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MANAGEMENT OF DIABETES MELLITUS: A SYSTEMATIC REVIEW

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. This chronic metabolic disorder is a rapid-growing global problem with huge social, health and economic consequences. Current global estimates indicate that this condition affects 415 million people and is set to escalate to 642 million by the year 2040. In India, there are about 69.2 million people with diabetes and are expected to cross 123.5 million by 2040. An ageing population and obesity are two main reasons for the increase. Type 1 and type 2 diabetes arise from different etiologies but lead to similar metabolic derangements constituted by an absolute or relative lack of insulin that results in increased plasma glucose. The natural herbs for DM treatment target on lowering blood sugar, reducing the damaging effects of the disease and maintaining of a safe, healthy level of blood glucose. In this review, we provide an overview about the types, causes of diabetes, diagnosis, newly investigated drugs, their side effects, herbs and other alternative therapies available for the management and treatment of diabetes.

Keywords *– Diabetes, Insulin, Risk factors, Diagnosis, Current Treatment, Alternative therapy.*

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may occur due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. This chronic metabolic disorder is a rapid-growing global problem with huge social, health and economic consequences [1]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [2].

Classification of DM is based on its etiology and clinical presentation. As such, there are four classes of diabetes mellitus viz; type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes and prediabetes. Type 1 diabetes accounts for only a minority of the total burden of diabetes in a population although it is the major type of the diabetes in younger age. 85 to 95% of all diabetes in high-income countries is of type 2 accounting for an even higher dominance in developing countries [3]. Genetics, ageing, diet, obesity and lack of exercise may play a role in developing diabetes, especially Type 2 diabetes. Current global estimates indicate that this condition affects 415 million people and is set to escalate to 642 million by the year 2040 [4].

In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. In India, there are about 69.2 million people with diabetes and are expected to cross 123.5 million by 2040 [5].

2. TYPES OF DIABETES

a) Type 1 Diabetes (T1D)

This type of diabetes is categorized as autoimmune disease and occurs when the body's misdirect immune system attacks and destroys insulin producing beta cell in the pancreas. Although genetic or environmental triggers are suspected, the exact cause of Type 1 diabetes is not completely understood.

About 5-10 percent of people with diabetes have T1D. People with Type 1 diabetes must take insulin daily to manage their condition [6].

b) Type 2 Diabetes (T2D)

This type of diabetes occurs when your body becomes resistant to insulin, and sugar builds up in your blood [7]. T2D most often develops gradually with age and is characterized by insulin resistance in the body. About 90 percent of people are suffering from T2D [8]. Family history and genetics play a major role in developing T2D.

c) Gestational Diabetes

Gestational diabetes is high blood sugar during pregnancy. It affects 7% of all pregnancies worldwide and in India. It ranges from 6 to 9% in rural and 12 to 21% in urban area [9]. Left undiagnosed or untreated, it can lead to problems such as high birth weight and breathing problem for the baby. All pregnant women are tested for gestational diabetes at between 24 to 28 weeks of pregnancy, as this is when this problem usually occurs. Insulin-blocking hormones produced by the placenta cause this type of diabetes [10].

d) Pre-diabetes

Although Pre-diabetes is not technically diabetes, some experts now consider it to be the first step to Type 2 diabetes. Pre-diabetes occurs when your blood sugar is higher than normal, but it's not high enough for a diagnosis of type 2 diabetes. Pre-diabetes increases not only your risk of developing diabetes but also your risk of heart disease and stroke [11].

3. SYMPTOMS [12]

Diabetes symptoms are caused by rising blood sugar.

1) Unexplained weight loss
2) Frequent urination
3) Slow healing
4) Blurred vision
5) Impotence
6) Excessive fatigue
7) Polydipsia

The general symptoms of diabetes such as polyuria, polydipsia and polyphagia occur commonly in T1D, which has a rapid development of severe hyperglycemia and also in T2D. Severe weight loss is common sign only in T1D. Unexplained weight loss, fatigue and restlessness and body pain are also common signs of undetected diabetes.

