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A REVIEW ON STUDY OF DIABETES, ITS PATHOGENESIS & TREATMENT WITH SPECIAL REFERENCE TO VARIOUS HERBAL FORMULATIONS

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ABSTRACT

Diabetes is a metabolic disorder characterized by chronically elevated blood glucose above the normal range. It is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. According to WHO media centre, 347 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of high fasting blood sugar. More than 80% of diabetes deaths occur in low- and middle-income countries. WHO projects that diabetes will be the 7th leading cause of death in 2030. Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use can prevent or delay the onset of type II diabetes.

KEYWORDS: Diabetes, insulin, blood glucose, herbal formulations, diabetes mellitus.

INTRODUCTION

Greek and Roman physicians used the term "Diabetes" to refer to conditions that result in large urine volume and are classified it into two types.[1]

- Diabetes mellitus in which the urine tasted sweet.
- Diabetes inspidus in which the urine tasted tasteless.

Regulation of Blood Glucose and Diabetes

Diabetes mellitus is the most important disease involving the endocrine pancreas. The secretion of the pancreas is digestive in function and the internal secretions plays a major role in the regulation of metabolism. The hormones which regulates the level of blood glucose are mainly two –

- Glucagon from the α–cells, and
- Insulin from the – β cells of the islets of langerhans.

Diabetes mellitus is characterized by

1. Hyperglycemia with a deranged secretion of insulin and possibly glucagons.
2. Altered metabolism of lipids, carbohydrates and proteins.
3. An increased risk of complications from vascular disease.

Diabetes is characterized by symptoms like polyuria (increase in urine output), increase in thirst (polydipsia), loss of weight and polyphagia (increased appetite) as major symptoms of insulin deficiency.[2,3,4] Beside these, hyperglycemia (increase in blood glucose concentration), glucosuria (presence of glucose in urine), ketonuria and ketonemia (increased concentration of ketone bodies in the blood and urine) and muscular weakness have also been reported. Long-term complications involve cardiovascular diseases (stroke and myocardial infraction), renal disease (diabetic nephropathy), loss of nerve function (diabetic neuropathy) and proliferative scarring of the retina (diabetic retinopathy).[5,6]

The symptoms of Diabetes mellitus results from real or apparent insufficient insulin secretion or possibly from over abundance of some insulin-inhibiting factor such as hyper-secretion of anterior pituitary gland or adrenal gland. The result is as elevated blood glucose level; as the blood glucose level exceeds its renal threshold, glucose appears in the urine. With the increase in the blood glucose concentration, the blood volume increases, thereby enhancing the urine output. This triggers the compensatory adjustment, which leads to increase in thirst. A need for alternate source of energy due to the inability of glucose to enter some tissues increases the concentration of ketone bodies synthesized by liver in the blood and urine.

Insulin promotes lipogenesis and inhibits their breakdown. The failure of normal utilization of glucose

in the tissue is accompanied by increased production of free fatty acids, which are formed more rapidly than they are consumed. Hypoglycemia stimulates ketogenesis. Fragments such as acetoacetic acid, acetone and α - hydroxy butyric acid are formed in excessive amount and accumulate in the blood and tissue resulting into diabetic acidosis, ketosis and finally coma and death.[8]

Types of Diabetes Mellitus

There are two types of Diabetes mellitus.[7]

1. Type I Diabetes (insulin-dependent Diabetes or IDDM, also called as juvenile onset Diabetes mellitus), and
2. Type II Diabetes (non-insulin dependent Diabetes or NIDDM, also called maturity onset Diabetes).

Etiology of Type I Diabetes

Type I Diabetes usually develops due to autoimmune disorders. Body's immune system behaves in appropriately and starts seeing one of its own tissues as foreign. In the case of Type I Diabetes, the islet cells of the pancreas that produce insulin are seen as the "enemy" by mistake.

Causes of type I Diabetes include –

- **Genetic factors:** Certain genetics markers in the human leukocyte antigen system are strongly linked with type I Diabetes mellitus. In addition many patients have a family history of the disease that is 50% of many individuals having an identical twin type I Diabetes mellitus.
- **Environmental factors:** Viruses (e.g. mumps, rubella, and cytomegalovirus, measles, influenza, encephalitis, polio or Epstein – Barr virus) and toxic chemicals are among the environmental factors that may affect pancreas and causes β –cell destruction in individuals who are generally predisposed to Diabetes mellitus.
- **Autoimmunity:** An autoimmune component is suggested by the presence of antibodies to support the autoimmune hypothesis. Both humoral and cell-mediated abnormalities have been described. An abnormal immune response could cause the body to destroy β -cells because it identifies it as foreign body (antigen).

