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Systematic Review

Type-2 Diabetes Mellitus: A Review of Current Trends

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ABSTRACT

Diabetes mellitus type 2 is a chronic metabolic condition whose incidence has been continuously growing around the world. As a result of this tendency, it is quickly becoming an epidemic in some parts of the world, with the number of individuals affected anticipated to double in the next decade as the world's population ages, adding to the already existing load on healthcare providers, particularly in poor developing countries. World Health Organization (WHO) guidelines are still used for screening and diagnosis, which include both clinical and laboratory characteristics. There is currently no cure for the disease; however, therapy options include lifestyle changes, obesity management, oral hypoglycemic medications, and insulin sensitizers such as metformin, a biguanide that reduces insulin resistance which is used as first line medication especially for obese patients. The traditional herbal medicine like garlic, neem, bitter gourd, aloe vera, onion, methi, amla, jamun, baheda etc. are also used for the treatment of the diabetes. Other effective medication includes non-sulfonylurea secretagogues, thiazolidinediones, alpha glucoside inhibitors, and insulin. Recent research into the biology of type 2 diabetes has led to the development of new medications such as glucagon-like peptide 1 analogues: dipeptidyl peptidase inhibitors, sodium glucose cotransporter 2 inhibitors, and 11-hydroxysteroid dehydrogenase 1 inhibitors, insulin releasing glucokinase activators. The novel drug delivery improves the treatment of diabetes by the inhaled insulin.

Keywords: Type 2 diabetes mellitus; Diabetes complications; Diabetes diagnosis; Diabetes management; Antidiabetic newer drugs; Antidiabetic herbal drugs

INTRODUCTION

Diabetes mellitus is a chronic disorder of carbohydrate, fats and protein metabolism. A defective or deficient insulin secretory response, which translates into glucose use, is a characteristic feature of diabetes mellitus. As it results in hyperglycaemia diabetes mellitus is commonly referred to as a "sugar" and it is the most common endocrine disorder and usually occurs when there is deficiency or absence of insulin or rarely, impairment of insulin activity. The international diabetes federation estimates the total number of diabetic subjects to be around 40.9 million in India [1–3]

Insulin and glucagon hormones both are secreted by the pancreas. insulin is secreted by the β- cells and glucagon is secreted by the α-cells both are located in the islets of langerhans. Insulin decreases the blood glucose level by the glycogenesis and transport glucose into the muscle, liver and adipose tissue. Neutral tissue and erythrocytes do not required insulin for glucose utilization whereas α-cell plays important role in controlling blood glucose by producing the glucagon and it increases the blood glucose level by accelerating the glycogenolysis in addition to increased risk of obesity, metabolic and cardiovascular disorders, and malignancy in future life for foetus after delivery. Type 2 diabetes mellitus comprises 80% to 90% of all cases of diabetes mellitus. [4,5]

CLASSIFICATION OF DIABETES

Insulin dependent diabetes mellitus

This form of diabetes is also known as autoimmune diabetes, and it was previously referred to as juvenile onset or ketosis prone diabetes. Other autoimmune disorders that the person may seek treatment for include Grave's disease, Hashimoto's thyroiditis, and Addison disease. [6] Type 1 diabetes mellitus, commonly known as insulin-dependent diabetes mellitus, is a type of diabetes that affects primarily children and young

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adults.[4]

Non-insulin dependent diabetes mellitus

Adult-onset diabetes is another name for type 2 diabetes mellitus in the background of insulin resistance.[7] The action of insulin is frequently resistant in people with this kind of diabetes. Both types of diabetes have long-term problems in the blood vessels, kidneys, eyes, and nerves, which are the leading causes of morbidity and death.[1] Obesity, sedentary lifestyle, increasing age, and genetic factors are all predisposing factors, and such patients are at an increased risk of developing macrovascular and microvascular complications.[8,9]