4. RISK FACTORS OF DIABETES

a) Type 1 Diabetes

You're more likely to get type 1 diabetes if you're a child or teenager, you have a parent or sibling with the condition, or you carry certain genes that are linked to the disease [13].

b) Type 2 Diabetes [14]

Your risk for type 2 diabetes increases if you:

- are overweight
- are age 45 or older
- have a parent or sibling with the condition
- aren't physically active
- have had gestational diabetes
- have pre-diabetes
- have high blood pressure, high cholesterol, or high triglycerides.

5. DIABETES COMPLICATIONS

The long term complications of diabetes are broadly divided into micro vascular and macro vascular.

Micro vascular complications include neuropathy, nephropathy, and retinopathy, while macro vascular complications consist of cardiovascular disease, stroke, and peripheral artery disease (PAD) [15].

1) Retinopathy

2) Neuropathy

3) Cardiovascular Disease (CVS)

4) Nephropathy

5) Peripheral Artery Disease (PAD)

6) Dementia

6. DIAGONOSIS

The following tests are used for the diagnosis of diabetes;

a) Fasting Plasma Glucose (FPG) Test

b) Oral Glucose Tolerance (OGT) Test

c) A1C Test

a) Fasting Plasma Glucose (FPG) Test

The FPG is most suitable when done in the morning.

If fasting glucose level is 100 to 125 mg/dl, then it shows form of pre-diabetes called impaired fasting glucose (IFG) [16].

A level of 126 mg/dl or above, confirmed by repeating the test on another day, means that you have diabetes.

Plasma Glucose Result (mg/dl)	Diagnosis
99 and above	Normal
100 to 125	Pre-diabetes
Above 125	Diabetes*

b) Oral Glucose Tolerance (OGT) Test

The OGT Test requires fast for at least eight hours before the test.

Plasma glucose is measured immediately before and two hours after you drink a liquid containing 75 grams of glucose dissolved in water.

If blood sugar level is between 140 and 199 mg/dl 2 hours after drinking the liquid, then it shows form of pre-diabetes called impaired glucose tolerance or IGT [17].

A two-hour glucose level of 200 mg/dl or above, confirmed by repeating the test on another day, means that you have diabetes.

2-Hour Plasma Glucose Result (mg/dl)	Diagnosis
139 and above	Normal
140 to199	Pre-diabetes
200 and above	Diabetes*

c) A1C Test

The A1C test is a blood test that measures the percentage of sugar attached to hemoglobin, a protein in your red blood cells (RBCs). The higher the A1C, the higher your average blood sugar levels have been running over the past two or three months.

A normal A1C is below 5.7 percent, which corresponds to an estimated average blood sugar level that's lower than 117 milligrams per deciliter (mg/dl).

An A1C between 5.7 percent and 6.4 percent suggests pre-diabetes. An A1C of 6.5 or more indicates type-2 diabetes if the test is confirmed [18].

Estimate average blood glucose level (mg/dl)	Diagnosis
Below 117	Normal
117 to 137	Pre-diabetes
138 and above	Diabetes*

7. CURRENT TREATMENT

7.1 Type 1 Diabetes (T1D)

The cause of type 1 diabetes is the lack of endogenous insulin secretion and autoimmune destruction of β-cells in the pancreas. Insulin therapy itself is the basis in treatment of type 1 diabetes [19].

Presently, the most widespread route of insulin delivery is via a subcutaneous injection by the help of an insulin pens and single-use thin needles.

Metformin is the most widely used drug, in combination with sodium-glucose co-transporters 2 (SGLT2) inhibitors, amylin analogues, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. The climax of administration of these medicaments gives good outcomes in patients with T1D [20].

Insulin pumps are programmed to release specific amounts of rapid-acting insulin automatically. This steady dose of insulin is known as your basal rate, and it replaces whatever long-acting insulin you were using [21].

