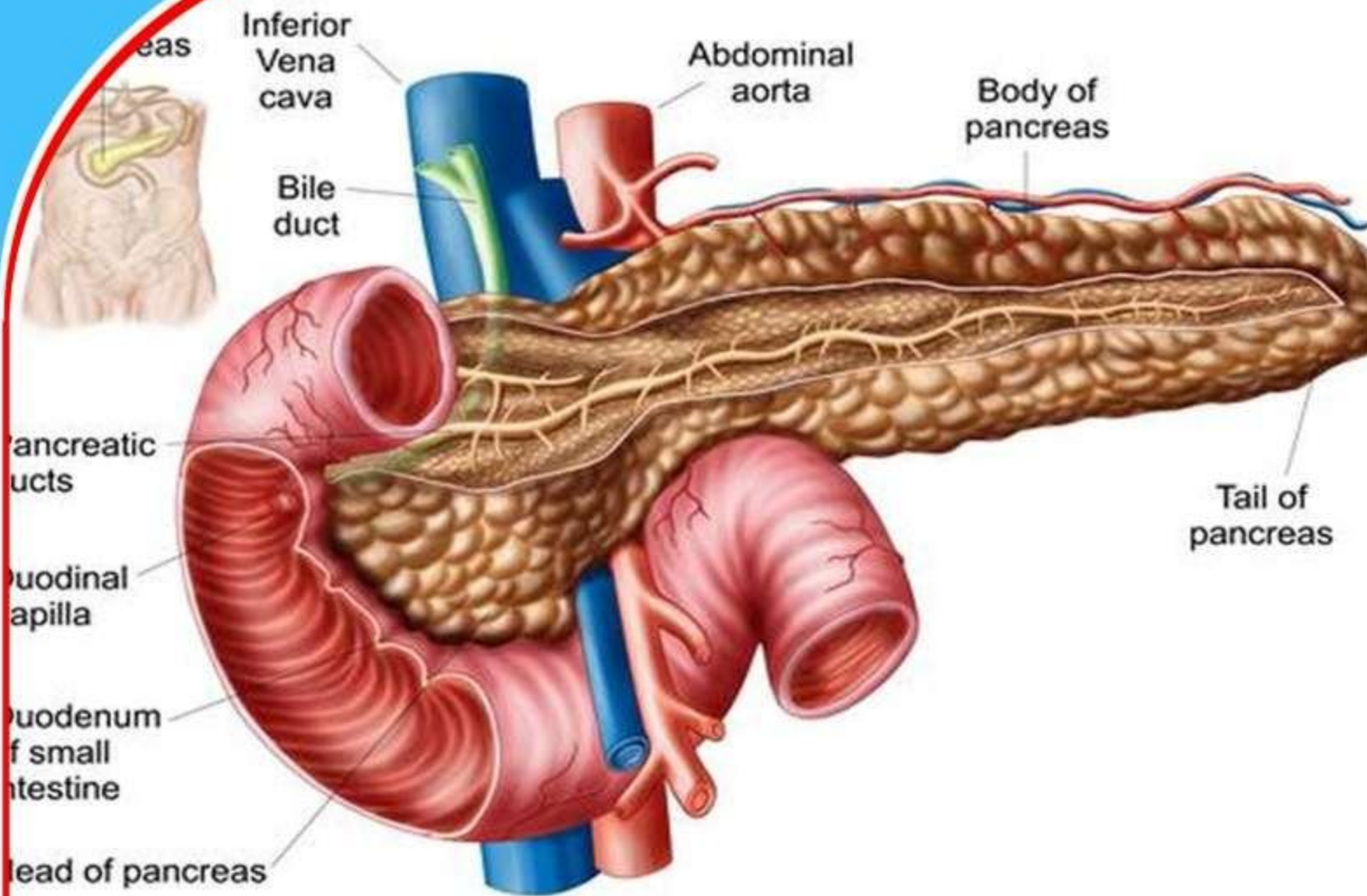


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A MODERN OVERVIEW ON DIABETES MELLITUS: A CHRONIC ENDOCRINE DISORDER