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) refers to glucose intolerance that occurs for the first time or is diagnosed during pregnancy.[2] Gestational diabetes mellitus is a term used to describe women who develop type 1 diabetes mellitus during pregnancy or women who have undetected asymptomatic type 2 diabetes mellitus that is identified during pregnancy.[10] GDM can develop during pregnancy and subside after delivery; however, children born to mothers who have GDM are more likely to develop obesity and type 2 diabetes later in life, a condition attributed to the consequences of intrauterine hyperglycaemia.[6]

Monogenic types diabetes

The most prevalent type of monogenic diabetes is caused by a mutation on chromosome 12 in the hepatic transcription factor hepatocyte nuclear factor (HNF)-1α, which is also known as a genetic deficiency of beta cells.[11] These types of diabetes are often marked by the beginning of hyperglycaemia at a young age. A few families have been discovered with genetic anomalies that result in the inability to convert proinsulin to insulin, and such features are inherited in an autosomal dominant way. They account for less than 10% of all DM cases.[12]

PATHOPHYSIOLOGY

Insulin sensitivity is a symptom of Type 2 diabetes, which is caused by insulin resistance, decreased insulin production, and eventually pancreatic β-cell loss.[13,14] As a result, glucose transport into the liver, muscle cells, and fat cells is reduced. Hyperglycemia causes an increase in the breakdown of fat. Impaired α-cell function has recently been identified as a factor in the pathogenesis of type 2 diabetes.[15]

Insulin is the primary hormone that controls the uptake of glucose from the blood into most body cells, particularly the liver, adipose tissue, and muscle, with the exception of smooth muscle, where insulin acts through the IGF-1 receptor. As a result, insulin insufficiency or receptor insensitivity play a key role in all types of diabetes mellitus.[16]

The breakdown of glycogen (glycogenolysis), the storage form of glucose found in the liver, and gluconeogenesis, the production of glucose from non-carbohydrate substrates in the body, are the three main sources of glucose in the body. Insulin is a hormone that regulates glucose levels in the body. Insulin can stop glycogen or protein from being broken down.[17]

Insulin is released into the bloodstream by β-cells in the pancreas' islets of Langerhans in reaction to rising blood glucose levels, usually after eating. About two-thirds of the body's cells utilise insulin to take glucose from the bloodstream for use as fuel, conversion to other molecules, or storage. Insulin releasability is reduced when glucose levels are low.[18] If the amount of insulin available is insufficient, or if cells respond poorly to insulin's effects (insulin resistance), or if the insulin itself is defective, glucose is not absorbed effectively by the body cells that require it, and it is not stored appropriately in the liver and muscles. The end result is elevated blood glucose levels, inadequate protein synthesis, and other metabolites., such as metabolic acidosis in cases of complete insulin deficiency.[17] When glucose concentration in the blood remains high over time, the kidneys reach a threshold of reabsorption, and the body excretes glucose in the urine (glycosuria).[19] This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume is replaced osmotically from water in body cells and other body compartments, causing dehydration and increased thirst (polydipsia).[16]

SOME COMMON SIGN AND SYMPTOMS

Diabetes mellitus causes cells to fail to properly metabolise glucose, causing them to starve.[2] The long-term effects of diabetes mellitus, which include the progressive development of retinopathy, which can lead to blindness, nephropathy, which can lead to renal failure, and neuropathy, which can lead to foot ulcers, and autoimmune dysfunction and sexual dysfunction people with diabetes are increase risk of disease.[20]

Other symptoms include are weight loss, polyuria (increase urination), polydipsia (increased thirst) and polyphagia (increased hunger). The common symptoms like blurred vision, headache, fatigue, slow healing of wounds, itchy skin and rashes of skin are also included.[2]

ETIOLOGY OF DIABETES MELLITUS

Etiology is the science of finding causes and origin of arise of disease, it includes:-

1. The changes in structure of β-cell of islets of pancreas also cause insulin dependent diabetes.
2. Viruses may also play a role in the etiology of diabetes

3. The various medication side effect and stress condition also produce diabetes
4. The genetic mutation also plays role in the etiology of diabetes is controversial as yet.