7.1.1 Potential future treatments

i) **Pancreas transplant:** With a successful pancreas transplant, patient would no longer need insulin. But pancreas transplants aren't always successful and the procedure poses dangerous risks. Because these risks can be more dangerous than the diabetes itself, pancreas transplants are generally reserved for those with very difficult to manage diabetes, or for people who also need a kidney transplant [22].

ii) Islet cell transplantation: Researchers are experimenting with islet cell transplantation, which provides new insulin-producing cells from a donor pancreas. Although this experimental procedure had some problems in the past, new techniques and better drugs to prevent islet cell rejection may improve its future chances of becoming a successful treatment [23].

7.2 Type 2 Diabetes (T2D)

To obtain good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary.

7.2.1 Lifestyle management

Changes in lifestyle have proven to be beneficial for a diabetic patient but for many patients is a complication keep long term. Food intake and regular physical exercise are the two main determinants of the energy balance, and they are supposed as a basic base in the treatment of patients with diabetes [24].

7.2.2 Newly investigated drugs [25-28]

i) Class: Sulfonylureas

Drugs: Gliclazide, Glyburide, Glimepiride

Mechanism: Sulfonylureas are widely used to treat non-insulin dependent diabetes mellitus. These drugs exert their hypoglycemic effects by stimulating insulin secretion from the pancreatic beta-cell. Their primary mechanism of action is to close ATP-sensitive K-channels in the beta-cell plasma membrane, and so initiate a chain of events which results in insulin releases.

Side Effect:

- Signs of low blood sugar, such as sweating, dizziness, confusion, or nervousness
- Hunger
- Weight gain
- Skin reactions
- Upset stomach
- Dark-colored urine

ii) Class: Meglitinides

Drugs: Repaglinide

Mechanism: They bind to the SUR1 receptor on the β-cell, although with lower affinity than sulfonylureas, and stimulate insulin release in the same way.

Side Effects

- Headache
- Stuffy nose
- Runny nose
- Loose stools (diarrhea)
- Joint pain
- Back pain
- Hypoglycemia

iii) Class: Biguanides

Drugs: Metformin

Mechanism: These drug decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Side Effect:

- Gastrointestinal distress
- Diarrhea
- Cramps
- Nausea & vomiting
- Increased flatulence
- Lactic acidosis
- Heartburn

iv) Class: Thiazolidinedione (TZD)

Drugs: Pioglitazone, Rosiglitazone

Mechanism: These drugs exert their anti-diabetic effects through a mechanism that involves activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR gamma), a nuclear receptor.

Side Effect:

- Edema
- Weight gain
- Macular edema
- Heart failure
- Hypoglycemia when combined with other anti-diabetic drugs
- Increased bone fracture risk

v) Class: Alpha-glucosidases inhibitor

Drugs: Acarbose

Mechanism: They inhibits enzymes (glycoside hydrolases) needed to digest carbohydrates, specifically, alpha-glucosidase enzymes in the brush border of the small intestines, and pancreatic alpha-amylase. Inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates.

Side Effect:

- Severe stomach pain
- Severe constipation
- Diarrhea that's watery or bloody
- Purple or red pinpoint spots under your skin
- Dark urine or clay-colored stools
- Yellowing of the eyes or skin (jaundice)

vi) Class: Dipeptidyl-peptidase-4 (DPP-4) Inhibitor

Drugs: Linagliptin, Sitagliptin, Saxagliptin, Alogliptin

Mechanism: The mechanism of these drugs is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.

Side Effect:

- Diarrhea
- Stomach pain
- Runny nose
- Sore throat
- Painful skin followed by a red or purple rash

vii) Class: Glucagon-like peptide (GLP-1) Agonist

Drugs: Exenatide, Dulaglutide, Liraglutide, Semaglutide

Mechanism: They target the GLP-1 hormone, which is partly responsible for insulin release and for attenuating hyperglycemia during meals (i.e the incretin effect)

Side Effect:

- Nausea and vomiting
- Diarrhea
- Weakness
- Dizziness
- Abdominal pain

viii) Class: Sodium Glucose Co-transporter 2 (SGLT-2) Inhibitor

Drugs: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

Mechanism: They block the SGLT2 protein involved in 90% of glucose reabsorption in the proximal renal tubule, resulting in increased renal glucose excretion and lower blood glucose levels.

