysfunction by reducing glucolipid levels [78].

The use of these natural compounds as drugs or as nutritional supplements is still in the early stages, and further studies are needed to better understand potential future toxicities and drug-drug interaction. Many of the above mentioned natural compounds have anti-T2DM effects, however, over-reduction of glycemia leads to hypoglycaemia (which is one of the most severe adverse reactions). Therefore, further research is needed on standard characterisation, preparations, chronic adverse reactions and toxicities of natural products. Some of the natural products have beneficial effects in vitro, but their activity cannot be confirmed in vivo. Most of the natural products that have anti-diabetes effects have not been clinically tested [79].

Table 2. List of natural products with anti-T2DM properties [80].

Natural products	Model	Mechanisms of action
Flavonoids		
Naringenin	STZ and HFD induced rats	By reducing inflammation and oxidative stress, it reduces blood sugar levels and serum lipids and improves glucose tolerance
	Nicotinamide/STZ-induced rats	Insulinotropic and improving insulin by increasing the expression of the insulin receptor, adiponectin and GLUT4
Apigenin	STZ and HFD induced rats	Improving impaired glucose tolerance and reducing blood sugar serum lipid and by downregulating inflammation and oxidative stress
Luteolin	KK-Moon mice	By inhibiting lipid synthesis, it improves blood sugar, insulin, HbA1c and HOMA-IR levels
Luteolin-7-O-glucoside	KK-Moon mice	By inhibiting lipid synthesis, it improves blood sugar, insulin, HbA1c and HOMA-IR levels
Tangeretin	STZ-induced rats	can be used to modulate hepatic enzymes by increasing insulin secretion and lowering blood sugar
Kaempferitrin	STZ-derived mice C2C12 cells	It can also be used to lower blood sugar levels and increase 6-phosphofructo-1-kinase (PFK) activity Increases lactate production, glucose consumption, and modulates the activity of glycolytic enzymes
Kaempferol	STZ and HFD induced rats	Attenuate IR by reducing inflammation, decreasing ICC and inhibiting the NF-kB pathway

Myricetin	STZ-Cd-induced rats	Increased expression of glycogen, insulin, insulin signaling glycogen synthase and molecules
Bavachin	3T3-L1 adipocytes	Maximizes glucose uptake through GLUT4 translocation via activation of Akt/AMPK signaling pathway
Icariin	C2C12 mouse muscle cells	Addition of adiponectins and modulation of AMPK/Insulin
Polyphenols		
Eugenol	C57BL/6J mice induced with HepG2 cells and HFD	Inhibition of AGE formation and α-glucosidase Reduce hyperglycaemia by inhibiting liver gluconeogenesis by modulating CAMKK-AMPK-CREB
Paeonol	STZ-induced rats	Glycosylated Serum Proteins, Reduced Blood Glucose and AGE Levels by Activation of NF-kB/ AGEs/Rage
Hydroxytyrosol	HFD-induced rats	Improving impaired glucose and reducing adiposity and insulin tolerance
	3T3-L1Cells	CB1 receptor gene transcription regulation 3T3-L1 cell differentiation inhibition gene transcription
Polydatin	db/db mice	Downregulation of SphK1-S1P signaling pathway
	Palmitic acid-induced HepG2 cells and db/db mice	Improves glucose and lipid metabolism by downregulating proprotein converting subtilisin/kexin type 9 (PCSK9)
	STZ and HFD induced rats	Improving lipid and glucose metabolism by activating Akt signaling pathway
p-coumaric acid	STZ-induced rats	Improve glucose tolerance, reduce inflammation, antioxidant status and inhibit apoptosis
	STZ-induced rats	Reduced blood sugar levels and gluconeogenic and enzymes modulated glucoseand lipid metabolism by activation of GLUT 2
Caffeic acid	db/db mice	Reducing hepatic glucose output and increasing adipocyte glucose uptake, antioxidant and insulin secretion
Ferulic Acid	OLETF mice	Lowering blood sugar, increase serum adiponectin levels and reduce oxidative inflammation and stress
	HFD- and fructose-induced rats	Improve insulin sensitivity and liver glycogen synthesis, suppress gluconeogenesis, and suppress insulin signalin
Gallic acid	STZ and HFD induced rats	Improve insulin sensitivity in adipose tissue, regulate adipogenesis, increase adipose glucose metabolism and protect β-cells