CAUSES OF DIABETES MELLITUS

Disturbances or anomalies in B-cell gluco-receptors that cause them to respond to higher glucose concentrations or relative ß-cell insufficiency. In either situation, insulin secretion is impeded, which can lead to ß-cell failure.[21] The direct consequences of hyperglycemia on neuronal metabolism is the basic principle behind microvascular disease that results in neural hypoxia.[22]

1. Insulin sensitivity in peripheral tissues is reduced due to the decrease in the number of insulin receptors and insulin receptor 'down regulation.' Many people are hypersensitive and hyperinsulinaemic, but their blood sugar levels are normal; they also have dyslipidaemia, hyperuricaemia, and abdominal obesity. As a result, there is relative insulin resistance, especially in the liver, muscle, and fat.[23]
2. Excessive hyperglycemia hormone (glucagon)/obesity results in a relative insulin deficit, causing the ß cells to lag behind. Abnormalities in nitric oxide metabolism have been demonstrated in two models, resulting in altered perineural blood flow and nerve injury.[21]
3. Various rare types of diabetes mellitus include "maturity onset diabetes of the young" other endocrine abnormalities, pancreatectomy, and gestational diabetes mellitus, which are caused by specific genetic flaws (GDM).[23]
4. Diabetes mellitus can be caused by an imbalance of certain receptors. Glucagon-like peptide-1(GLP-1) receptor, peroxisomes proliferator-activated receptor γ, ß3-adrenergic receptor, and enzymes such as glycosidase, dipeptidyl peptidase IV enzyme, and others are some of the particular receptors.[23]
5. The polyol pathway, oxidative stress, advanced glycation-end products, protein kinase C are all topics in diabetic neuropathy research right now.[22]

LIFESTYLE, GENETIC, AND MEDICAL CONDITION

Type 2 diabetes is caused mostly by genetics and lifestyle choices.[24] A number of lifestyle factors have been linked to the development of type 2 diabetes. Physical inactivity, sedentary lifestyle, cigarette smoking, and excessive alcohol use are all examples.[25] Obesity has been linked to around 55 percent of type 2 diabetes occurrences.[26] Toxic substances in the environment could be a factor in the recent rises of diabetes. Toxins in the environment may be playing a role in the recent rise in type 2 diabetes rates.[27]

Obesity has a substantial genetic component. There are a variety of medical issues that can cause or exacerbate type 2 diabetes. Obesity, hypertension, high cholesterol, and the condition known as metabolic syndrome are among them.[28] Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and medications are among the other reasons. Aging, high-fat diets, and a less active lifestyle have all been linked to an increased risk of type 2 diabetes.[29] The various drug treatments are also causes of the diabetes like statins,[30] glucocorticoids, β-adrenergic agonists.[31]

COMPLICATIONS

Complications of diabetes mellitus include problems that develop rapidly (acute) or over time (chronic) and may affect many organs and systems. The complications of diabetes can dramatically impair quality of life and cause long-lasting disability.

Acute complication

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is a serious and life-threatening condition that should always be treated as a medical emergency. Low insulin levels allow the liver to convert fatty acids to ketone bodies as a source of energy; ketone bodies are intermediate substrates in this metabolic process. This is typical when it happens on a regular basis, but it can become a major concern if it continues. DKA is caused by high quantities of ketone bodies in the blood, which lowers the pH of the blood. Ketoacidosis can quickly progress to the point of causing hypotension, shock, and death. Ketoacidosis is substantially more common in people with type 1 diabetes than in people with type 2 diabetes.

Diabetic coma

Diabetic coma is a medical emergency in which a person with diabetes mellitus becomes unconscious due to one of the following acute diabetic complications:[32]

- **Severe diabetic hypoglycaemia**

Diabetic keto-acidosis advanced enough to result in unconsciousness from combination of severe hyperglycaemia, dehydration and shock.