Side Effect:

- Kidney failure
- Hyperkalemia
- Increased bladder cancer risk.
- Hypotension
- Ketoacidosis
- Increased cholesterol levels
- Serious urinary tract infections.

7.2.3 Herbal Treatment

i) *Gymnema Sylvestre* [29]

Gymnema sylvestre is known as one of the plants with potent anti-diabetic properties. Leaves of gymnema plant are used in the treatment of diabetes. The active compound of the plant is a group of acids termed as gymnemic acids.

Mechanism of action: This is attributed to the ability of gymnemic acids to delay the glucose absorption in the blood. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. These molecules fill the receptor locations on the taste buds thereby preventing its activation by sugar molecules present in the food, thereby curbing the sugar craving.

ii) Fenugreek

Fenugreek has found to be potent herb in the treatment of type 2 diabetes. **S**eed of fenugreek is widely used for the treatment purpose although leaves are also used but has found to be less potent. Various constituents of fenugreek seed are responsible for hypoglycemic activity, one of them being fenugreek galactomannan. Fenugreek galactomannan is one of the constituents of fenugreek seed, and shows promising antidiabetic properties [30].

Mechanism of action: Fenugreek has antidiabetic effect. However, the exact mechanism of action is still unclear and being studied, and more work is needed.

The antidiabetic effect of Fenugreek was thought to be due to formation of a colloidal-type suspension in the stomach and intestines when the mucilaginous fiber of the seeds is hydrated, therefore affecting gastrointestinal transit, slowing glucose absorption [31].

iii) Ginseng

Ginseng root (Araliaceous) has been used for over 2,000 years in the Far East for its health-promoting activities. It consist triterpene glycosides (saponins), commonly known as ginsenosides, peptides, polysaccharides, fatty acids and polyacetylene alcohol [32].

Mechanism of action: The hypoglycemic effect of ginseng root may be attributed to blocking intestinal glucose absorption and inhibiting hepatic glucose- 6-phosphatase activity resulting in delaying of food digestion and carbohydrate absorption rate. Ginseng polypeptide, isolated from the root was effective in decreasing liver glycogen and blood-sugar levels while, its aqueous extract showed a remarkable hypoglycemic activity, increasing insulin production, reducing pancreatic β-cells death and resistance to insulin, thus improving postprandial glycemia in diabetic patients [33].

iv) *Momordica charantia* [34]

A well-known plant (bitter melon) belonging to family Cucurbitaceae that widely used in folk therapy for the treatment of diabetes. Oral administration of the fruit juice or seed powder resulted in a significant decline in FBG and pronounced amelioration of glucose tolerance exerting both insulin secretagogue and insulin mimetic activities.

Mechanism of action: This potent antidiabetic activity mainly attributed to the presence of an insulin-like polypeptide known by polypeptide- P, similar in structure to the bovine insulin, which reduces plasma sugar levels when injected subcutaneously into type I diabetic patients and appears to inhibit gluconeogenesis. In addition, it improves glucose tolerance in type II diabetes. Other reported hypoglycemic agents isolated from *Momordica charantia* comprise the sterol glucoside mixture charantin isolated from fruit and the pyrimidine nucleoside vicine abundant in the seeds.

v) Tinospora

It is commonly known as Gaduchi a member of family Menispermaceae.

It is widely used as tonic and for treatment of endocrine metabolic disorders, including diabetes. The major constituents are diterpenoids, alkaloids, steroids, lactones, glycosides, phenolics, aliphatic compounds, sesquiterpenoid, and polysaccharides [35].