All type I diabetics require insulin replacement therapy.

Etiology of Type II Diabetes

The type II Diabetes is caused by decreased sensitivity of target tissue to the metabolic effect of insulin. This reduced sensitivity of insulin is often referred as insulin resistance. The prevalence of type II Diabetes among adults varies from less than 5% to over 40% depending on the population in question. Due to increasing obesity and dietary habits in both Western and developing countries the prevalence of type II Diabetes mellitus is growing at an exponential rate.[8]

Its causes may be –

- Pancreatic: Following the destruction of Islets of Langerhans.
- Adrenal: Due to over production of glucocorticoids which oppose the action of insulin.
- Pituitary: Associated with overproduction of growth hormone of due to the presence of insulin antagonist in plasma.

Type II Diabetes tends to be fairly hereditary in contrast to Type I Diabetes.

Some common features of type II Diabetes are –

1. Most type II diabetics are over 40 years and obese.
2. Disease onset is typical and gradual.
3. In most cases, type II DM is characterized by insensitivity to insulin in the target tissue, deficient response of pancreatic β –cells towards glucose.
4. Ketoacidosis is prevented because some insulin is secreted.
5. Only a minority of type II diabetics requires insulin replacement therapy.

Obesity is the major problem and therefore this syndrome is referred as adult/maturity onset Diabetes mellitus. There is no or moderate reduction in β -cell mass. Insulin in circulation is low, normal or even high. Typical features include –

- No anti- β cell antibody is demonstration.
- High degree of genetics predisposition.
- Causes may be abnormality in glucoreceptor of β -cell so that they respond at high glucose concentration.

Impaired Glucose Tolerance (Pre-diabetes)

Pre-diabetes is a condition that occurs when a person blood glucose levels are higher than normal but not high enough for diagnosis of type II Diabetes.

Gestational Diabetes

Diabetes occurring in pregnancy is gestational Diabetes it affects about 4% of all pregnant women.

Diabetes due to Pancreatic Disease

Diabetes can also result from illness that damages the pancreas. These include chronic pancreatitis, most often associated with alcohol abuse, haemo-chromatosis, an iron overload disease and cystic fibrosis.

Diabetes due to other Disease Conditions – Secondary Diabetes

Diabetes can also result from the glandular or endocrine diseases. When other endocrine glands overproduce their own hormone, the balance between insulin and glucose can be upset. It may arise from such condition as endocrine disorder (e.g. Cushing's syndrome), pregnancy, pancreatic disease and use of drugs that antagonize insulin (e.g. thiazide diuretics, adrenocorticiods).

Pathology of Diabetes

The β -cells of the pancreas decrease in number or are degranulated in Diabetes. The reduction in the number of β -cells corresponds to the lack of insulin. In type I Diabetes there are no β –cells while in type II Diabetes, only about one half of them are present. In some cases these cells are infiltrated with lymphocytes, suggesting an autoimmune mechanism for type I Diabetes. The presence of anti-islet antibodies also supports an autoimmune hypothesis in type I Diabetes. The atherosclerosis occurs frequently in females than males and at an early age. In kidneys, nodular glomerulosclerosis is seen, which is the deposition of glycoprotein in wall like masses in the mesangium regions of the capillary tuft's. Diffuse glomerulosclerosis, which is the deposition of glycoprotein in mesangium, and tubular basement membrane thickening was observed. Diabetic retinopathy is micro aneurysms. Proliferative retinopathy, the formation of new blood vessels around the optic disk, occurs with long standing diabetic. Repeated hemorrhages cause scar formation that may lead to retinal detachment. The changes of hypertensive retinopathy are also seen in diabetics with hypertension.[9,10]

PATHOPHYSIOLOGY

Type I Diabetes

Postulated mechanism in the pathogenesis of type I susceptibility to the development of Diabetes is enhanced by HLA-D linked genes (HLADQ/DR) which serve to activate or amplify autoimmune reaction to β –cell. Either environmental or other susceptibility genetics determines are though to alter cell and make them antigenic (Figure-1.1)