Hyperosmolar nonketotic coma, in which extreme hyperglycaemia and dehydration are sufficient to induce unconsciousness.

- **Hypoglycaemia**

Hypoglycaemia, or excessively low blood glucose, is a serious side effect of several diabetes medications. Otherwise, it is uncommon in both diabetic and non-diabetic patients. The patient may become agitated, hot, weak, and show many

other indications of sympathetic autonomic nervous system activation, including feelings of dread and paralysing fear. Consciousness can be altered or even lost in extreme cases, leading to coma, seizures, or even brain damage and death.[33]

- **Hyperglycaemia hyperosmolar state**

HNS (nonketotic hyperosmolar coma) is an acute complication with many of the same symptoms as DKA, but a distinct cause for therapy. Water is osmotically pulled out of cells into the blood in a person with very high blood glucose levels, and the kidneys finally begin to discharge glucose into the urine. This causes water loss and a rise in blood osmolarity. The osmotic effect of elevated glucose levels, together with the loss of water, will eventually lead to dehydration if fluid is not supplied. As water is removed from and discharged from the body's cells, they become increasingly dehydrated. Electrolyte abnormalities are also prevalent and can be fatal.[34]

Chronic complications

Microangiopathy

Diabetic nephropathy is kidney damage caused by diabetes that can progress to chronic kidney disease and necessitate renal dialysis. Adult renal failure is most commonly caused by diabetes.[35]

Diabetic neuropathy is characterised by aberrant and diminished sensation, which manifests itself in a 'glove and stocking' pattern that begins with the feet and progresses to other nerves, most commonly the fingers and hands. Mononeuritis or autonomic neuropathy is another type of diabetic neuropathy. Diabetic amyotrophy is a type of muscle weakening caused by neuropathy in diabetics.[35]

Diabetic retinopathy is characterised by the formation of fragile and low-quality new blood vessels in the retina, as well as macular edoema, all of which can result in significant vision loss or blindness. The most common cause of blindness in non-elderly persons is retinopathy.[35]

Diabetic cardiomyopathy is damage to the heart muscle that leads to poor relaxation and blood filling of the heart (diastolic dysfunction) and finally heart failure; this condition can develop independently of blood vessel damage caused by high blood glucose levels over time.[36]

Macrovascular disease

Macrovascular disease leads to cardiovascular disease, which is exacerbated by accelerated atherosclerosis:

- Coronary artery disease which leads to angina pectoris[14]
- Muscle wasting
- Peripheral vascular disease
- Stroke
- Skin ulcer
- Gangrene
- Female infertility

SCREENING & DIAGNOSIS OF DIABETES MELLITUS

A single abnormal blood glucose measurement should never be used to diagnose diabetes in an asymptomatic individual. If a patient is diagnosed with diabetes, the practitioner must be confident that the diagnosis is correct, as the repercussions for the patient are severe and long-term. Urine sugar, blood sugar, glucose tolerance test, renal glucose threshold, diminished glucose tolerance, increased glucose tolerance, renal glycosuria, extended glucose tolerance curve, cortisone stressed glucose tolerance test, intravenous glucose tolerance test, and oral glucose tolerance test are all used to diagnose diabetes mellitus.[11]

There are several ways of diagnose diabetes. Each way usually needs to be repeated on a second day to diagnose diabetes. The various tests for diagnosis of diabetes are:

Random plasma glucose test

This test is a blood check at any time of the day if one has severe diabetes symptoms. Diabetes is diagnosed at blood sugar of greater than or equal to 200 mg/dl.[11]

- **A1C test**

The A1C test measures average blood sugar for the past two to three months. The advantages of being diagnosed this way are that patients don't have to fast or drink anything. Diabetes is diagnosed at an A1C of greater than or equal to 6.5%.[11]

- **Fasting plasma glucose (FPG)**

This test checks fasting blood sugar levels. This test is done first thing in the morning, before breakfast. Diabetes is diagnosed at fasting blood sugar of greater than or equal to 126 mg/dl.[11]

