

Diabetes and the Nutrition and Diets for Its Prevention and Treatment: A Systematic Review and Dietetic Perspective

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Citation

Chinaza Godswill Awuchi, Chinelo Kate Echeta, Victory Somtochukwu Igwe. Diabetes and the Nutrition and Diets for Its Prevention and Treatment: A Systematic Review and Dietetic Perspective. *Health Sciences Research*. Vol. 6, No. 1, 2020, pp. 5-19.

Received: December 21, 2019; **Accepted:** January 9, 2020; **Published:** February 4, 2020

Abstract: The systematic review widely focused on diabetes and the developments in nutrition and diets required to prevent or control all types of diabetes. Diabetes is characterized by high blood sugar level over prolonged period. If left untreated, diabetes causes many health complications. Acute complications can include hyperosmolar hyperglycemic state, diabetic ketoacidosis, or even death. Serious long-term health complications include chronic kidney disease, foot ulcers, damage to the eyes, cardiovascular disease, and stroke. Diabetes occurs due to either the inability of the pancreas to produce enough insulin, or the body cells improperly responding to the insulin produced. Type 1, Type 2, and the Gestational diabetes are the three major types of diabetes mellitus, although there is a collection of other specific types. The Type 1 diabetes results from the failure of pancreas to produce enough insulin due to the loss of beta cells caused by an autoimmune response. Type 2 diabetes begins with the insulin resistance, a condition in which the cells fail to properly respond to insulin. As the disease keeps progressing, a lack of insulin may develop. A combination of insufficient exercise and excessive body weight is the most common cause. Gestational diabetes is third major form, and occurs when a pregnant woman without previous history of diabetes develops high blood sugar levels. Adequate dieting, with good nutrition and regular exercise are very important in preventing or controlling diabetes. Prevention and treatment of diabetes involve maintaining healthy diet, regular physical exercise, normal body weight, and also avoiding use of tobacco. Maintaining a healthy diet, low-fat diet, low-calorie diet, paleolithic diet, very low carbohydrate diet, raw foodism, and/or ketogenic diet can help prevent or manage diabetes.

Keywords: Diabetes Mellitus, Diabetes Causes, Diabetes Prevention, Nutrition and Diets for Diabetes Prevention, Nutrition and Diets for Diabetes Control

1. Introduction

Diabetes mellitus (DM), commonly called diabetes, is a group of metabolic disorders and diseases characterized by high blood sugar levels over prolonged period. The symptoms of high blood glucose (sugar) levels include increased thirst, increased hunger, and frequent urination [1]. Diabetes can cause many complications if not carefully treated and controlled. So far, there is no known cure for diabetes. Acute complications can include hyperosmolar hyperglycemic state, diabetic ketoacidosis, or death [1]. Serious long-term complications are cardiovascular disease,

stroke, foot ulcers, damage to the eyes, and chronic kidney disease. Diabetes is as a result of either pancreas not making enough insulin, or cells of the body improperly responding to the insulin produced [3].

There are three main types of diabetes, and a collection of "other specific types". Diabetes type 1 results from failure of pancreas to produce enough insulin caused by loss of beta cells. Diabetes type 1 was earlier referred to as the juvenile diabetes or insulin-dependent diabetes mellitus (IDDM). The loss of beta cells is as a result of an autoimmune response [4]. The cause of the autoimmune response is unknown [1]. Type 2 diabetes begins with the insulin resistance, a

condition where cells fail to properly respond to insulin. As the disease progresses, lack of insulin may develop. This form was previously known as "adult-onset diabetes" or "non-insulin-dependent diabetes mellitus" (NIDDM). The most common cause is combination of excessive body weight (obesity) and insufficient exercise [1]. Gestational diabetes is the third most common form, and occurs when a pregnant woman without previous history of diabetes mellitus develops high blood sugar levels [1].

Prevention and treatment of diabetes involve maintaining healthy diet, regular physical exercise, normal body weight, and also avoiding tobacco use. Control of blood pressure, eye care, and maintaining proper foot care are important for individuals with the disease [1]. Type 1 diabetes must be properly managed with insulin injections. The type 2 diabetes may be treated with medication with or without insulin. The Insulin and some oral medication can cause low blood sugar [5]. Weight loss surgery in individuals with obesity is sometimes very effective measure in people with type 2 diabetes. Gestational diabetes often resolves after birth of the baby [6]. Diabetic patients are advised to avoid sugars and sugary soft drinks. They may instead opt for diet soft drinks sweetened with sugar substitutes such as sugar alcohols [7, 8] which contribute little or no-calorie.

In 2017, an estimated 425 million individuals had diabetes worldwide [2], with type 2 diabetes making up around 90% of the cases [9]. This represents 8.8% of adult population, with equal rates in both men and women. Trends suggest that the rates will continue to rise [2]. Diabetes at least doubles an individual's risk of early death. In 2017 alone, diabetes resulted in about 3.2 to 5.0 million deaths [2]. The global economic costs of diabetes-related health expenditures in 2017 were estimated at US\$727 billion [2]. Average medical expenditures among individuals with diabetes are around 2.3 times higher [10].

2. Diabetes Mellitus (DM)

2.1. Signs and Symptoms of Diabetes

The classic symptoms of untreated diabetes include unintended weight loss, polydipsia (increased thirst), polyphagia (increased hunger), and polyuria (increased urination) [11]. Symptoms may develop rapidly (in weeks or months) in type 1 diabetes, whereas they usually develop much more slowly (years or decades) and may be absent or subtle in type 2 diabetes. Some other symptoms of diabetes are tiredness and weight loss.

Several other signs and symptoms mark the onset of diabetes though they are not specific to diabetes. In addition to the known signs and symptoms above, they also include blurred vision, slow healing of cuts, itchy skin, headache, and fatigue. Prolonged high blood glucose may cause glucose absorption in lens of the eye, which results in changes in its shape, leading to changes in vision. Long-term vision loss may also be caused by diabetic retinopathy. Numerous skin rashes that occur in diabetes are collectively called diabetic

dermadromes [12].