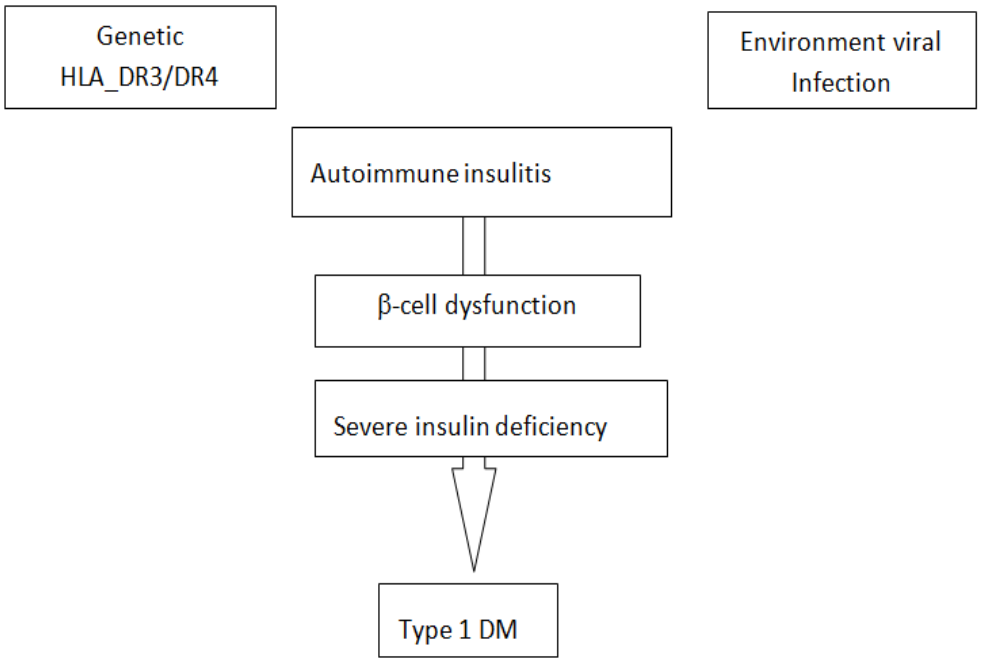


Figure 1.1: Pathogenesis of Type I Diabetes Mellitus.

Type II Diabetes

In type II Diabetes the genetic factors are of even greater importance than in Type I Diabetes. Unlike Type I, the disease is not linked to any HLA haplotypes and there is no evidence that autoimmune mechanism is involved. Obesity and overeating play an important role in type II Diabetes and there is co-relation between the disease and ageing.

Type II Diabetes is characterized by two metabolic defects –

1. Derangement in insulin secretion.
2. Insulin resistance is inability of peripheral tissue to respond to insulin.

There is a decrease in the number of insulin receptors as well as an additional deficit is in the insulin receptors' tyrosine kinase activity. In addition, there is a post receptor defect associated in some patients with reduced or impaired activity of glucose transport (**Figure-1.2**)

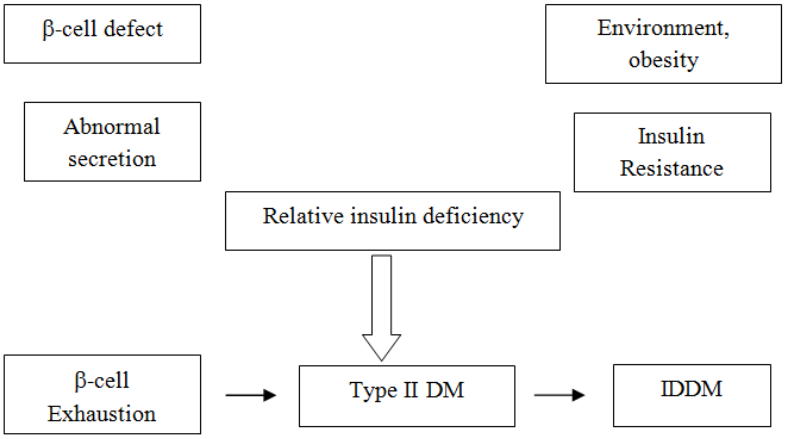


Figure 1.2: Pathogenesis of Type II Diabetes Mellitus.