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Abstract

Diabetes mellitus is one of the most common endocrine disorders that affect the body's ability to make or use insulin. Diabetes mellitus (DM), or simply diabetes, is a group of chronic metabolic diseases in which a person experience high blood sugar, either because the pancreas does not produce enough insulin or because the body cells do not effectively use or respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Conventionally, diabetes has been divided into three types namely: Type 1 DM or insulin-dependent diabetes mellitus (IDDM) in which body fails to produce insulin, and presently requires the person to inject insulin or wear an insulin pump. This is also termed as "juvenile diabetes". Type 2 DM or noninsulin-dependent diabetes mellitus (NIDDM), results from insulin resistance, a condition in which cells fail to use insulin properly, with or without an absolute insulin deficiency. This type was previously referred to as or "adult-onset diabetes". The third main type is gestational diabetes which occurs when women without a previous history of diabetes develop a high blood glucose level during her pregnancy and may metamorphose to type 2 DM after giving birth. Currently available pharmacotherapy for the treatment of diabetes mellitus includes insulin and oral hypoglycemic agents. Thus, the present review underscores the issues surrounding the symptoms, diagnosis and treatment (especially use of anti-diabetic herbal species) of this killer disease with a view to suppressing its global spread and resurgence.

Keywords: *Diabetes, pancreas, symptoms, treatment, herbal therapy*

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by a deficiency in insulin production and its action or both which leads to prolonged hyperglycemia with disturbances in most metabolic processes inside the human body (Bastaki, 2005). Insulin is a hormone produced in the pancreas that helps transport glucose (blood sugar) from the bloodstream into the cells so they can break it down and use it for fuel (Preethi, 2013). People cannot live without insulin. Alternatively, DM can be regarded as the condition in which the body does not properly process food for use as energy. The pancreas, an organ that lies near the stomach, makes a hormone called insulin to help glucose get into the cells of our bodies. The body of a diabetic patient is either doesn't make enough insulin or can't use its own insulin as well as it should and this causes sugars to build up in the blood. Diabetes can cause serious health complications including heart disease, blindness, kidney failure, and lower-extremity amputations.

Diabetes mellitus is a disorder that affects the body's ability to make or use insulin. Insulin is a hormone produced in the pancreas that helps transport glucose (blood sugar) from the bloodstream into the cells so they can break it down and use it for fuel. People cannot live without insulin. Diabetes results in abnormal levels of glucose in the bloodstream. This can cause severe shortterm and long term consequences ranging from brain damage to amputations and heart disease (Preethi, 2013). Diabetes is characterized by hyperglycemia and disturbances in carbohydrate, fat and protein metabolism. It is associated with an absolute or relative deficiency in the secretion of insulin (Diabetes Mellitus 1, DM1) or with insulin resistance (Diabetes Mellitus 2, DM2) (Savage *et al.*, 2007; Stumvoll *et al.*, 2005). DM 2 is the most common form of the disease, accounting for 85 to 90% of all recorded cases (Tiwari and Rao, 2002).

Diabetes mellitus is the most common endocrine disorder. More than 150 million people are suffering from the disease worldwide (Tripathi, 2003) and it is likely to increase up to 300 million by 2025. According to WHO, the global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025 majorly in the developing countries (Jayaprasad *et al.*, 2011), presently, India, has the largest number of diabetic patients in the world and has been infamously known as the “**diabetic capital of the world**”(Abate *et al.*, 2007). The classical symptoms of type 1 diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss (Plevyak, 2011). **Etymology**

The terms "Diabetes" and "Mellitus" are derived from Greek. "Diabetes" denotes "a passer through; a siphon" whereas the "Mellitus" denotes "sweet". It is thought that the Greeks named it so due to the excessive amounts of urine produced by diabetics attracted flies and bees. The traditional way of diagnosing diabetes mellitus in ancient Chinese was by observing whether ants are attracted to a person's urine or not. In medieval ages, the European doctors tested for diabetes by tasting the urine themselves, a scene occasionally depicted in Gothic beliefs (Patlak, 2002).