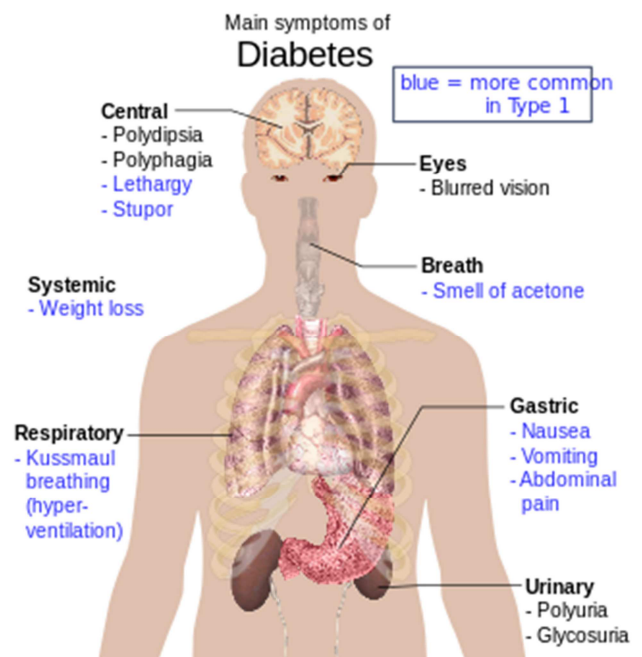


Figure 1. Overview of the most important symptoms of diabetes.

2.1.1. Diabetic Emergencies

Individuals (usually with type 1 diabetes) can also experience the episodes of diabetic ketoacidosis (DKA). DKA is a metabolic disturbance characterized by vomiting, abdominal pain, and nausea, deep breathing known as Kussmaul breathing, the smell of acetone on the breath, and in severe cases decreased level of consciousness [13]. A rare but equally severe likelihood is hyperosmolar hyperglycemic state (or HHS), which is more common in the case of type 2 diabetes and is mostly the result of dehydration [13].

Treatment-related hypoglycemia (low blood sugar) is common in individuals with type 1 diabetes (and also type 2) depending on the medication used. Most cases can be mild and are not regarded as medical emergencies. The effects can range from the feelings of unease, trembling, increased appetite, and sweating in mild cases to the more serious effects such as changes in behavior such as aggressiveness, unconsciousness, seizures, confusion, and (rarely) permanent, irreversible brain damage or even death in severe cases [14]. Rapid breathing and sweating, pale skin, cold are characteristic of low blood sugar (hypoglycemia) but not definitive. The mild to moderate cases can easily be self-treated by consuming foods or drinking beverages high in sugar; but not sugar substitutes used as sugar replacement [8]. Severe cases can result in unconsciousness and have to be treated with injections with glucagon or intravenous glucose, as soon as possible.

2.1.2. Complications and Risks of Diabetes

All forms of diabetes increase the risks of long-term complications. These usually develop after several years (10 to 20) but may be the first symptoms in people who have otherwise not received diagnosis before that time. Retinopathy, neuropathy, and nephropathy are the potential

complications of diabetes. Major long-term complications relate to the damage to the blood vessels. Diabetes doubles the risks of cardiovascular diseases and about 75% of death in individuals with diabetes are caused by coronary artery disease [15]. Other macro-vascular diseases include peripheral artery disease, and stroke.

The primary complications of diabetes as a result of damage in the small blood vessels are damage to the eyes, nerves, and kidneys. Damage to the eyes, called diabetic retinopathy, is caused by the damage to blood vessels in the eye retina, and can result in gradual loss of vision and eventual blindness [16]. Diabetes also increases the risks of having cataracts, glaucoma, and other eye problems. People with diabetes are recommended to visit an eye specialist or doctor once a year. The damage to the kidneys (called diabetic nephropathy) can lead to urine protein loss, tissue

scarring, and eventually chronic kidney diseases, sometimes requiring kidney transplantation or dialysis. Damage to the body nerves (called diabetic neuropathy) is the most common diabetes complication [16]. The symptoms can include pain, altered pain sensation, tingling, and numbness, which can result in damage to the skin. A number of diabetes-related foot problems (such as the diabetic foot ulcers) can occur, and may be difficult to treat, sometimes requiring amputation. In addition, proximal diabetic neuropathy causes a painful muscle atrophy and weakness. Also, there is a link between diabetes and cognitive deficit. Compared to individuals without diabetes, people with the disease have a 1.2 – 1.5-fold higher rate of decline in cognitive functions. Having diabetes, particularly when on insulin, increases risk of falls in older individuals [17].

2.2. Causes of Diabetes

Table 1. Comparison of type 1 and 2 diabetes.

Feature	Type 1 diabetes	Type 2 diabetes
Age at onset	Mostly in children	Mostly in adults
Autoantibodies	Usually present	Absent
Body size	Thin or normal	Often obese
Concordance in identical twins	50%	90%
Endogenous insulin	Low or absent	Normal, decreased or increased
Ketoacidosis	Common	Rare
Onset	Sudden	Gradual
Prevalence	~10%	~90%

The term "diabetes", without reservation, refers to diabetes mellitus. Normally, diabetes mellitus is broadly classified into four categories: type 1, type 2, the gestational diabetes, and the "other specific types". "Other specific types" are a group of few dozen individual causes. Diabetes mellitus is a more variable disease than once thought and people may have combinations of forms [18].

2.2.1. Type 1 Diabetes

The type 1 diabetes is characterized by the loss of the insulin-producing beta cells of pancreatic islets, resulting in insulin deficiency. Type 1 can be further classified as idiopathic or immune-mediated. The majority of type 1 diabetes has the nature of immune-mediated, in which T cell-mediated autoimmune attack results in loss of beta cells and consequently insulin [19]. It causes around 10% of diabetes mellitus cases in the North America and the Europe. Most affected individuals are otherwise healthy and of healthy weight when onset takes place. Sensitivity and responsiveness to insulin are often normal, especially in early stages. Though it has been referred to as the juvenile diabetes due to its frequent onset in children, majority of people currently living with type 1 diabetes are adults.

The term "Brittle" diabetes, also called labile diabetes or unstable diabetes, was traditionally used to describe the recurrent and dramatic swings in glucose level, often occurring for no just apparent reason in the insulin-dependent diabetes. However, the term has no biologic basis and ought not to be used. Type 1 diabetes can be accompanied by

unpredictable and irregular high blood sugar levels, and also the potential for serious low blood sugar levels or diabetic ketoacidosis. Other complications include impaired counter-regulatory response to a low blood sugar level, infection, endocrinopathies (e.g., Addison's disease), and gastroparesis (which results in erratic absorption of dietary carbohydrates). These phenomena are understood to occur no more regularly than in 1% - 2% of people with type 1 diabetes.