Cinnamic acid	STZ-induced rats	It lowers blood sugar, play a role in Improve glucose tolerance and stimulate insulin secretion
Vanillic acid	HFD-induced rats	Improve insulin resistance by enhancing insulin signaling in the liver and reducing inflammation pathways
Protocatechuic acid	STZ-diabetic rats	Decreased HbA1c and plasma glucose provided an increased plasma insulin
Chlorogenic acid	db/db mice	Reducing HbA1c and plasma glucose by modulating the adiponectin receptor signaling pathway
	STZ-induced rats	lowering blood sugar
Ellagic acid	KK-Moon mice	Reduce serum resistin and activate liver PPARα to improve liver steatosis as well as serum lipid composition
Terpenoids		
Ursolic acid	Non-obese T2DM mice	Lowering plasma TC,FFA and VLDL-cholesterol levels, lowering hepatic G6Pase and increasing GLUT2, glucokinase activity and glycogen content
Betulinic acid	Mice fed HepG2 cells and HFD	Reduce hyperglycaemia by reducing liver gluconeogenesis through modulation of CAMKK-CREB-AMPK
Asiatic acid	Goto-Kakizaki rats	Lowering insulin levels and glucose and improving islet fibrosis
	diabetic mice	Normalization of Lipid Peroxidation Products,Plasma Glucose, Antioxidants and Activation of GLUT4 In PI3K / Akt Signaling
Maslinic acid	KK-Moon mice	Modulating glucose metabolism, in part by reducing insulin resistance
	HepG2 cells and HFD-induced mice	Modulating glycogen metabolism by enhancing the insulin signaling pathway and inhibiting glycogen phosphorylase
Corosolic acid	KK-Moon mice	Inhibition of cholesterol acyltransferase activity
Glycyrrhetinic acid	STZ-induced rats	have an antihyperglycemic effect
Tormentic acid	HFD-rats	To exert an antihyperlipidemic effect by down-regulating hepatic SREBP-1c and apolipoprotein C-III and increasing PPAR-a
Alkaloids		
Caffeine	T2DM patients	Building benefits for blood sugar control
	KK-Moon mice	Regulate the decreased total drinking water and blood insulin level

Tetrandrine	Alloxan-induced rats	Amelioration of pancreatic islet injury by downregulating miRNA-155 and TNF-α by reducing oxidative stress in the NF-kB signaling pathway
Colchicine		Reducing NLRP3-activated inflammation and improving metabolic dysregulation
Capsaicin	KK-Moon mice	Regulate decreased total drinking water and blood insulin level
Galantamine	metabolic syndrome patients	Alleviate inflammation and insulin resistance and reduce plasma insulin and HOMA-IR
Huperzine A	STZ-induced rats	Generating modulating oxidative stress, inflammation and apoptosis
Piperine	Alloxan-induced mice	help lower blood sugar
Theobromine	STZ-induced hypertensive rats	Increasing Sirt-1/NAD+ activity
Matrine	High-fat-fed mice	Reduce glucose intolerance, increase plasma insulin levels, and liver triglyceride (TG) levels, decrease lipid synthesis, and increase fatty acid oxidation
Oxymatrine	STZ and HFD induced rats	Reduce blood sugar, serum creatinine and blood urea nitrogen, oxidative stress
Evodiamine	KK-Moon mice	Improving glucose tolerance and preventing insulin resistance by inhibiting mTOR-S6K signaling and IRS1 serine phosphorylation
Fangchinoline	STZ-diabetic mice	Lowering blood sugar level
Arecoline	3T3-L1 adipocytes	Eliminate lipid storage by controlling insulin signals