Symptoms of Diabetes

In long-standing diabetes mellitus even when, treated with insulin, is a leading cause of blindness.[11]

Symptoms of Type I Diabetes

Type I Diabetes is much less common than type II Diabetes and typically affects younger individuals. Type I Diabetes usually begins before age 40 although there are exceptions. In the United States, the peak age of diagnosis is around 14. Type I Diabetes is associated with deficiency (or lack) of insulin. It is not known why, but the pancreatic islet cells quit producing insulin in the quantities needed to maintain a normal blood glucose level. Without sufficient insulin, the blood glucose rises to levels which can cause some of the common symptoms of hyperglycemia. These individuals seek medical help when these symptoms arise, but they often will experience weight loss developing over several days associated with the onset of their diabetes. The onset of these first symptoms may be fairly abrupt or more gradual.

Symptoms of Type II Diabetes

Many people have no signs or symptoms. Symptoms can also be so mild that you might not even notice them. The symptoms of type 2 diabetes includes increased thirst, increased hunger, fatigue, increased urination especially at night, weight loss, blurred vision and sores that do not heal. Sometimes people have symptoms but do not suspect Diabetes. They delay scheduling a checkup because they do not feel sick. Many people do not find out that they have the disease until they have Diabetes complications, such as blurred vision or hearth trouble. It is important to find out early if you have Diabetes because treatment can prevent damage to the body from Diabetes.

Diabetic Complications

There are considerable amounts of data indicating that the chronic elevations of plasma glucose cause many of the major complications of Diabetes including nephropathy, retinopathy, neuropathy and macro and micro-vascular damage[12], however, increased level of free fatty acids are positively correlated with both insulin resistance[13, 14] and the deterioration of β -cell function in the context of concomitant hyperglycemia.[15,16] This effect is attributed to oxidative stress.

Acute Complications

Life threatening complications of diabetes mellitus include diabetic ketoacidosis and hyperglycemic coma.

1. **Diabetic ketoacidosis:** Usually affecting only type I diabetes. This disorder typically arises after a short period of deteriorating glycemic control. Hyperglycemia and ketonemia trigger osmotic diuresis, electrolyte loss and metabolic acidosis. Diabetes acidosis is often the presenting disorder in children with previously undiagnosed type I Diabetes mellitus.

2. **Hyperglycemic hyperosmolar nonketotic coma (HHNC):** It occurs in type II Diabetes and has a higher mortality rate than diabetic ketoacidosis. Precipitating factors include various illnesses and conditions that increase insulin requirement e.g. severe burns, gastrointestinal bleeding, central nervous system injury, and acute myocardial infarction.

3. **Diabetic neuropathy typically involves both the autonomic and peripheral nervous system.**

- Gastric agony, incontinence diarrhea and importance reflect autonomic involvement.
- Peripheral neuropathy may give rise to impaired perception of pain and temperature.
- Ischemia may cause skeletal muscle atrophy and motor abnormalities.

4. Skin and mucous membrane complications

- Diabetes has an increased risk for infections such as candid infections of skin and vagina. Erythema commonly develops beneath the breasts and between fingers. Eruptive xanthomas occur most often in long standing poorly controlled diabetes mellitus.
- Atrophic lesions (round painless lesion) and diabetic dermopathy (reddish-brown spots) are common especially on the extremities.

- An ulcerating necrotic lesion called necrobiosis lipodica diabeticorum may develop on the anterior leg surface or the dorsum of the ankle.
- Injury, infection, neuropathy, vascular disease or ischemia may lead to gangrene, which is 20 times more common in diabetic than non-diabetics.
- Use of certain drugs (e.g. steroids, glucagons, thiazide diuretics, cimetidine, and propranolol) also can trigger Hyperglycemic hyperosmolar nonketotic coma (HHNC).
- Peritoneal dialysis increases the risk of Hyperglycemic hyperosmolar nonketotic coma (HHNC).

5. COMA

In type I Diabetes, insulin deficiency can lead to very high levels of blood sugar and the accumulation of acid and compound called ketones, leading to a condition called as ketoacidosis. In addition to difficulty in breathing, the patient may experience a depression of consciousness, which if left untreated can lead to coma or even death within hours.