Type 1 diabetes is partly hereditary, with multiple genes, including some HLA genotypes, known to have influence on the risks of diabetes. In genetically susceptible individuals, the onset of diabetes can also be triggered by at least one environmental factor, such as diet or a viral infection. Several viruses have been implicated, however, to date there is no stringent or reliable evidence to support the hypothesis in humans [20, 21]. Some traditionalists claim that some alkaloids are therapeutic against diabetes [22]. Among dietary factors, data suggest that a protein present in gluten, called gliadin, may play a role in development of type 1 diabetes, although the mechanism is not completely understood [23].

Type 1 diabetes mellitus (type 1 DM) can occur at any age, and significant proportion is commonly diagnosed during adulthood. The latent autoimmune diabetes of adults (the LADA) is a diagnostic term applied when the type 1 diabetes develops in adults; and it has a slower onset than same condition in children. With this difference given, some use the informal term "type 1.5 diabetes" to refer to this condition. Adults with the LADA are frequently

misdiagnosed initially as having type 2 diabetes, relying on age rather than cause [24].

2.2.2. Type 2 Diabetes

The type 2 diabetes is characterized by an insulin resistance, which can be combined with relatively reduced secretion of insulin. The defective responsiveness of the body tissues to insulin is understood to involve the insulin receptors. However, the specific defects are unknown. Diabetes mellitus cases due to known defect are classified separately. The type 2 diabetes is the most seen and common type of diabetes mellitus [1]. Many individuals with type 2 diabetes have the evidence of prediabetes (impaired glucose tolerance and/or impaired fasting glucose) before meeting criteria for type 2 diabetes [25]. The progression of prediabetes to the overt type 2 diabetes can be reversed or slowed by medications and/or lifestyle changes that reduce the liver's glucose production or improve insulin sensitivity [26]. Type 2 diabetes mellitus is mostly caused by lifestyle factors and genetics. Many lifestyle factors are known to contribute to the development of the type 2 diabetes, including obesity (a body mass index, BMI, of greater than 30), poor diet, stress, urbanization, and lack of physical activity. Excess body fat is connected with 30% of the cases in those of Japanese and Chinese descent, 100% of Pacific Islanders and Pima Indians, and 60 to 80% of cases in individuals of European and African descent. Even those who are not obese usually have a high waist-hip ratio.

The dietary factors also have influence on the risk of developing type 2 diabetes. Excessive consumption of sugar-sweetened drinks is associated with an increased risk [28]. The type of fats and oils in the diet is also important; saturated fat and trans fats increase the risk, while monounsaturated and polyunsaturated fat decrease the risk [27]. Eating too much white rice may also increase the risk of diabetes, while other whole grains substitution including brown rice for white rice may lower the risks of diabetes. Lack of physical activity is understood to cause 7% of cases [29]. Reduced secretion and absorption of insulin leads to high blood glucose levels.

2.2.3. Gestational Diabetes

Gestational diabetes mellitus (or GDM) is similar to type 2 diabetes in various respects, involving a combination of relatively insufficient insulin secretion and responsiveness. GDM occurs in about 2 to 10% of all pregnancies and may disappear or improve after delivery. However, after pregnancy about 5 to 10% of women with gestational diabetes mellitus are found to have diabetes mellitus, most commonly type 2 diabetes. GDM is entirely treatable, but requires a careful medical supervision all through the pregnancy. Management may include blood glucose monitoring, dietary changes, and in most cases, insulin may be required [30].

Though it may be short-term, untreated gestational diabetes mellitus can damage the health of the mother or fetus. Risks to the baby include congenital abnormalities of the heart and central nervous system, skeletal muscle

malformations, and macrosomia (high birth weight). Increased levels of insulin in fetus's blood may inhibit the fetal surfactant production and cause an infant respiratory distress syndrome. High blood bilirubin levels may result from the destruction of red blood cell. In severe cases, perinatal death can occur, most commonly due to poor placental perfusion as a result of vascular impairment. Labor induction might be indicated with a decreased placental function. Caesarean section may be done if there is an increased risk of injury connected with macrosomia, such as the shoulder dystocia, or marked fetal distress [31].

2.2.4. Other Types of Diabetes Rarely Encountered

The maturity-onset diabetes of the young (the MODY) is an unusual autosomal dominant inherited form of diabetes, as a result of one of various single-gene mutations causing defects in production of insulin [32]. It is significantly less common than type 1, type 2, and GDM, constituting 1 to 2% of all cases. The name MODY refers to the early hypotheses as to its nature. Occurring due to a defective gene, the disease varies in the age at presentation and in the severity according to specific gene defect; as a result there are at least 13 MODY subtypes. People with MODY commonly can control it without using insulin [33].

Some diabetes cases are caused by body's tissue receptors unresponsive to insulin (even when the levels of insulin are normal, and is what separates it from the type 2 diabetes); this form is quite uncommon. Genetic mutations (mitochondrial or autosomal) can lead to defects in the function of beta-cell. Abnormal insulin actions may also have been determined genetically in some cases. Any disease causing extensive damage to the pancreas can lead to diabetes; for example, cystic fibrosis and chronic pancreatitis. Diseases associated with excessive insulin-antagonistic hormones secretion can cause diabetes (which is normally resolved once the excess hormone is removed). Some toxins damage pancreatic beta cells and a number of drugs impair insulin secretion, while others increase insulin resistance (especially the glucocorticoids which may provoke "steroid diabetes"). ICD-10 (1992) diagnostic entity, the *malnutrition-related diabetes mellitus* (MRDM), was deprecated by the WHO when the current taxonomy was announced in 1999 [34].

The following is a list of disorders and impairments that may increase the risks of diabetes:

- a) Genetic defects of β -cell function
 - a. The maturity-onset diabetes of the young
 - b. The Mitochondrial DNA mutations
- b) Genetic defects in insulin action or insulin processing
 - a. Defects in proinsulin conversion
 - b. The insulin receptor mutations
 - c. The insulin gene mutations
- c) Exocrine pancreatic defects
 - a. Cystic fibrosis
 - b. Fibrocalculous pancreatopathy
 - c. Hemochromatosis

- d. Pancreatectomy
- e. Pancreatic neoplasia
- f. The Chronic pancreatitis
- d) Endocrinopathies
 - a. Cushing syndrome
 - b. Glucagonoma
 - c. Growth hormone excess (acromegaly)
 - d. Hyperthyroidism
 - e. Hypothyroidism
 - f. Pheochromocytoma
- e) Infections
 - a. Cytomegalovirus infection
 - b. Coxsackievirus B
- f) Drugs
 - a. Glucocorticoids
 - b. Statins
 - c. Thyroid hormone
 - d. β -adrenergic agonists

2.3. Pathophysiology and diagnosis

Insulin is the major hormone that regulates the glucose uptake from the blood into most body cells, especially liver, muscle, and adipose tissue, except smooth muscle, wherein insulin acts via IGF-1. Therefore, insulin deficiency or the insensitivity of insulin receptors play a key role in all forms of diabetes.