9.2 Alternative Treatments for Type 1 Diabetes

9.2.1 Gene therapy and Type 1 Diabetes Mellitus

Gene therapy is the process of transferring or altering genetic material within cells to treat disease. The goal of gene therapy is to repair the faulty genes that cause disease and effectively prevent disease onset or stop disease progression. The three primary intervention techniques used in gene therapy are: the insertion of a novel gene into the body

replacement of defective genes with functional genes inactivation of defective genes that cause [81].
Gene therapy has become one of the most popular treatments today because it can treat a wide range of diseases that cannot be treated with conventional treatments, including autoimmune diseases, diabetes, cancer and heart disease [82].

T1DM is an immune system infection caused by T cells self-destructing of insulin-secreting β cells in your pancreas. As with any autoimmune disease, T1DM is complicated and may be caused by environmental as well as genetic factors. In recent decades, several genes have been successfully identified to be responsible for T1DM. Alternating or manipulating these genes through a gene therapy approach may provide a more comprehensive approach to disease management and potentially cure T1DM [83].

9.2.2 Stem Cell Transplantation is a Treatment for Type 1 Diabetes Mellitus

Stem cells are cells that come back from the dead and can be used to create almost anything. There are four main types of stem cells, depending on where they come from - adult stem cells, fetal stem cells, embryonic stem cells and induced pluripotent stem cells (iPSCs). Pluripotent Stem Cells (iPSCs), Human Embryonic Stem Cells (ESCs) and Adult Stem Cells (ASCs) are pluripotent, unipotent or oligopotent stem cells. Human-derived pluripotent PSCs, such as iPSCs and ESCs, provide a reliable source of human stem cells at an early developmental stage, with the capability to generate any type of cell in the adult body. Stem cells, such as iPSCs, CB-SCs, HSCs, and MSCs, have been used to protect islets and regenerate and maintain β-cells. In general, stem cells increase the weight of islets, with the capacity to differentiate into organoids similar to β-cells and restore immunocompetence by suppressing the immune responses of T cells and Th1 cells through TGF- β and inflammatory pathways. T1DM is an autoimmune disease, with immune cells attacking and destroying pancreatic β-cell. The immunomodulatory characteristics of stem cells and their ability to differentiate into insülin-producing cells, indicate that stem cell therapy could be a promising treatment option for T1DM [84].

9.2.3 The Role of β-Cell Replation in the Treatment of Type 1 Diabetes

The goal of β-cell replacement therapy is to restore normal blood glucose levels by restoring endogenous and regulated insulin and other hormone secretion from the Langerhans islets. This approach first emerged in the late 1960's with pancreatic transplants. In Type 1 Diabetes, transplants of the pancreas from non-diabetic donors can normalize blood glucose levels. If immunosuppression can prevent an alloimmune or autoimmune response, normal blood glucose levels are typically maintained. Pancreatic transplantation has been shown to improve quality of life and may improve patient survival in patients with diabetes microangiopathy or macroangiopathy [85]. The goal of allogeneic islet transplants is to restore adequate levels of insulin, glucagon and other islet hormones to insulin-dependent diabetic recipients, typically through pancreatic islet grafts in Type 1 Diabetes patients. Islets are harvested from a donor's pancreas and infused through a portal vein to the liver with immunosuppression of the recipient [86].

CONCLUSION

Diabetes is a serious health issue that affects people, their families and the economy. Furthermore, uncontrolled diabetes can lead to severe chronic complications including blindness, kidney disease and heart failure. Research is being done on new antidiabetic agents to reduce this problem. Because modern treatments have been proven to have adverse effects, traditional medicines have taken the lead. Moreover, today plant extracts

can be used together with standard medicines for the treatment of diabetes. Herbal natural products contain active ingredients that reduce blood sugar levels and control diabetes complications. More research will be conducted in the future to isolate, purify and identify bioactive compounds in plants. Alternative therapy is attracting more attention.

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