Epidemiology

It is estimated that 366 million people had DM in 2011 and the figure is expected to increase up to 439 Million by the year 2030. DM caused 4.6 million deaths in 2011(Olokoba *et al.*, 2012)8. More than half of the deaths due to diabetes occur in people less than 60 years old. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and

middle-income countries (Chinmay and Anurekha, 2015). The global prevalence of diabetes is about 4% in 1995 and will rise to 5.4% by the year 2025. This increase in prevalence is expected to be more in the Middle Eastern 1 crescent, Sub-Saharan Africa and India (Motala, 2002). In Africa, the estimated prevalence of diabetes is 1% in rural areas, up to 7% in urban sub-Saharan Africa, and between 8-13% in more developed areas such as South 2 Africa and in population of Indian origin. The prevalence in Nigeria varies from 0.65% in rural, Mangu (North) to 11% in urban Lagos (South) (Akinkingbe, 1997) and data from the World Health Organization (WHO) suggests that Nigeria has the greatest number of people living with 1 diabetes in Africa (Wild *et al.*, 2004).

Nigeria has the largest population in Africa (about 170 million) and of this, the adult population (aged 20–79 years), is approximately 79 million (IDF, 2013). One third of all the cases of diabetes are in the rural communities, while the rest are in the urban centers. About two million of the cases of diabetes in Nigeria are undiagnosed. Deaths related to diabetes in Nigeria in 2013 were estimated to be 105,091 cases (IDF, 2013). Nigeria has the highest burden of diabetes in Africa, followed by South Africa with 2.6 million cases, Ethiopia 1.9 million, and Tanzania 1.7 million. Studies in Nigeria show that up to 73% of diabetes patients do not practice self-monitoring of blood glucose (Chinenye *et al.*, 2008; Ogbera *et al.*, 2007). In a recent study the prevalence of hypertension and peripheral neuropathy in Nigeria was more than 50%, while the prevalence of retinopathy was 35%, cataract 25%, cardiovascular disease 5%, foot ulcers 16%, and nephropathy 3% (Ogbera *et al.*, 2007). It was obvious from this and other surveys that the status of glycemic control and other targets such as lipids, glycated hemoglobin (HbA1c), blood pressure and education were below expectations (Ogbera *et al.*, 2007; IDF, 2006)

Classification of Diabetes Mellitus

There are several forms of diabetes. Scientists are still defining and categorizing some of these variations and establishing their prevalence in the population. Types of diabetes include:

i. Type 1 Diabetes

An autoimmune disease in which the immune system mistakenly destroys the insulin-making beta cells of the pancreas. This causes diabetes by leaving the body without enough insulin to function normally and this is called an autoimmune reaction, or autoimmune cause. It account for almost about 5-10% cases of diabetes globally and typically develops more quickly than other forms of diabetes. It is usually diagnosed in children and adolescents, and sometimes in young adults. To survive, patients must administer insulin medication regularly. The following triggers may be involved with this type of diabetes; viral or bacterial infection, chemical toxins within food, unidentified component causing autoimmune reaction and underlying genetic disposition may also be a type 1 diabetes cause (Mohammad, 2017). Type 1 diabetes used to be called juvenile diabetes and insulin-dependent diabetes mellitus (IDDM). However, those terms are not accurate because children can develop other forms of diabetes, adults sometimes develop type 1, and other forms of diabetes can require insulin therapy (Preethi, 2013).

Causes

1. Autoimmune Destruction of Beta Cells

Type 1 diabetes usually develops due to an autoimmune disorder. This is when the body's immune system behaves inappropriately and starts seeing one of its own tissues as foreign. The islet cells of the pancreas that produce insulin are seen as the "enemy" by mistake. The body then creates antibodies to fight the "foreign" tissue and destroys the islets cells leading to their inability to produce insulin. The lack of sufficient insulin then results in diabetes. It is unknown why this autoimmune diabetes develops. Most often it is a genetic tendency; sometimes it follows a viral infection such as mumps, rubella, cytomegalovirus, measles, influenza, encephalitis and polio (Menser, *et al.*, 1978). Certain people are more genetically prone to this happening although why this occurs is not known. Other less common causes of type 1 diabetes include injury to the pancreas from toxins, trauma, or after the surgical removal of the majority (or all) of the pancreas.

2. Genetic Susceptibility

Heredity plays an important part in determining who is likely to develop type 1 diabetes. Genes are passed down from biological parent to child. Certain gene variants that carry instructions for making proteins called human leukocyte antigens (HLAS) on white blood cells are linked to the risk of developing type 1 diabetes (Zimmet *et al.*, 1995).