The body obtains glucose from three key sources: the intestinal absorption of food; breakdown of glycogen (glycogenolysis), a storage form of glucose in the liver; and by gluconeogenesis, the generation of glucose from the non-carbohydrate substrates in the body [3]. Insulin plays a crucial role in regulating the body glucose levels. Insulin can inhibit the process of gluconeogenesis or the breakdown of glycogen, it can stimulate storage of glucose in form of glycogen, and it can stimulate transport of glucose into fats

and muscle cells [3].

Mechanism of insulin release in the normal pancreatic beta cells. The insulin production is relatively constant within beta cells. Its release is usually triggered by food, mostly food containing absorbable glucose. Insulin is released normally into the blood by the β -cells (beta cells), found in the islets of the Langerhans in the pancreas, as a response to rising blood glucose levels, typically after eating food. Insulin is used by approximately two-thirds of the cells of the body to absorb glucose from blood for use as fuel, for storage, or for conversion to other required molecules. Lower glucose levels result in reduced insulin release from the β -cells and in the glycogen breakdown to glucose. This process is mostly controlled by the glucagon, a hormone which acts opposite to insulin [35].

If the amount of insulin available is not sufficient, or if the insulin itself is defective, or if cells poorly respond to the effects of insulin (known as insulin resistance), then glucose is improperly absorbed by the body cells which require it, and is not appropriately stored in the muscles and liver. The net effect is poor protein synthesis, persistent high levels of blood glucose, and other metabolic disorders, such as metabolic acidosis in the cases of complete insulin deficiency [3].

When the blood glucose concentration remains high with time, the kidneys reach threshold of reabsorption, causing the body to excrete glucose via urine (glycosuria) [36]. This increases osmotic pressure of the urine and inhibits the water reabsorption by the kidney, resulting in increased production of urine (polyuria) and increased loss of fluid. Lost blood volume is osmotically replaced from water in the body cells and other body compartments, resulting in dehydration and increased thirst (polydipsia) [3]. Additionally, deficiency of intracellular glucose stimulates appetite resulting in excessive food consumption (polyphagia).

Table 2. WHO diabetes diagnostic criteria.

Condition	2-hour glucose	Fasting glucose	HbA _{1c}	DCCT %
<i>Unit</i>	<i>mmol/l (mg/dl)</i>	<i>mmol/l (mg/dl)</i>	<i>mmol/mol</i>	
Diabetes mellitus	≥ 11.1 (≥ 200)	≥ 7.0 (≥ 126)	≥ 48	≥ 6.5
Impaired fasting glycaemia	< 7.8 (< 140)	≥ 6.1 (≥ 110) & < 7.0 (< 126)	42-46	6.0-6.4
Impaired glucose tolerance	≥ 7.8 (≥ 140)	< 7.0 (< 126)	42-46	6.0-6.4
Normal	< 7.8 (< 140)	< 6.1 (< 110)	< 42	< 6.0

Diabetes mellitus is characterized by persistent or recurrent high blood sugar, and diagnosed by demonstrating any of the following:

- 1) Fasting plasma glucose levels ≥ 7.0 mmol/l (126 mg/dl)
- 2) Glycated hemoglobin (HbA_{1c}) ≥ 6.5 DCCT % (≥ 48 mmol/mol) [37].
- 3) Plasma glucose levels ≥ 11.1 mmol/l (200 mg/dl) 2 hours after a 75 g oral glucose load as in glucose tolerance test (OGTT)
- 4) Symptoms of high blood sugar level and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

In the absence of unmistakable high blood sugar, a positive result should be confirmed by repeating any of the methods above on a different day. Preferably, a fasting glucose level

should be measured due to the ease of measurement and also the considerable time commitment of the formal glucose tolerance testing, which takes 2 hours to complete and provides no prognostic advantage over fasting test [38]. According to current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) is considered diagnostic for diabetes mellitus (DM).

According to the World Health Organization, persons with fasting glucose level from 110 - 125 mg/dl (6.1 - 6.9 mmol/l) are considered to have an impaired fasting glucose. Individuals with plasma glucose at least 140 mg/dl (7.8 mmol/l), but not above 200 mg/dl (11.1 mmol/l), 2 hours after a 75 g oral glucose load are considered to have an impaired glucose tolerance. Between these two prediabetic

states, the latter one in particular is major risk factor for the progression to full-blown diabetes mellitus (DM), and cardiovascular disease [39]. Since 2003, the American Diabetes Association (ADA) uses a marginally different range for the impaired fasting glucose of 100 – 125 mg/dl (5.6 – 6.9 mmol/l). The glycated hemoglobin is better than the fasting glucose for determining the risks of cardiovascular disease and the death from any cause [40].

2.4. Prevention of Diabetes

There preventive measure for type 1 diabetes is not known [1]. Type 2 diabetes—which accounts for 85 to 90% of all cases worldwide—can normally be prevented or delayed by engaging in physical activity, eating a healthy diet, and maintaining normal body weight [1]. Higher levels of physical activity (over 90 minutes per day) reduce the risks of diabetes by 28% [41]. Effective dietary changes known to help prevent diabetes include maintaining diet rich in fiber and whole grain, and choosing good fats, such as polyunsaturated fats found in vegetable oils, nuts, and fish [42]. Eating less red meat and other foods with saturated fat, in addition to limiting sugary beverages can also help prevent diabetes. The smoking of tobacco is also associated with increased risk of diabetes and its related complications, thus smoking cessation can be a key preventive measure as well [43].

The relationship between type 2 and the main modifiable risk factors (unhealthy diet, physical inactivity, tobacco use, and excess weight) is similar in all the regions of the world. In addition, there is increasing evidence that the fundamental determinants of diabetes mellitus are a reflection of the main forces driving social, cultural, and economic change: globalization, population aging, urbanization, and the general health policy environment [42].