In patients with type II Diabetes, prolonged elevations of blood glucose especially in more elderly patients, can lead to a condition called as hyperosmolar coma with severe dehydration, resulting in impaired consciousness. If left untreated, this can lead to coma and death. In both conditions, an acute illness such as infection, heart attack or stroke can lead to or aggravate the abnormalities and should be attended at the same time. Both conditions require intravenous insulin fluids.[15]

Chronic Complications

Diabetes mellitus is associated with a high risk for a number of chronic illnesses.

1. Cardiovascular disease

A. Atherosclerosis and peripheral vascular diseases are more severe and more common in diabetics than in non-diabetics. Also disease onset is typically earlier.

B. Microvascular changes characterized by thickening of the capillary basement membrane, may lead to retinopathy and skin changes.

C. Diabetes with insulin resistance has a higher incidence of hypertension than non-diabetics.

2. Ocular Complications

A. Premature cataracts are most common in Diabetes with severe chronic hyperglycemia.

B. Diabetic retinopathy, a consequence of microvascular changes, and affects approximately 50% of diabetics within 10 years of disease onset.

C. Diabetes is a major cause of blindness.

3. Renal Complications

Diabetes is the leading cause of end stage renal disease (Kidney failure).

4. Nerve Damage

About 60-70% of diabetics have neuronal damage, which can result in a sense of numbness and tingling typically occurring in the hands and feet, and or affect the function.

5. Vascular Disease

People with Diabetes suffer from damage to large and small blood vessels that supply the heart and brain.

6. Heart Disease and Stroke

Diabetic person is two to four times more likely to have heart disease or suffer a stroke. Inadequate control of high blood pressure and cholesterol also contributes to these conditions.

7. Amputations

Diabetes is the most frequent cause of non-diabetes traumation and lower limb amputation.

8. Sexual Dysfunction

Both males and females can have sexual dysfunction as a result of poor glucose control as well as damage to nerves and blood vessels.

9. Diabetics Nephropathy

Diabetic nephropathy another manifestation of microvascular pathology ultimately leads to renal insufficiency or failure. Diabetic nephropathy is characterized by protienuria, microalbuminuria, glomerular lesions and renal atherosclerosis.

DETECTION OF DIABETES

1. Fasting Blood Glucose (Blood Sugar) Level

Fasting glucose test measures blood glucose after patient has gone overnight without eating. This test is most reliable when done in the morning. Fasting glucose levels of 100 to 125 mg/dL are above normal but not high enough to be called diabetes. This condition is called pre-diabetes or impaired fasting glucose, and it suggests probably insulin resistance for some time. Impaired fasting glucose is considered a pre-diabetic state.

2. The Oral Glucose Tolerance Test

A glucose tolerance test measures the blood glucose after an overnight fast and 2 h after drinking sweet liquid. If blood glucose falls between 140 and 199 mg/dL 2 h after drinking the liquid, glucose tolerance is above normal but not high enough for Diabetes. This condition, also a form of pre-diabetes, is called impaired glucose tolerance and, like impaired fasting glucose, it points towards a history of insulin resistance and a risk for developing diabetes.

NORMAL REGULATION OF BLOOD GLUCOSE

Insulin and glucagon play important role in normal regulation of the blood glucose.

Insulin

- **Purpose**: Regulates blood glucose (sugar) in the normal range.
- **Actions**: Forces many cells of the body to absorb and use glucose thereby decreasing blood sugar levels.
- **Secreted in response to**: High blood glucose.
- **Secretion inhibited by**: Low blood glucose.
- **Disease due to deficient action**: Diabetes.
- **Disease due to excess action**: Hypoglycemia.
- **Tumor called**: Insulinoma.

Glucagon

- **Purpose:** Assists insulin in regulating blood glucose (sugar) in the normal range (actions are opposite of insulin).
- **Actions:** Forces many cells of the body to release (or produce) glucose (increasing blood sugar).
- **Secreted in response to:** Low blood glucose.
- **Secretion inhibited by:** High blood glucose.
- **Disease due to deficient action:** Sometimes nothing, sometimes, hypoglycemia.
- **Disease due to excess action:** Hyperglycemia.
- **Tumor called:** Glucagonoma.