3. Environmental Factors

Environmental factors, such as foods, viruses, and toxins, may play a role in the development of type 1 diabetes, but the exact nature of their role has not been determined. Some theories suggest that environmental factors trigger the autoimmune destruction of beta cells in people with a genetic susceptibility to diabetes (Harikumar *et al.*, 2015).

4. Viruses and Infections

A virus cannot cause diabetes on its own, but people are sometimes diagnosed with type 1 diabetes during or after a viral infection, suggesting a link between the two. Viruses possibly associated with type 1 diabetes include coxsackievirus b, cytomegalovirus, adenovirus, rubella, and mumps (Harikumar *et al.*, 2015).

5. Infant Feeding Practices

Some studies have suggested that dietary factors may raise or lower the risk of developing type 1 diabetes. For example, breastfed infants and infants receiving vitamin D supplements may have a reduced risk of developing type 1 diabetes, while early exposure to cow's milk and cereal proteins may increase risk (Hother *et al.*, 1988).

ii. Type 2 Diabetes

This is a kind of metabolic disorder, usually involving excess weight and insulin resistance. In these patients, the pancreas makes insulin initially, but the body has trouble using this glucosecontrolling hormone. Eventually the pancreas cannot produce enough insulin to respond to the body's need for it (i.e. the insulin is insufficient to bring about its proper effect). Type 2 diabetes is by far the most common form of diabetes, accounting for 85 to 95% of cases in developed nations and an even higher percentage in developing nations, as stated by the International Diabetes Federation. This disease may take years or decades to develop. It is usually preceded by pre diabetes, in which levels of glucose (blood sugar) are above normal but not high enough yet for a diagnosis of diabetes. People with pre diabetes can often delay or prevent the escalation to type 2 diabetes by losing weight through improvements in exercise and diet, as the Diabetes Prevention

Program and other research projects have demonstrated. Type 2 diabetes used to be called adult-onset diabetes and non-insulin-dependent diabetes mellitus (NIDDM). Those terms are not accurate because children can also develop this disease, and some patients require insulin therapy (Preethi, 2013).

Type 2 diabetes has multifactorial causes. These include: anxiety, stress, advance age, obesity, sedentary life style, irregular diet etc. Obesity has been found to contribute to approximately 55% type II diabetes and decreasing consumption of saturated fats (Mohammad, 2017).

Twenty percent of people with this type 2 diabetes have antibodies to their islet cells, which are detectable in their blood resulting in the possibility of incomplete islet cell destruction. These patients often tend to respond early to oral drugs to lower blood sugar but may need insulin at some point. **Causes**

The causes of type 2 diabetes are multifactorial and complex. But even though there is no single cause, there are some well-known predisposing factors- the most overwhelming being obesity (environmental factors) and a family history (hereditary factors) of type 2 diabetes.

Type 2 diabetes is as a result of both insulin resistance (where the cells don't respond well to insulin and cannot easily absorb glucose from the blood) and progressive beta-cell damage, resulting in too little insulin being secreted by the pancreas.

For various years, type II DM was observed only in adults, nowadays it has started to be seen also in children (i.e. Maturity Onset Diabetes of the Young). Until present the exact causes for the development of type II diabetes are unknown, some significant risk factors being pointed out. The most significant ones include: excess body weight, physical inactivity and poor nutrition. Other factors which impacted are ethnicity, family history of DM, past history of gestational diabetes and advancing age (WHO, 2016; Olokoba *et al.*, 2012; Standards of Medical Care in Diabetes, 2014; Standards of Medical Care in Diabetes, 2015). Wrong medication often leads to the high incidence of diabetes mellitus.

iii. Gestational Diabetes

This is a temporary metabolic disorder that any previously non-diabetic woman can develop during pregnancy, usually during the second or third trimester. Hormonal changes contribute to this disease, along with excess weight and family history of diabetes. About 4% of pregnant women develop gestational diabetes or 135,000 cases annually, according to the American Diabetes Association (Preethi, 2013).

Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy period. About 20% - 50% of affected women develop type 2 diabetes later in life (Lawrence *et al.*, 2008).

Causes

It is not known exactly why some women develop gestational diabetes, but there is often a positive family history of diabetes mellitus. As pregnancy progresses, the placenta produces insulinblocking hormone, which might result in woman's blood glucose levels becoming elevated if there is no enough insulin to counter this effect. **iv. Secondary Diabetes**

Diabetes caused by another condition. There many potential sources of secondary diabetes ranging from diseases such as pancreatitis, cystic fibrosis, Down syndrome and hemochromatosis to

medical treatments including corticosteroids, other immunosuppressive, diuretics and pancreatectomy (Riaz, 2009).