2.5. Diabetes Management

The management of diabetes focuses on keeping blood sugar levels very close to normal, without causing a low blood sugar level. This can often be accomplished with dietary changes, weight loss, exercise, and use of appropriate medications (oral medications, insulin). Learning about the disease and also actively participating in the treatment is very important, since complications are usually less severe and far less common in individuals who have well-managed their blood sugar levels [44]. Per the American College of Physicians (ACP), the goal of the treatment is attaining an HbA_{1c} level of 7 to 8% [45]. Attention is also given to other health issues that may accelerate negative effects of diabetes, including smoking, high blood pressure, lack of regular exercise, and metabolic syndrome obesity. Specialized footwear is used widely to reduce the risks of ulcers in at-risk diabetic feet, though evidence for the efficiency of this remains equivocal [46]. In some developing countries, many untrained traditionalists claimed that some bitter phytochemicals are helpful in the treatment of diabetes [22].

2.5.1. Lifestyle

Those with diabetes can benefit from the education about the disease and its treatment, dietary changes required, and exercise, with the aim of keeping both the short-term and the long-term blood glucose levels within adequate and acceptable bounds. Additionally, given the associated higher risk of cardiovascular disease, modifications of lifestyle are recommended to control blood pressure [47, 48], including healthy eating, regular exercise, and maintaining normal weight (BMI 18 to 25).

Weight loss can prevent progression from the prediabetes to type 2 diabetes, result in a partial remission in those with diabetes, or decrease the risks of cardiovascular disease [49, 50]. No single dietary pattern is the best for all individuals with diabetes [51]. Healthy dietary patterns, such as Mediterranean diet, low-carbohydrate diet DASH diet, are usually recommended, although no evidence support one over the others [49, 50]. According to the ADA, reducing the overall carbohydrate intake for people with diabetes has shown the most evidence for glycemic improvement, and for those with type 2 diabetes who are unable to meet the glycemic target or where reducing anti-glycemic medication is a priority, very-low or low carbohydrate diets are viable approach [50]. For overweight individuals with diabetes type 2, a diet that achieves loss of weight is effective [51].

2.5.2. Medications for Diabetes Mellitus

i. Glucose Control

Most medications used for diabetes treatment act by lowering blood sugar level through different mechanisms. There is general consensus that when those with diabetes maintain tight control of glucose (i.e. keeping the glucose level in their blood within normal range), they experience fewer complications like kidney and eye problems [52, 53]. However, there is discussion as to whether this is cost-effective and appropriate for people later in life where hypoglycemia risk may be more significant [54]. There are a few different classes of anti-diabetic medication. Diabetes type 1 can only be treated using insulin, typically with a combination of NPH and regular insulin, or synthetic analogs of insulin. Type 2 diabetes can also be treated with insulin at the later stages. Some medications for diabetes type 2 are available by oral, such as metformin, while others are available by only injection such as the GLP-1 agonists.

Generally, metformin is recommended as first-line treatment for diabetes type 2, as there is adequate evidence that it decreases mortality. Metformin works by reducing the liver's production of [55]. Several other groups of medications, mostly given by mouth, can also decrease blood sugar levels in type 2 diabetes. They include sulfonylureas (agents that increase insulin release), SGLT2 inhibitors (agents that increase excretion of glucose in the urine), acarbose (agents that decrease the absorption of sugar from intestines), and Thiazolidinedione (agents that make body more sensitive to insulin) [55]. When insulin is used in diabetes type 2, a long-acting formulation is often initially added, while continuing oral medications. Then the doses of

insulin are increased to the glucose targets.

ii. Blood Pressure

Since cardiovascular disease is serious complication associated with diabetes mellitus, blood pressure levels lower than 130/80 mmHg have been recommended. However, evidence supports lower than or equal to anywhere between 140/90 mmHg – 160/100 mmHg. The only added benefit found for blood pressure target below this range was an isolated reduction in risk of stroke, and this was accompanied by increased risks of other serious adverse events [56]. A review in 2016 found potential harm to treating less than 140 mmHg [57]. Among medications that lower blood pressure, the angiotensin-converting enzyme inhibitors (the ACEIs) improve the outcomes in individuals with diabetes whereas the similar medications, known as angiotensin receptor blockers (ARBs), do not [58]. Aspirin is also recommended for individuals with cardiovascular problems, however the routine use of aspirin is not found to improve the outcomes in uncomplicated diabetes mellitus.

iii. Surgery

Weight loss surgery in people with type 2 diabetes and obesity is usually an effective measure. Many can maintain normal blood sugar level with little or no medications following a surgery and long-term mortality is often decreased [59]. There is, however, short-term mortality risk of below 1% from the surgery [60]. The body mass index (BMI) cutoffs for when the surgery is appropriate are still unclear [59]. It is recommended, however, that this option be considered in individuals who are not able to get both their blood sugar and body weight under control. A pancreas transplant can be occasionally considered for those with diabetes type 1 who have severe complications of their diseases, including end-stage kidney disease demanding kidney transplantation.

iv. Support

In countries using a system of general practitioner, such as the UK, care may take place mostly outside hospitals, with hospital-based specialists care used only in the case of difficult blood sugar control, complications, or research projects. In other circumstances, the specialists and general practitioners share care in team approach. The home telehealth support may be an effective management technique [61].

2.6. Epidemiology

In 2017, a record of 425 million individuals had diabetes in the whole world, up from an estimated 382 million in 2013 and from about 108 million in 1980 [62]. Accounting for shifting age structure of global population, diabetes prevalence is 8.8% among adults, nearly the double rate of 4.7% in 1980 [62]. Type 2 makes up around 90% of the cases. A number of data indicate rates are approximately equal in men and women, but male excess in diabetes is found in many populations with higher incidence of type 2 diabetes, likely due to sex-related differences in the insulin sensitivity, the consequences of obesity and the regional body fat depositions, and other contributing factors such as

tobacco smoking, alcohol intake, and high blood pressure [63].

The WHO estimates that diabetes caused 1.5 million deaths in 2012, making diabetes the 8th leading cause of death [62]. However another 2.2 million deaths in the whole world were attributable to high blood glucose levels and the increased risks of cardiovascular diseases and other associated complications, such as kidney failure, which usually lead to premature death and are usually listed as the underlying cause of death certificates rather than diabetes [62]. For example, in 2017, [2] estimated that diabetes caused 4 million deaths worldwide (a significant increase from the WHO report in 2012), using modeling to estimate total number of deaths that may be directly or indirectly associated with diabetes.