The human body wants blood glucose (blood sugar) maintained in a very narrow range. Insulin and glucagon are the hormones which make this happen. Both insulin and glucagon are secreted from the pancreas, and thus are referred to as pancreatic endocrine hormones. The picture shows the intimate relationship of insulin and glucagon with each other. It is the production of insulin and glucagon by the pancreas which ultimately determines if a patient has diabetes, hypoglycemia, or some other sugar problem. Insulin and glucagon are hormones secreted by islet cells. They are both secreted in response to blood sugar levels.

Insulin is normally secreted by the β -cells (a type of islet cells) of the pancreas. Although there is always a low level of insulin secreted by the pancreas, the amount secreted into the blood increases as the blood glucose rises. Similarly, as blood glucose falls, the amount of insulin secreted by the pancreatic islets goes down. Insulin has an effect on a number of cells, including muscle, red blood cells, and fat cells. In response to insulin, these cells absorb glucose out of the blood, having the net effect of lowering the high blood glucose level into the normal range.

Glucagon is secreted by the β -cells of the pancreatic islets in much the same manner as insulin except in the opposite direction. If blood glucose is high, then no glucagon is secreted. When blood glucose goes low, however, (such as between meals, and during exercise), more and more glucagon is secreted. Like insulin, glucagon has an effect on many cells of the body, but most notably the liver. The effect of glucagon is to make the liver release the glucose it has stored in its cells into the blood stream, with the net effect of increasing blood glucose. Glucagon also induces the liver (and some other cells such as muscle) to make glucose out of building blocks obtained from other nutrients found in the body (e.g., protein).

Our bodies desire blood glucose to be maintained between 70 mg/dl and 110 mg/dl (mg/dl means milligrams of glucose in 100 milliliters of blood). Below 70 is terms "hypoglycemia". Above 110 can be normal if have eaten within 2 to 3 hours. That is why doctor wants to measure blood glucose while you are fasting. It should be between 70 and 110. Even after eaten, however, glucose should be below 180. Above 180 is termed "hyperglycemia" (which translates to mean "too much glucose in the blood"). If two blood sugar measurements above 200 after drinking a sugar water drink (glucose tolerance test), then is diagnosed with diabetes.[17]

Antidiabetic Drugs

As insulin is ineffective when given orally, the search was continued for an orally effective agent, Synthalin-A, a biguanide was the earliest oral hypoglycemic agent to be used in therapy by was found to be too toxic. It is now of historical interest. A chance observation by Janbon (1942) led to the discovery of the hypoglycemic action of sulfonamides. Frank and Fuchs had confirmed this in 1955, who observed the blood glucose lowering effect of carbutamide, a sulfonamide, during its trial in infectious diseases. Since then many sulfonylurea were used successfully as oral anti-diabetic agents. In 1957, biguanides stages a comeback in diabetotherapy when Unger introduced phenformin as an effective and less toxic oral antidiabetic agent.[18]

Therapy of Diabetes mellitus

Following therapies are available for the treatment of diabetes mellitus.

A. Parenteral antidiabetic therapy

E.g. Insulin and its preparations.

B. Oral antidiabetic therapy

E.g. Sulphonylureas, Biguanides, Thiazolidinediones, etc.

Oral hypoglycaemic agents

Treatment is according to the type of Diabetes. The drugs used are:

(a) Sulfonylureas

All members of this class of drugs are substituted aryl sulfonylureas. The sulfonylureas are divided traditionally into 2 groups or generation, as shown in **Table 1.1**.

General Structure

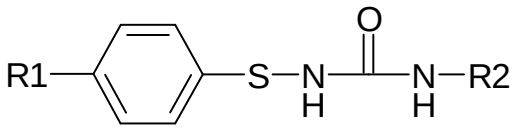
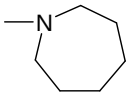
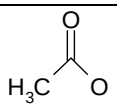
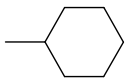
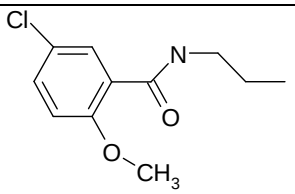
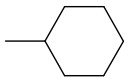
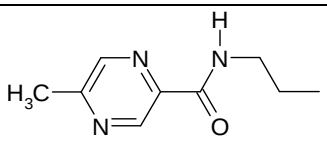
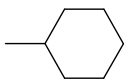


Table 1.1: Sulfonylureas – First generation analogs.