Signs and Symptoms

The signs and symptoms of diabetes mellitus are many. This is a reason why diabetes is termed the silent killer. It is important to bear in mind that these symptoms may be mistaken for an ailment in themselves or for some other disease. The most commonest and typical symptoms of diabetes are:

i. Polyurea

This is the excessive or frequent urination experienced by diabetic individuals, and it is the commonest sign of diabetes. Due to the excess sugar present in the urine, it possesses sugary taste. Normally, the body reabsorbs glucose as it passes through the kidney during urine formation. But when diabetes elevate the blood sugar level, the kidneys may not be able to bring it all back in. this causes the body to make more urine, and then takes fluid. **ii.**

Polydipsia

Because of the quantity of the water lost through frequent urination, the body experience dryness of mouth and excessive thirst. The patient has an intense craving for water and yet is never satiable. **iii. Polyphagia**

This refers to the excessive hunger often experienced by diabetic patient. This excessive hunger arises due to body reaction to lack of glucose which has been lost as a result of polyuria, thus starving the body cells. The patient is tempted to eat more quantity of food than usual, and this elevate the level of blood glucose, and more increase in body weight. More so, the body converts the food we eat into glucose which the cells use for energy with the help of insulin. If the body does not make enough insulin, or if the cells resist the insulin made by the body, the glucose cannot get into them and therefore no energy. This can make a person to become more hungry and tired than usual.

iv. Blurred vision

Changing fluid levels in the body could make the eye lenses to swell up. They change shape and lose their ability to focus.

Other symptoms include:

v. Unplanned weight loss

If the body could not get enough energy from the food, it will start burning muscle and fat for energy instead. This may leads to loss of weight even though you haven't change the way you eat.

vi. Nausea and vomiting

When the body resorts to burning fat, it makes ketones. These can build up in the blood to dangerous level, possibly a life-threatening condition called diabetic ketoacidosis. Ketones can make you feel sick to your stomach.

vii. Slow-healing sores or cuts

Over time, high blood sugar can affect the blood flow and causes nerve damage that makes it hard for the body to heal wound.

Other signs comprises of; sexual dysfunction in men, vaginal infections in women, numbness/tingling in hands and feet, itchy or flaky skin, skin and yeast infections plus frequent gum and bladder infections.

Diagnosis of Diabetes Diabetes Testing

Three blood tests are available to diagnose pre-diabetes and diabetes in people suspected to be associated with the disease. They are;

i. Casual Plasma (Blood) Glucose Test

The criterion for a diagnosis of diabetes with this test is the presence of diabetes symptoms and blood glucose level of 11.1 mmol/L (200 mg/dl) or higher.

ii. Fasting Plasma Glucose (FPG) Test

A diagnosis of diabetes is made when the fasting blood glucose level is 7.0 mmol/L (126 mg/dL) or higher on at least two tests. Values of 100–125 mg/dl indicate pre-diabetes. A normal fasting blood glucose level is less than 100 mg/dl.

iii. Oral Glucose Tolerance Test

The criterion for a diagnosis of diabetes with this test is two-hour blood glucose level of 200 mg/dl or higher. Pre-diabetes is diagnosed if the two-hour blood glucose level is 140–199 mg/dl.

iv. Postprandial Blood Glucose Test

Measures blood glucose levels 2 hours after eating a meal. Postprandial blood glucose is usually done in people who have symptoms of hyperglycemia, or when the results of a fasting glucose test suggest possible diabetes, but are inconclusive. Values of 200 mg/dl or more indicate diabetes.

Control, Management and Prevention of Diabetes

Regardless of the type of diabetes, patients are required to control their blood glucose with medications and/or by adhering to an exercise program and a dietary plan. The major components of the treatment of diabetes are; A) Drug treatment for diabetes

B) Non drug treatment for diabetes

A) Drug Treatment for Diabetes

Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, Exenatide, and Pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral anti hyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors.

Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in Type I, which must be injected or inhaled. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Treatments include agents which increase the amount of insulin secreted by the pancreas, agents which increase the sensitivity of target organs to insulin and agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract.

i. Insulin

Insulin is usually given subcutaneously, either by injections or by an insulin pump. Research is underway of other routes of administration. In acute care settings, insulin may also be given intravenously. There are several types of insulin, characterized by the rate which they are metabolized by the body. Insulin is essential for the treatment of type1 diabetes. For many years it was assumed, as an act of faith, that normalizing plasma glucose would prevent diabetic complications. The diabetes control and complications trial (American diabetes association, 1993)

showed that this faith was well placed: type 1 diabetic patients were randomly allocated to intensive or conventional management. **ii. Insulin Sensitizers**

Oral hypoglycemic agents including insulin are useful in the treatment of type 2 DM and those agents include Sulphonylureas, Alpha glucosidase inhibitors, Biguanides and Thiazolidinediones. The main aim is to correct metabolic disorder like resistance to insulin and insufficient insulin secretion.

a. Sulphonylureas

Sulphonylureas were the first widely used oral hypoglycemic medications. They are insulin secretagogues, triggering insulin release by direct action on the K_{ATP} channel of the pancreatic beta cells. Examples include; Glimepiride, Glibenclamide, Chlorpropamide, Glipizide, Glyburide etc.

b. Meglitinides

Meglitinides help the pancreas produce insulin and are often called "short-acting secretagogues." Their mode of action is original, affecting channels. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, hence enhancing insulin secretion. Eg: Repaglinide, Nateglinide, Nateglinide.

c. Biguanides

Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle. Although it must be used with caution in patients with impaired liver or kidney function, metformin has become the most commonly used agent for type 2 diabetes in children and teenagers. Eg: Metformin, Phenformin, Buformin.

d. Thiazolidinediones

Thiazolidinediones (TZD) or glitazones, belong to the medications of type II diabetes. Their chemical structure consists of thiazolidine group which produce the main action of these active ingredients. Their mechanism of action involve activation of peroxisome proliferator-activated receptor (PPAR gamma), a nuclear receptor. This action changes the transcription of several genes play a role in glucose and lipid metabolism and energy balance (Hauer, 2002). The main derivatives of TZDs are Pioglitazone, Rosiglitazone and Lobeglitazone.

e. Glucosidase Inhibitors

Alpha-glucosidase inhibitors, also known as "diabetes pills" but not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. They are mainly delivered to the patients via oral route so as to decrease blood glucose. Alpha-Glucosidase Inhibitors inhibit alpha- glucosidases that convert polysaccharide carbohydrates into monosaccharides in upper GI system. These drugs slow the absorption of glucose. Acarbose, was the first medication approved by FDA in 1995 and miglitol was following in 1996. Their use is quite limited because they must administer in multiple daily doses while some gastrointestinal (GI) side effects have been recorded.

f. Incretin based-therapies

Incretins consist a group of hormones (the two main are GLP-1 and glucose dependent insulinotropic peptide) produced by GI that raise insulin secretion in a glucose-dependent manner. Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).

g. Glucagon-Like Peptide (GLP) Analogs and Agonists

GLP agonists bind to a membrane GLP receptor. As a consequence of this, insulin release from the pancreatic beta cells is increased. Endogenous GLP has a half-life of only a few minutes; thus an analogue of GLP would not be practical. Exenatide, Liraglutide.

h. DPP-4 inhibitors (Gliptins)

Dipeptidyl peptidase-4 (DPP-4) inhibitors are new class of oral diabetic drugs which help in weight loss as well as decrease in blood sugar level and they work by an enzyme which destroys a group of gastrointestinal hormones called incretins. DPP-4 inhibitors are prescribed for type 2 diabetes mellitus patients who do not well respond to metformin and sulphonyl ureas (Deepthi *et al.*, 2017).

i. Amylin analogues or agonist

These are injectable which are used in treating both type 1 & type 2 Diabetes and are administered before meals. They inhibit the release of glucagon while eating, slows food emptying from the stomach. Pramlintide acetate (SYMLIN) is the class of drug available in US which is administered by subcutaneous injections. In the UK it is unapproved by National Institute for Health and Care Excellence (NICE) because it can significantly raise the risk of severe hypoglycemia (Deepthi *et al.*, 2017).