- **Oral glucose tolerance test (OGTT)**

The OGTT is a two-hour test that checks your blood sugar levels before and two hours after you drink a special sweet drink. It tells the doctor how your body processes sugar**.** Diabetes is diagnosed at 2- hour blood sugar of greater than or equal to 200 mg/dl.[11]

MANAGEMENT

By altering one's lifestyle and diet, studies have shown that a combination of maintaining a body mass index of 25 kg/m^2, eating a diet high in fibre and unsaturated fat and a diet low in saturated and trans-fats and glycaemic index, regular exercise, quitting smoking, and moderate

alcohol consumption can significantly reduce the incidence of type 2 diabetes. This suggests that majority of type 2 DM can be prevented by lifestyle modification. Patients with type 2 DM should receive a medical nutrition evaluation; lifestyle recommendations should be tailored according to physical and functional ability.[37] Studied by Asif et al proved that Lifestyle modification with moderate exercise and consumption of antioxidant-rich fish oil is a novel and easy therapeutic intervention in the treatment of multifactorial syndrome of fatigue observed as a diabetic complication.[38]

PHARMACOLOGICAL AGENTS

Biguanides

Metformin is a biguanide that inhibits hepatic glucose synthesis, increases insulin sensitivity, promotes glucose uptake by phosphorylating GLUT-enhancer factor, increases fatty acid oxidation, and lowers glucose absorption from the gastrointestinal system. When compared to sulfonylureas, it has a low rate of hypoglycaemia.[39]

Sulfonylureas

These are generally well tolerated, although they can cause hypoglycaemia because they enhance endogenous insulin secretion.[37] Individuals with DM who are treated with sulfonylureas are 36% more likely to develop hypoglycaemia than younger patients.[40] When compared to glipizide, glyburide is linked to a greater rate of hypoglycaemia.[41] Age-related reduced renal function, concurrent use of insulin or insulin sensitizers, age above 60 years, recent hospital discharge, alcohol misuse, calorie restriction, multiple drugs, or medications that amplify sulfonylurea effects are all risk factors for hypoglycaemia.[42] In senior diabetic individuals, long-acting sulfonylureas like glyburide should be avoided.[37]

Meglitinides

Repaglinide and nateglinide are non-sulfonylurea secretagogues that stimulate insulin release by acting on the ATP-dependent K-channel in pancreatic β cells, similar to sulfonylurea, however the binding location is different.[43] Because meglitinides have a quick onset and a brief duration of action (4-6 hours), they reduce the risk of hypoglycaemia. Meglitinides are used to control blood glucose levels after meals. Pre-prandial administration gives you more freedom if you miss a meal without risking hypoglycaemia.[44] Because repaglinide is mostly processed in the liver and excreted in very small amounts through the kidneys, dose adjustments are not required in patients with renal insufficiency, with the exception of those with end-stage renal disease.[43]

Thiazolidinediones

Thiazolidinedione is an insulin sensitizer that binds to the peroxisome proliferator activated γ transcription factor.[44] Pioglitazone does not cause hypoglycaemia and can be administered in the presence of renal impairment, making it well tolerated in the elderly.[45] However, its usage in women may be restricted due to concerns of peripheral adenoma, fluid retention, and fracture risk. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in patients with class III-IV heart failure.[46]

α-Glucosidase Inhibitors

Although Acarbose, Voglibose, and Miglitol have not been widely used to treat type 2 diabetes, these are likely to be safe and effective. These medications work well for postprandial hyperglycemia and should be avoided in patients with severe renal impairment. Due to the high likelihood of adverse effects such as diarrhoea and flatulence, their use is usually restricted.[47] The newest of the medications, Voglibose, has been proven in a study to enhance glucose tolerance in terms of delayed disease development and the number of patients who reach normoglycemia.[48]