	R1	R2
First Generation Analogs.		
Tolbutamide	H_3C—	C_4H_9—
Chlorpropamide	Cl—	C_3H_7—
Tolazamide	H_3C—	
Acetohexamide		
Second Generation Analogs		
Glyburide (Glibenclamide)		
Glipizide		

Sulfonylureas causes hypoglycemia by stimulating insulin release from pancreatic β –cells. Their effects in the treatment of diabetes, however, are more complex. The acute administration of sulfonylurea to NIDDM patients increases insulin release from the pancreas. Sulfonyurea also may further increases insulin levels by reducing hepatic clearance of the hormone. Sulfonylurea also stimulates release of somatostatin, and they may suppress secretion of glucagons slightly. The effect of the sulfonylurea are initiating by binding to and blocking at ATP-sensitive K^+ channel.[10] Now a day's great deal of attention has been directed towards the cardiovascular effects of sulfonylureas.[18]

(b) Biguanides

Biguanides (**Table 1.2**) has extra pancreatic spectrum of action of does not depend upon exo or endogeneous insulin in the body. They stimulate the peripheral utilization of glucose. They increase the sensitivity of the muscle to insulin action. They reduce the intestinal absorption of glucose.

General Structure

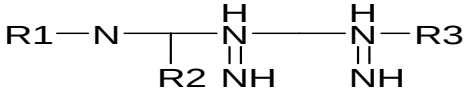
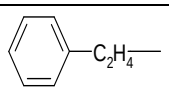


Table 1.2: Biguanides

Name	R_1	R_2	R_3
Metformin	CH_3	CH_3	H-
Phenformin		H-	H-

(c) Thiazolidinediones

Thiazolidinediones were introduced in 1997. These agents bind to peroxisome proliferators activated receptor gamma resulting in increased glucose uptake in muscle and reduced endogenous glucose production. The very first agent in this class, troglitazone was withdrawn from the market in United States in 2000 because of an association with hepatic toxicity. The two other agents rosiglitazone and pioglitazone, as shown in **Table 1.3**, are used worldwide.[9]

General Structure

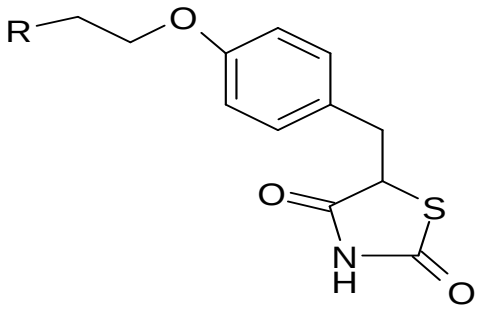
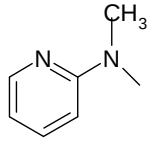
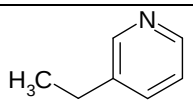


Table 1.3: Thiazolidinediones.

Name	R
Rosiglitazone	
Pioglitazone	

HERBAL TREATMENT OF DIABETES

Diabetes mellitus is a systemic metabolic disease characterized by hyperglycemia, hyper lipedemia, hyper aminoacidemia, and hypo insulinaemia it leads to decrease in both insulin secretion and insulin action. It is frequently associated with the development of micro and macro vascular diseases which include neuropathy, nephropathy, cardiovascular and cerebrovascular diseases.[19] The disease is associated with reduced quality of life and increased risk factors for mortality and morbidity. Diabetes mellitus, commonly referred to as diabetes was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycemia) lead to spillage of glucose into the urine, hence the term sweet urine. Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates (for example, after eating food), insulin is released from the pancreas to normalize the glucose level.[20] In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia. Diabetes is a chronic medical condition, meaning that although it can be controlled, it lasts a lifetime. There are different approaches to the treatment of diabetes, like insulin treatment in type 1 diabetes: Sulphonylureas, which release insulin from pancreas by blocking the ATPsensitive potassium channels. Biguanides, which decrease the insulin resis-tance; Thizaolidinediones, which increase the insulin sensitivity; alphaglucodase inhibitors like acarbose, which decrease glucose absorption from intestine, thereby decreasing postprandial hyperglycemia; metiglinides like repaglimide and nateglamide, which are insulin secretogogues. Traditional herbal mineral plays an important part in the treatment of diabetes. If we able to even identify some 5-6 herbal drugs that can reduce dose of insulin by increasing resistance sensitivity, reducing insulin resistance, then we would have positively contributed in the treatment of diabetes.