B) Non Drug Treatment for Diabetes

1. Change in Life Style

Life style change is defined as the way of living which has been altered by variety manner. Life style has seven principles of good diabetes care including: learning much about diabetes, getting regular care for diabetes, learning on how to control your diabetes, prevent long term diabetes problems, get checked for long term problems and treat them etc.

2. Exercise

It is very important in helping to prevent diabetes and is having vital role of our treatment. Physical exercise is very vital because, it helps in losing weight, reduces blood glucose levels and keeps it low for several hours after words, can reduce cholesterol and blood pressure, helps reduce stress. Exercise makes the tissues in the body more sensitive to the effects of insulin. This allows insulin to push more glucose out of the blood stream in tour cells, which will reduce the level of glucose in our blood.

3. Dieting

The diet recommends placing an emphasis on foods that are higher in fiber and low in fat. A high fiber and low fat diet can make body more sensitive to insulin. Diet also involves weight loss which is another way to increase diabetic patient's body sensitivity to the effects of insulin. **Limitations Associated With Hypoglycemic Drugs**

Oral anti-diabetic agents exert their effects by various mechanisms: stimulation of beta cells in the pancreas to produce more insulin (sulfonylureas and meglitinides), increasing the sensitivity of muscles and other tissues to insulin (thiazolidinediones), decreasing gluconeogenesis by the liver (biguanides), and delaying the absorption of carbohydrates from the gastrointestinal tract (alpha-glucosidase inhibitors). These treatments have their own drawbacks, ranging from the

developing of resistance and adverse effects to lack of responsiveness in large segment of patients population. Sulfonylureas lose effectiveness for 44% of patients within six years. Also, these treatments are associated with side effects or even toxic effects (e.g., thiazolidin-ediones may cause liver toxicity; sulphonylureas might worsen heart disease, lower the glucose below the normal range and increase the body weight gain; bloating, flatulence, diarrhea and abdominal discomfort and pain are the major complaints with glucosidase inhibitors) (Michael *et al.*, 2005; Dey *et al.*, 2002; DeFronzo, 1999). According to literature, two-thirds of medications prescribed for use in children have not been proven safe or effective for this patient population (Michael *et al.*, 2005). Moreover, none of these glucose-lowering agents adequately controls the hyperlipidemia that frequently met with the disease (Derek, 2001). The limitations of currently-available oral antidiabetic agents either in terms of efficacy/safety coupled with the emergence of the disease into a global epidemic have encouraged a concerted effort to discover drugs that can manage type 2 diabetes more efficiently (Ranjan *et al.*, 2002). Also, with increasing incidence of diabetes mellitus in rural population throughout the world and due to adverse effects of synthetic medicine, there is a clear need for development of indigenous, inexpensive botanical sources for anti-diabetic crude or purified drugs (Venkatesh *et al.*, 2003). **The Way Forward: Herbal Remedies**

In the last few decades eco-friendly, bio-friendly, cost effective and relatively safe, plant-based medicines have moved from the fringe to the main stream with the increased research in the field of traditional medicine (Deshmukh and Jain, 2015). As per ancient literature, more than 800 plants are reported to have anti-diabetic properties (Eddouks *et al.*, 2004). Ethno pharmacological surveys indicate that more than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity (Kesari *et al.*, 2007). Medicinal plants, since times immemorial, have been used in virtually all cultures as a source of medicine.

There are vast numbers of hypoglycemic herbal species that are widely used around the world across different sociocultural context. In Africa, the most commonly used species are; *Pileostigma thonningii* Milne-Redh., *Xylopia aethiopica* (Dun.) A. Rich., *Combretum micranthum* G. Don., *Ficus capensis* Thunb., *Cassia sieberiana* DC., *Nauclea pobeguini* Petit, *Ocimum sanctum* L., *Anacardium occidentale* L., *Jatropha curcas* L., *Nauclea latifolia* Smith, *Allium sativum* L., *Citrus medica* Linn., *Moringa oleifera* Lam., *Persea americana* Mill., *Catharanthus roseus* (L.) G. Don., *Landolphia heudeloti* DC., *Tamarindus indica* L., *Azizelia africana* Smith ex Pers., *Andansonina digitata* L., *Carica papaya* L., *Euphorbia hirta* L., *Garcinia kola* Heckel, *Landolphia dulcis* (Sabine) Pichon, *Mesonerum benthamianum*, *Ocimum viridae* Willd, *Psidium guajava* L., *Pterocarpus ericens* Poir., *Scoparia dulcis* L. and *Uvaria chamae* P. Beauv (Balde *et al.*, 2006). Plants-based products have been popular all over the world for the centuries. In diabetes, some herbal alternatives are proven to provide symptomatic relief and assist in the prevention of the secondary complications of the disease. Some herbs have also been proven to help in the regeneration of β -cells and in overcoming resistance. In addition to maintaining normal blood sugar level, some herbs are also reported to possess antioxidant activity and cholesterol-lowering action. The management of type 2 diabetes mellitus (NIDDM) is possible with the drugs that can lower the blood sugar level in one hand and restore the liver glycogen level on the other. In modern system of medicine, there is no drug, which is reported to possess both of these properties