Incretin-Based Therapies

The core of incretin-based therapeutics is glucagon-like peptide 1 (GLP-1) analogues, which are designed to target this hitherto unknown component of DM pathophysiology, resulting in lasting improvements in glycaemic control and body weight control.[48] In individuals with diabetes, they can be used as a monotherapy, as an adjuvant to diet and exercise, or in combination with oral hypoglycaemic medications. Liraglutide and Exenatide, an incretin mimetic are also used in type 2 diabetes. With the administration of GLP-1, there is no danger of hypoglycaemia.[37] Furthermore, new research reveals that incretin-based medicines may benefit inflammation, cardiovascular and hepatic health, sleep, and the central nervous system.[49]

Dipeptidyl-Peptidase IV Inhibitors

DPP IV inhibitors inhibit dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme that rapidly inactivates both GLP-1 and GIP, increasing active levels of both hormones and improving islet function and glycaemic management in type 2 diabetes.[50] DPP-4 inhibitors are a novel family of anti-diabetic medications that are comparable to current treatments in terms of efficacy. They work as a monotherapy in people who can't control their diabetes with diet and exercise, and as an add-on therapy with metformin, thiazolidinediones, and insulin. The DPP-4 inhibitors are well tolerated, carry a low risk of producing hypoglycaemia and are weight neutral. However, they are relatively expensive.[50]

Insulin

Insulin is used alone or in combination with oral hypoglycaemic medications to control blood sugar levels. If some β-cell function remains, augmentation therapy with basal insulin can help. If β-cell fatigue occurs, basal-bolus insulin replacement is required. In cases of glucose poisoning, replacement therapy is required, which should mirror the normal release of insulin by the pancreas β-cells. Insulin is available in four different types of injectables: rapid acting, short acting, intermediate acting, and long acting. When compared to short-acting versions, long-acting forms are less likely to cause hypoglycaemia.[51]

Insulin analogues

Insulin therapy's capacity to replicate normal physiologic insulin production was restricted. Traditional intermediate and long acting insulin have variable absorption and activity peaks, which can lead to hypoglycaemia. The new insulin's analogues pharmacokinetic characteristics differ from those of normal insulin, and their onset and duration of action range from rapid to long. Two rapid-acting insulin analogues, insulin lispro and insulin as part, are currently available, as well as one long-acting insulin analogue, insulin glargine.[52,53]

Others

Inhibitors of the sodium-glucose co-transporter 2, which improve renal glucose clearance, and inhibitors of 11β-hydroxysteroid dehydrogenase 1, which limit glucocorticoid effects in the liver and fat. Insulin-releasing glucokinase activators, pancreatic G-protein-coupled fatty-acid-receptor agonists, glucagon-receptor antagonists, and metabolic inhibitors of hepatic glucose production are currently being investigated.[54]

HERBAL DRUGS

The herbal drugs are most popular in the developing and developed countries as well, because their natural origin and less side effects. The many traditional herbal medicines are used to treat the various diseases which are included in the Indian traditional system called the Ayurveda.[55] According to WHO the 2500 species of medicines are present in India, out of which 150 species are used commercially on a fairly large scale.[56]

There are various Indian traditional drugs used in the treatment of the diabetes mellitus are found in Ayurveda. Our Vedic literature like charak Samhita, sushrut Samhita, ashtanghridayam, ashtangsangraham already report the use of plants to treat diabetes. More than 400 plants are incorporated in Vedic literature with various recipes to treat diabetes.[57]

Acacia

Acacia has various pharmacological effects like antihypertensive, antimutagenic, antibacterial, antifungal, antidiarrheal and also antidiabetic effect. Acacia is taken for one week to exhibit hypoglycaemic effect in the body which lowers the blood glucose level. Acacia gives hypoglycaemic effect by the mechanism of direct or indirect stimulation of β-cells of islets of Langerhans to secret more insulin which lower the blood glucose level.[58]