Diabetes occurs all over the world but is more common (mostly type 2 diabetes) in more developed countries. However, the highest increase in the rates has been found in low- and middle-income countries [62], where over 80% of diabetic deaths occur [64], mainly due to poor management and treatment of the disease. The fastest prevalence increase is expected in Africa and Asia, where most individuals with diabetes will most likely live in 2030 [65]. The increase in rates in developing nations follows the trend of lifestyle changes and urbanization, including less physically demanding work, increasingly sedentary lifestyles, and the global nutrition transitions, marked by the increased consumption of foods that are highly energy-dense but with poor nutrient profile (often high in saturated fats and sugar, sometimes called the "Western-style" diet) [62, 65]. The global number of diabetes cases may increase by over 48% between 2017 and 2045 [2].

2.7. Societal and Cultural Significance

The 1989 St. Vincent Declaration [66] was the result of internationally concerted efforts to improve care accorded to the people with diabetes. Doing so is vital not only in terms of life expectancy and quality of life but also economically and productivity-related resources for the governments and healthcare systems; expenses due to diabetes have shown to be major drain on health.

Several countries established more and less fruitful national diabetes programmes for improvement of treatment of the disease [67]. People with diabetes who have symptoms of neuropathy such as tingling or numbness in the feet or the hands are two times as likely to be unemployed as people without the symptoms. In 2010, the diabetes-related emergency room (ER) rates of visit in the US were higher among individuals from the lowest income communities (i.e. 526 per 10,000 population) than from highest income communities (i.e. 236 per 10,000 population). Around 9.4% of diabetes-related emergency room visits were for the uninsured [68].

2.8. Other Animals

In other animals, diabetes is most often encountered in cats

and dogs. Middle-aged animals are most usually affected. Female dogs are two times as likely to be affected as the males, whereas according to some sources, the male cats are also more susceptible than females. In both species, all the breeds may be affected, but a number of small dog breeds are most likely to develop diabetes, such as the Miniature Poodles. The feline diabetes is strikingly related to human diabetes type 2. The Burmese breed, together with the Russian Blue, Norwegian Forest, and Abyssinian cat breeds, indicated an increased risk of diabetes, while several breeds showed lower risks. There is a connection between overweight and an increased feline diabetes risks. The symptoms may relate to polyuria and fluid loss, but the course may also be insidious (producing harm in a stealthy, usually, gradual manner). Diabetic animals are more susceptible to infections. The long-term complications acknowledged in humans are much infrequent in animals. The principles of treatment (oral antidiabetics, subcutaneous insulin, weight loss) and management of emergencies (for example, ketoacidosis) are similar to those treatments in humans.

2.9. Research Development

Inhalable insulin has been developed [69]. The original products were withdrawn because of side effects [69]. In June 2014, Afrezza, under development by pharmaceuticals company MannKind Corporation, was permitted by the US FDA for general sale. An advantage to inhaled insulin is more convenient and easy to use. The transdermal insulin in form of cream has been developed and many trials are being conducted on individuals with type 2 diabetes [70].

2.10. Diets and Nutrition for Diabetes and Its Prevention

Maintaining a healthy diet, low-fat diet, low-calorie diet, paleolithic diet, very low carbohydrate diet, raw foodism, and/or ketogenic diet can help prevent or manage diabetes.

2.10.1. Healthy Diet

A healthy diet is any diet that helps to improve or maintain overall health. Healthy diet provides the body with the essential nutrition: fluid, micronutrients, macronutrients, and

adequate calories [71]. A *healthy diet* is essential for *nutrition and good health*. It protects an individual against numerous chronic noncommunicable diseases, such as diabetes (especially type 2), heart disease, and cancer [72]. *Eating* a variety of diets and consuming less salt, saturated and industrially-produced trans-fats, and sugars are essential for a *healthy diet*.

A healthy diet may contain whole grains, fruits, and vegetables, and includes little or no processed foods and sweetened beverages. Requirements for a healthy diet may be met from a variety of animal-based and plant-based foods, though a non-animal source of the vitamin B12 is required for those following a vegan diet [73]. Various nutrition guides are published by the governmental, medical, and nutritional institutions to educate people on what to be eating to be healthy. The nutrition facts labels are also compulsory in many countries to allow the consumers to choose foods based on components relevant to health, rather than just merely satisfying their appetite.

The World Health Organization makes the following 5 recommendations with respect to both individuals and populations: [72]

1. Eat 400 g of fruits and vegetable or above per day (cassava, potatoes, sweet potatoes, and other starchy root crops do not count). A healthy diet also contains legumes (for example, beans, lentils), whole grains and nuts.
2. Limit intake of fats. Less than 30% of total calories should come from fat. Prefer unsaturated fats to saturated fats. Shun trans fats.
3. Limit the intake of the simple sugars to below 10% of calorie (below 25 grams or below 5% of calories per day may even be better).
4. Limit sodium and salt from all sources and make sure that salt is iodized. Below 5 g of salt per day have been shown to reduce the risks of cardiovascular diseases.
5. Maintain healthy weight by consuming approximately the same number of calories the body is using.

Table 3. The three healthy patterns.

Food group/subgroup (units)	U.S. style	Med-style	Vegetarian
Fruits (cup equivalent, eq)	2	2.5	2
Vegetables (cup eq)	2.5	2.5	2.5
Dark green	1.5 per week	1.5 per week	1.5 per week
Red/orange	5.5 per week	5.5 per week	5.5 per week
Starchy	5 per week	5 per week	5 per week
Legumes	1.5 per week	1.5 per week	3 per week
Others	4 per week	4 per week	4 per week
Grains (oz eq)	6	6	6.5
Whole	3	3	3.5
Refined	3	3	3
Dairy (cup eq)	3	2	3
Protein Foods (oz eq)	5.5	6.5	3.5
Meat (red and processed)	12.5 per week	12.5 per week	--
Poultry	10.5 per week	10.5 per week	--
Seafood	8 per week	15 per week	--
Eggs	3 per week	3 per week	3 per week
Nuts/seeds	4 per week	4 per week	7 per week

Food group/subgroup (units)	U.S. style	Med-style	Vegetarian
Processed soy (including tofu)	0.5 per week	0.5 per week	8 per week
Oils (g)	27	27	27
Solid fats limit (g)	18	17	21
Added sugars limit (g)	30	29	36

Source: [74]

2.10.2. Low-fat Diet

A low-fat diet is a diet that restricts fats, and often cholesterol and saturated fat as well. Low-fat foods are intended to reduce occurrence of conditions such as heart diseases and obesity, which increases the risks of diabetes and can worsen diabetes in already diabetic patients. For weight loss, low-fat diets perform similarly to low-carbohydrate diets, since macronutrients compositions do not determine weight loss success [75]. Fat provides 9 calories/g while carbohydrates and protein each provide 4 calories/g. The Institute of Medicine recommends restricting fat intake to 35% or less of total calories to control the intake of saturated fat [76]. Although low fats may affect the functional properties of foods [77, 78], restricting fats intake within the recommended limit is required for healthy living and managing diabetes.