(Shrabana *et al.*, 2003). However, the hypoglycemic effect of some herbal extracts have been confirmed in human and animal models of type 2 diabetes and conventional drugs have been derived from the active molecules of these medicinal plants. Metformin, a less toxic biguanides and potent oral glucose-lowering agent, was developed from *Galega officianalis* and used to treat diabetes (Daniel and Norman, 2001). Out of dozens of oral medications for diabetes, only one medication (metformin) is approved for use in children and it has been originated from herbs (Michael *et al.*, 2005).

Mechanism of Action of Herbal Anti-diabetics Agents

The anti-diabetic activity of herbs depends upon variety of mechanisms. The mechanism of action of herbal anti-diabetic could be grouped as;

- α –amylase inhibition.
- Inhibition in renal glucose reabsorption.
- Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes.
- Cortisol lowering activities.
- Insulin resistance reduction.
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the β -cells.
- Regenerating and/or repairing pancreatic β cells.
- Increasing the size and number of cells in the islets of Langerhans.
- Stimulation of insulin secretion.
- Stimulation of glycogenesis and hepatic glycolysis.
- Inhibition of β -galactocidase and α –glucocidase.
- Protective effect on the destruction of the β cells.
- Improvement in digestion along with reduction in blood sugar and urea.
- Prevention of pathological conversion of starch to glucose (Pulok *et al.*, 2006; Mohamed *et al.*, 2006; Manisha *et al.*, 2007).

Future Perspectives

A number of potential therapies for DM are recently being investigated (Mehmet *et al.*, 2017). The current insulin therapy includes subcutaneous injection, which regularly fails to emulate the glucose homeostasis that normal individuals eventuate. This fact generates numerous experiments in order to develop a safer and more effective non-invasive route for insulin delivery. It is widely reported that oral delivery is the most convenient administration route. However, insulin cannot be well absorbed orally because can be rapidly degrade via enzymatic cleavage in the gastrointestinal tract. Nanotechnology plays a key role in future marketed products. Several polymeric nanoparticles and nanocarriers such as liposomes, dendrimers and micelles have been studied in order to safely develop new medications (Sharma *et al.*, 2015; Alai *et al.*, 2015; Subramani and Pathak, 2012). The main properties of such nanoparticles are to present stability in gastrointestinal tract, be nontoxic and biocompatible as well as to be easily developed on a large scale. Moieties conjugation in order to prepare permeation enhanced properties and high bioavailability revealed

promising results indicating that nanoparticle based systems for insulin delivery could be advantageous for DM managements. Among others, herbal plants possess therapeutic values against DM. In fact, some ingredients of folklore medicinal plants seem to reveal hypoglycemic activity, and antioxidant action with desirable properties (Ezuruike and Prieto, 2014; Patel *et al.*, 2012; Rahimi, 2015).

Conclusion

Diabetes is a serious metabolic disorder affecting reasonable number of people globally. Differences in social structure, psychic stress, obesity, hormonal imbalance and heredity are optimizing the growth of its pandemic. At present, the treatment of diabetes mainly involves a sustained reduction in hyperglycemia by the use of hypoglycemic drugs in addition to insulin. Nanotechnology has been predicted as the main future alternative vehicle for a safe delivery and passage of insulin into bloodstream via gastrointestinal tract. More so, myriads of medicinal plants seem to reveal potential hypoglycemic activity and antioxidant action with desirable properties. Thus, there is need to further explore these plants to identify the lead compound with a view to developing promising antihyperglycaemic drugs. **Conflict of Interest** None to declare.

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