Mechanism of action: Oral administration of T. cordifolia root aqueous or alcohol extracts to alloxan diabetic rats produced a significant antidiabetic effect through enhancing the glucose metabolism as evidenced by an obvious suppression in plasma glucose, brain lipid values, serum acid phosphatase, alkaline and lactate dehydrogenase and hepatic glucose- 6-phosphatase, with consequent elevation in body weight, hepatic hexokinase and total hemoglobin [36].

vi) *Neem* (*Azadirachta Indica*)

It belongs to the family Meliaceae and has been used for a long time in traditional medicine in treating several ailments, including diabetes. Its leaves, stem, bark and seeds possess hypoglycemic activity via increasing insulin secretion from the beta cells of the pancreas.

Mechanism of action: Its leaves are characterized by the presence of high fiber content that is potent in diabetes management and controlling of post-prandial hyperglycemia through delaying gastric emptying, increasing viscosity of GIT content thus, suppressing digestion and absorption of carbohydrate with no risk of hypoglycemia, hyperinsulinemia and undesirable weight gain [37].

8. ALTERNATIVE THERAPIES USED FOR MANAGEMENT OF DIABETES

a) Diet

A diabetes diet is a healthy-eating plan that's naturally rich in nutrients and low in fat and calories. Key elements are fruits, vegetables and whole grains. In fact, a diabetes diet is the best eating plan for most everyone.

Recommended Foods

i) Healthy carbohydrates. During digestion, sugars (simple carbohydrates) and starches (complex carbohydrates) break down into blood glucose. Focus on the healthiest carbohydrates, such as fruits, vegetables, whole grains, legumes (beans, peas and lentils) and low-fat dairy products.

ii) Fiber-rich foods. Dietary fiber includes all parts of plant foods that your body can't digest or absorb. Fiber moderates how your body digests and helps control blood sugar levels. Foods high in fiber include vegetables, fruits, nuts, legumes (beans, peas and lentils), whole-wheat flour and wheat bran.

iii) Heart-healthy fish. Eat heart-healthy fish at least twice a week. Fish can be a good alternative to high-fat meats. For example, cod, tuna and halibut have less total fat, saturated fat and cholesterol than do meat and poultry. Fish such as salmon, mackerel, tuna, sardines and bluefish are rich in omega-3 fatty acids, which promote heart health by lowering blood fats called triglycerides. Avoid fried fish and fish with high levels of mercury, such as tilefish, swordfish and king mackerel [38].

b) Exercise

Exercise lowers blood sugar in two ways:

First, exercise increases insulin sensitivity. This means that your cells are better able to use available insulin to absorb sugar from the bloodstream to be used as energy for your body. Second, exercise stimulates another mechanism that allows your muscles to absorb and use sugar for energy, even without insulin.

The American Diabetes Association (ADA) recommends the following physical activity for adults with type 2 diabetes for blood sugar benefits and overall health:

- At least two and a half hours of moderate to vigorous intensity physical activity per week (i.e., brisk walking, water aerobics, swimming, or jogging).
- Two to three sessions of resistance exercise per week. Resistance exercise is physical activity that strengthens muscle strength, such as lifting five-pound weights or doing pushups [39-41].

c) Aromatherapy

Aromatherapy is another alternative therapy used to reduce stress. It involves smelling essential oils to promote relaxation. Smelling of essential oils like fenugreek, cinnamon, cumin, and oregano helped to lowered blood glucose levels when used in combination [42].

d) Meditation

While meditation may not burn calories, it can help relieve stress. Meditation can be mantra-based, like repeating an uplifting thought or statement. Meditation can also involve breathing techniques. Examples of meditation techniques include Vipassana, Transcendental, and Zen meditation [43].

9. CONCLUSION

Diabetes is a slow killer with no known curable treatments. However, its complications can be reduced through proper awareness and timely treatment. Three major complications related to blindness, kidney damage and heart attack. It is important to keep the blood glucose level of patients under strict control for avoiding the complications. One of the difficulties with tight control of glucose level in the blood is that such attempts may lead to hypoglycemia that create much severe complication than an increased level of blood glucose. Researchers now look for alternative methods for diabetes treatment. This approach plays a major role in the management of diabetes through balance diet and exercise. It believes that diabetes is one of the highly demanding research topics of the new century and wants to encourage new researchers to take up the challenges.

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