According to the National Academies Press, high-fat diet often contain unacceptably high amounts of saturated fats, even if saturated fats from tropical oils and animal products are avoided. This is due to all fats contain some levels of saturated fatty acids. For instance, if an individual chose fats with 20% saturated fatty acids, the setting of fat intake at 35% of the total calories mean that 7% of the calories would come from the saturated fat. For this reason, Institute of Medicine and many nutritional institutions recommend consuming no more than 35% of the calories from fat [79]. Low-fat diets have been promoted to prevent heart disease and obesity. Lowering fat intake from 35 to 40% of total calories to 15 to 20% of total calories has shown to reduce total and LDL cholesterol by 10 – 20%; however, most of this reduction is due to a decrease in saturated fat intake [80].

2.10.3. Paleolithic Diet

The Paleolithic diet, caveman diet, stone-age diet, or Paleo diet is a modern fad diet requiring sole or predominant consumption of foods acknowledged to have been available to human during the Paleolithic era [81]. The digestive abilities of the anatomically modern humans, however, are, to a large extent, different from those of the pre-*Homo sapiens* humans, and has been used to criticize the core premise of the diet [82]. While there is wide variation in the way the paleolithic diet is interpreted [83], the diet typically includes fruits, nuts, vegetables, meat, and roots, and typically excludes foods such as sugar, processed oils, alcohol, salt, etc. The diet is based on avoiding processed food and the foods humans began eating after Neolithic Revolution when humans transitioned from the hunter-gatherer lifestyles to settled agriculture [81].

The scientific literatures commonly use the term "Paleo nutrition pattern", which is variously described as:

- 1) vegetables, nuts, roots, meat, organ meats, and fruits;
- 2) vegetables (including root vegetables), nuts, fish, meat, eggs, and fruit (including fruit oils, e.g., coconut oil, palm oil, and olive oil), and it excluded dairy, legumes, extra sugar, grain-based foods, and nutritional products of industry (such as refined carbohydrates and refined fats); and
- 3) avoids processed foods, and lay emphasis on eating vegetables, nuts and seeds, fruits, eggs, and lean meats [83].

As of 2016 there are limited information on the metabolic effects on the humans eating a paleolithic diet, but data are based on the clinical trials which have not been enough to have a sufficient statistical significance to allow the call for generalizations [81, 83]. These preliminary trials have indicated that participants consuming a paleolithic nutrition pattern had better metabolic and cardiovascular health than individuals eating a standard diet [81, 84], though the evidence is sufficient enough to recommend the paleolithic diet for treatment of metabolic syndrome [84], but it may also be used to reduce the risks of diabetes and other nutritional diseases. As of 2014 there was lack of evidence that paleolithic diet is effective in treatment of inflammatory bowel disease [85].

2.10.4. Low-carbohydrate Diets (Carbohydrate-Restricted Diets)

Low-carbohydrate diets, also known as carbohydrate-restricted diets (CRDs) are the diets that restrict consumption of carbohydrate relative to the average diet. Diets high in carbohydrates (e.g., pasta, sugar, bread) are limited, and replaced with the foods containing higher percentage of protein (e.g., meat, shellfish, eggs, cheese, poultry, fish, nuts, and seeds) and fat, as well as low carbohydrate foods, such as chard, collards, spinach, kale, and other fibrous vegetables. However, there is a lack of general standardization of how much carbohydrates low-carbohydrate diets must have, which has complicated research [86]. A low-carbohydrate diet reduces body exposure to high glucose levels, leads to weight loss, decrease the risk of obesity, and prevent or control diabetes, and other related metabolic imbalance. A definition, from American Academy of Family Physicians, identifies low-carbohydrate diets as having below 20% carbohydrate content [87].

There is no enough evidence that eating low-carbohydrate provides any particular health benefits, apart from weight loss where low-carbohydrate diets also achieve similar outcomes to other diets, since weight loss is determined mainly by calorie restriction and adherence [88]. Nevertheless, a loss of weight is required in obese people to reduce the risks of diabetes, maintain healthy lifestyle, and

reduce the risk of cardiovascular diseases. Consequently, it is scientific and logically conclusive to say that, for those with obesity and overweight, maintaining and adhering to low-carbohydrate diets is essential for reducing the risk of diseases such as diabetes, cardiovascular disease, etc. An extreme form of a low-carbohydrate diet –ketogenic diet – is made as medical diet for treating epilepsy [85, 89]. Through celebrity endorsement it has come to be popular weight-loss food, but there is no evidence of distinctive benefits for this purpose, and it can have a few initial side effects [89]. The British Dietetic Association (BDA) named it among the top 5 worst celeb foods to avoid in 2018 [89].

There is little evidence for effectiveness of low-carbohydrate diet for individuals with type 1 diabetes [86]. For some people, it may be feasible to adhere to a low-carbohydrate regime in combination with carefully-managed insulin dosing, it can be hard to strictly maintain and there are some concerns about the potential adverse health effect caused by the diet [86]. In general, individuals with type 1 diabetes are advised to maintain an individualized eating plan [86].

The proportion of carbohydrates of all types in a diet is not directly linked to the risks of diabetes type 2, although there is some evidence linking diets containing some high-carbohydrate products, such as white rice or sugar-sweetened drinks, are associated with increased risks of type 2 diabetes. Some evidence indicates that eating fewer carbohydrate foods can reduce biomarkers of diabetes type 2 [90, 91].

A 2018 report on diabetes type 2 by the European Association for Study of Diabetes (EASD) and the American Diabetes Association (ADA) found that low-carbohydrate diets may not be as good as Mediterranean diets for improving glycemic control, and also that although having healthy body weight is vital, there is no single ratio of intake of carbohydrate, proteins, and fat that is optimal for every individual with type 2 diabetes [92]. There is no sufficient evidence that diets with low-carbohydrate are better than conventional healthy diets, wherein carbohydrates typically account for over 40% of calories consumed [93]. Low-carbohydrate dieting has no effects on the kidney function of individuals who have type 2 diabetes [94].