Onion

Scientific name of onion is *Allium cepa*. It is used in the diabetes. The extract of onion clinically prove to be effective in diabetes mellitus and lower blood sugar level in body. The research result about active principle of onion showed that allyl propyl disulphide and S-methyl cysteine sulfoxide have an antidiabetic, anti-carcinogenic, and cardiovascular effects, and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase.[59,60]

Garlic

Scientific name of garlic is *Allium sativum*. Its extract has antidiabetic activity. Ethanolic extract of garlic and juice or oil of garlic remarkably lowers blood glucose level with efficiency compared to tolbutamide.[61] It also treats the diabetic cardiovascular complications. The chief constituents of the garlic are allicin and s-allyl cysteine sulfoxide (SACS). These constituents having an anti-hyperglycaemic mechanism which stimulate the insulin secretion from cells of pancreatic islets, which increases serum insulin level and improves glucose tolerance and increase glycogen synthesis. S-allyl cysteine, the precursor of allicin and garlic oil, is a sulphur containing amino acid which controls lipid peroxidation better than insulin. SACS also stimulate in-vitro insulin secretion from β-cell.[62]

Methi (fenugreek)

The scientific name of methi is *Trigonella foenum graecum* which belongs to Leguminosae family. Fenugreek seeds is the traditional drug having an antidiabetic activity and hypocholesterolemic activity in both animal and human.[63] Activity has been attributed largely to fenugreek's saponins, fiber content, the amino acid 4- hydroxyisoleucine and the major alkaloid trigonelline. Anti-hyperglycaemic effect is linked to delayed gastric emptying caused by the high fiber content, inhibiting of carbohydrate digestive enzymes and stimulation of insulin secretion.[64]

Aloe vera

The scientific name of the aloe vera is *Aloe barbadensis*, which belongs to Liliaceae family. The aloe vera has alloin as chief-constituent. The aloe vera containing the gel and

yellow exudate from pericyclic tubules.[65] Previous research concluded that aloe vera has hypoglycaemic effect in diabetic patient. Alloin stimulates insulin secretion from the pancreatic β-cell. It also has anti-inflammatory effect.[66,67]

Neem

The biological source of the neem is *Azadirachta indica* which belongs to Maliaceae family. The chief constituent of neem is azadirachtin. It has anti-hyperglycaemic activity to treat diabetes by increasing glucose uptake and glycogen deposition in body.[68,69] It has other activities like anti-bacterial, antioxidant, hepatoprotective effects.[70]

Bitter gourd

The biological source of bitter guard is *Momordica charantia* which belongs to Cucurbitaceae family. Its chief constituent is momordicin. It has antidiabetic effect as demonstrated in several studies reported earlier. It decreases the blood glucose level by inhibition of glucose-6-phosphate to fructose-1,6-biphosphate in liver and stimulation of hepatic glucose-6-phosphate dehydrogenase activities.[71]

Camellia sinensis

Camellia sinensis, commonly known as green tea, is a medicinal plant traditionally used to treat various health conditions, including diabetes, arthritis, bacterial infections and hyperlipidaemia. Kalagara et al. studied on combined therapy of Camellia sinensis extract and Glibenclamide. Diabetic rats were treated with Glibenclamide (4mg/kg), Camellia sinensis (300mg/kg) and its combination. This study provided experimental evidence of preventive and curative effect of Camellia sinensis as antioxidant and antinociceptive in animal model of diabetic neuropathy.[72]

Syzygium cumini

Both antidiabetic and ulcer-protective properties have been attributed to *Syzygium cumini* seeds. Annosha et al. assessed the anti-diabetic effects of an ethanolic extract of dried *Syzygium cumini* seed kernels and its comparative impact on gastric ulceration in comparison to standards such as the glucosidase inhibitor Acarbose and the naturally occurring standards Quercetin 50 mg/kg and 100 mg/kg. The combined effects of oral hypoglycemic medications and Syzygium cumini seed kernel extracts on diabetes-induced ulcers were also examined in the study. It has been demonstrated that *Syzygium cumini* and acarbose together constitute a possible treatment alternative for lowering the risk of stomach ulcerogenic stimuli caused by diabetes in type 2 diabetic individuals.[73]