Limiting carbohydrate consumption commonly results in improved glucose control, though without long-term weight loss [90], but there may be immediate (2 to 10 weeks) noticeable weight loss, depending on the amounts of other energy-giving nutrients, especially fats. Low-carbohydrate diet can be useful to help individuals with type 2 diabetes lose weight, although no single approach is proven to be consistently superior [95]. According to the American Diabetes Association, people with diabetes should be developing a healthy eating pattern rather than focusing on individual micronutrients, macronutrients, or single foods. ADA recommended that the carbohydrate in a diet should come from legumes, vegetables, fruits, dairy (yogurt and milk), and whole grains, while sugary drinks and highly-refined foods should be avoided [95]. The ADA also stated that reducing the overall intake of carbohydrate for people

with diabetes has shown the most evidence for glycemia improvement and may be applied in a range of eating patterns that meet individual requirements and preferences, and for people with type 2 diabetes who cannot meet the glycemic target or where reducing anti-glycemic medication is a priority, low or very-low-carbohydrate diets are viable approach.

2.10.5. Very-low-calorie Diet

A very-low-calorie diet (VLCD), also called semistarvation diet or crash diet [96], is type of fad diet with extremely or very low daily food energy consumption. VLCD is defined as a diet containing 800 kilocalories (3,300 kJ) or less per day [97, 98]. Modern medically supervised very-low-calorie diets (VLCDs) use total meal replacement, with regulated formulation in Europe and Canada which have the recommended daily requirements for fatty acids, protein, vitamins, minerals, trace elements, and electrolyte balance. Carbohydrates can be completely absent, or partly substituted for the protein; this choice has significant metabolic effects. Medically supervised very-low-calorie diets have specific therapeutic application for rapid loss of weight, such as before a bariatric surgery or in morbid obesity, using formulated, nutritionally complete liquid foods containing not more than 800 kilocalories per day for maximum of 12 weeks [97]. Unmonitored very-low-calorie diets with insufficient macronutrient and mineral intakes have the potential to cause electrolyte imbalance and unexpected death via ventricular tachycardia either upon refeeding or by starvation [99].

2.10.6. Raw Foodism

Raw foodism, also called rawism or following raw food diet, is dietary practice of consuming only or mostly foods that are unprocessed and uncooked. Depending on the philosophy, or the type of lifestyle and the results desired, raw food diets can include a selection of vegetables, nuts, fruits, seeds, eggs, meat, fish, and dairy products [100]. Also, the diet may include simply processed food, such as cheese, numerous types of sprouted seeds, and fermented foods such as sauerkraut, yogurts, kefir, or kombucha, but normally not foods that have been homogenized, pasteurized, or produced with synthetic pesticides, solvents, food additives, and fertilizers. Raw food diets are diets entirely or mostly composed of food that is uncooked or cooked at low temperatures. When uncooked, many starch molecules are more likely resistant to digestion in the body, thereby reducing the glucose levels. Cooking improves the digestibility of nutrients [77]. The medical authorities have defined raw foodism as a fad diet. The raw food diets, precisely raw veganism, fail to provide the essential minerals and nutrients such as iron, calcium, and protein. Claims held by the raw food proponents are pseudoscientific [101].

2.10.7. Ketogenic Diet

The ketogenic diet is high-fat, adequate-protein, and low-carbohydrate diet that is used primarily in medicine to treat

difficult-to-control (i.e. refractory) epilepsy in children. The ketogenic diet compels the body to burn fats instead of carbohydrates. The carbohydrates contained in food are normally converted into glucose, which is transported around the body and is mainly important in fueling the brain function. However, if little or no carbohydrate remains in the diets, the liver converts fat into ketone bodies and fatty acids. The ketone bodies pass into brain and replace glucose as energy source. Elevated level of ketone bodies in blood, known as ketosis, results in a reduction in frequency of the epileptic seizures. Around 50% of children and young individuals with epilepsy who have tried various form of this diet had the number of seizures dropped by at least 50%, and the effects persist even after discontinuing the diet [102]. Some evidence shows that adults with epilepsy can benefit from the diet, and that less strict diets, such as modified Atkins diet, is equally effective. Potential side effects may be constipation, high cholesterol, acidosis, kidney stones, and growth slowing.

The ketogenic diet, low in carbs and high in fat, can potentially change the way body stores and uses energy, easing the symptoms of diabetes. With the keto diet, body converts fat, rather than sugar, into energy. The keto diet was made in 1924 as treatment for epilepsy. The effects of this pattern of eating are also being studied for diabetes type 2. The ketogenic diet may improve blood glucose level while at the same time reducing the requirement for insulin in diabetic people. However, the diet comes with risks. Ketogenic diet has been studied for the potential therapeutic use in numerous neurological disorders other than epilepsy: amyotrophic lateral sclerosis (ALS), autism, Alzheimer's disease (AD), headache, pain, Parkinson's disease (PD), neurotrauma, and sleep disorders [103].

3. Conclusion

Diabetes mellitus, a group of metabolic disorders, is characterized by a high blood sugar level over a prolonged period. If left untreated, diabetes mellitus can cause many complications. The acute complications can include hyperosmolar hyperglycemic state, diabetic ketoacidosis, or even death. Serious long-term complications include chronic kidney disease, foot ulcers, cardiovascular disease, damage to the eyes, and stroke. Diabetes is due to either the cells of the body not responding properly to insulin produced or the pancreas not producing enough insulin. Three main types of diabetes mellitus are Type 1, Type 2, and Gestational diabetes. Type 1 diabetes results from the failure of pancreas to produce enough insulin due to loss of beta cells. The loss of the beta cells is caused by autoimmune response. The cause of the autoimmune response is unknown. Type 2 diabetes begins with the resistance of insulin, a condition in which the cells fail to properly respond to insulin. As the disease progresses, lack of insulin may develop. The most common cause is combination of insufficient exercise and excessive body weight. Gestational diabetes is the third major form, and occurs when pregnant women without previous history of diabetes develop a high

blood sugar level. Prevention and treatment of diabetes involve maintaining healthy diet, normal body weight, regular physical exercise, and avoiding use of tobacco. Maintaining a healthy diet, low-fat diet, low-calorie diet, paleolithic diet, very low carbohydrate diet, raw foodism, and/or ketogenic diet can help prevent or manage diabetes.

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