Terminalia bellirica

One of the oldest Indian medicinal plants, *Terminalia bellirica* (Gaertn.) Roxb., is a component of the Ayurvedic medicine triphala, which is used to treat diabetes as well as liver and digestive diseases. The antioxidant activity of *T. bellirica* may be effective in reducing the oxidative stress-induced nerve degeneration in diabetic neuropathy, whilst the antidepressant property may be useful for treating diabetic neuropathy-induced symptoms.[74]

Coccinia indica leaf extract

Coccinia indica belongs to Cucurbitaceae family, an ivy gourd that is native to India, is known as the "Indian insulin alternative" because of how well it manages hyperglycemia. There have been claims that *Coccinia indica* possesses anti-diabetic qualities. *Coccinia indica* leaf extract showed good glycemic control and a positive renoprotective impact when co-administered with a low dose of pioglitazone as anti-diabetic therapy, according to Basavarajappa et al. As seen from normalized nephropathic indicators in a diabetic rat model, combination therapy would reduce the dose of pioglitazone and also protect kidneys against drug-induced damage.[75]

The combined effects of *Coccinia indica* leaf extract and acarbose in type II diabetes-induced neuropathy in rats were assessed by Sanket Kohli et al. in 2014. Two weeks of HFD treatment were followed by a modest dose of 35mg/kg of STZ dissolved in 0.1M/l of citrate buffer administered intravenously. Blood glucose levels in diabetic rats treated with ethanolic extract of *Coccinia indica* leaf alone and in conjunction with mild doses of acarbose were significantly decreased. Diabetic rats left untreated exhibited a notable susceptibility to thermal stimulation. Histopathological analyses showed that the groups treated with the ethanolic extract of *Coccinia indica* and its combination with low doses of acarbose had no injury to their sciatic nerves.[76]

Emblica officinalis Gaertn (Amla)

Ayurveda uses *Emblica officinais* (*E. officinalis*; Family: Euphorbiaceae) as a strong rasayana, a class of plant-derived medications thought to increase defense against illnesses like diabetes and improve health and longevity. Prem Kumar and others demonstrated in animal models of diabetic neuropathy the preventative and therapeutic effects of *E. officinalis* on nerve function and oxidative stress. *E. officinalis* fruit may be tested as a preventive medication for diabetics at risk of developing neuropathy because it is already used in clinical settings for diabetic patients.[77]

Trigonella foenum graecum (Fenugreek seeds)

One of the medicinal plants that is crucial in the treatment of diabetes mellitus is *Trigonella foenum graecum*.

The medicinal plant serves as a good source of dietary supplements to existing therapies as well as a great source of oral antihyperglycemic bioactive substances for the discovery of novel pharmacological insights. Premkumar et al. Studied Fenugreek seed powder and reported to have both preventative and therapeutic effect on oxidative stress and nerve function in an animal model of diabetic neuropathy. In conclusion, fenugreek seed powder may be explored for preventive measures in diabetes patients at risk of developing neuropathy.[78]

FUTURE IN DRUG THERAPY

Inhaled Insulin

The inhaled version of quickly acting insulin was approved by the Food and Drug Administration for the treatment of type 1 and type 2 diabetes. It is fast-acting insulin that has the benefit of being delivered straight into the lungs, has been found in studies to be beneficial.[79]

CONCLUSION

Type-2 diabetes is the most common metabolic disorder for all over world which is not totally cured but also prevented primarily by lifestyle modification, diet control, obesity control and medicinal drugs like biguanides, sulfonylurea, meglitinides, thiazolidinediones along with cured by herbal drugs which are having less side effects but administered for prolonged period of time for treatment. Education provided to the people about this epidemic to control diabetic condition and lower the financial burden all over the world populations. Management of this epidemic improves the quality of life of individual with type-2 diabetes.

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