IMPORTANT MEDICINAL PLANTS HAVING ANTIDIABETIC POTENTIAL

1. Allium cepa L. (onion) (Liliaceae)

Allium cepa is known only in cultivation but related wild species occur in Central Asia. Various ether soluble fractions as well as insoluble fractions of dried onion powder show antihyperglycemic activity in diabetic rabbits. A. cepa is also known to have antioxidant and hypolipidemic activity. Administration of a sulfur containing amino acid, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues. It normalizes the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase.[20]

2. Allium sativum L. (garlic) (Liliaceae)

It is a perennial herb cultivated throughout India. Oral administration of the garlic extract significantly decreases serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, AST and ALT levels, while increases serum insulin in diabetic rats but not in normal rats when compared with antidiabetic drug glibenclamide. The antidiabetic effect of the extract was more effective than glibenclamide.[20]

3. Aloe vera (L) Burm

It grows in arid climates and is widely distributed in Africa, India and other arid areas. Aloe vera gel at 200 mg/kg possesses significant antidiabetic, cardioprotective activity, reduces the increased TBARS, maintains the Superoxide dismutase and Catalase activity up to the normal level and increases reduced glutathione by four times in diabetic rats.[20, 21]

4. Elephantopus scaber

Elephantopus scaber is an ethnomedicnal plant, having the property to reduce the blood glucose levels in streptozotocin induced diabetic rats signifcantly. It is popularly known as Elephant's foot, and it is family of Asteraceae. It is a scabrescent aromatic herb distributed in the moist deciduous forests of the central Western Ghats. As per the previous studies, the roots of Elephantopus scaber are used as an antipyretic, cardiotonic and diuretic and decoction of the roots and leaves is used as emollient and it was given in dysuria, diarrhea, dysentery and stomach pain. The aqueous extract of leaves is applied externally to treat eczema and ulcers.

5. Bidens pilosa L

It is known as Spanish Needle. The butanol fraction of B. pilosa inhibits the differentiation of naive helper T (ThO) cells into Thl cells but enhances their transition into type II helper T (Th2) cells, thus can prevent diabetes possibly via suppressing the differentiation of ThO cells into Thl cells and promoting that of ThO cells into Th2 cells, thus preventing autoimmune diabetes in non-obese diabetic mice.

6. Chaenomeles sinensis

Ethyl acetate fraction of Chaenomeles sinensis (C. sinensis) (Thouin) Koehne fruits is very good Antidiabetic effect. Chaenomeles sinensis is belongs to family Rosaceae. Doses which have antidiabetic activity were reported as 50 and 100 mg/kg body weight.

7. Artemis sphaerocephala Krasch

Antioxidant effect of Artemis sphaerocephala (A.sphaerocephala) gum on STZ induced diabetic rat. Levels of serum and liver tissue thiobarbituric acid reactive substances (TBARS) and +OH were increased in STZ induced rat. The activity levels of liver and serum superoxide dismutase were decreased. After administration of extract of A. sphaerocephala, levels of TBARS and +OH were decreased in serum and liver tissue. The significant increments in the levels of liver and serum SOD.

8. Mangifera indica L.

The aqueous extract produces reduction of blood glucose level in normoglycemic and glucose-induced hyperglycemia, but does not have any effect on streptozotocin-induced diabetic mice under the same conditions when compared with that of an oral dose of chlorpropamide. The result indicates that the aqueous extract of the leaves of M. indica possess hypoglycemic activity.[46]

9. Pterocarpus marsupium Roxb

It is widely used in 'Ayurveda' as 'Rasayana' for management of various metabolic disorders. An aqueous extract of P. marsupium wood, at an oral dose of 250 mg/kg, shows statistically significant hypoglycemic activity. Marsupin, pterosupin and Iiquiritigenin obtained from this plant show antihyperlipidemic activity, its active principle, has been found to be insulinogenic, enhancing insulin release and conversion of proinsulin to insulin in vitro. Like insulin, (-) epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of rat diaphragm in a dose dependent manner.

Herbal Drug Formulations

1. Diabecon manufactured by 'Himalaya' is reported to increase peripheral utilization of glucose, increase hepatic and muscle glucagon contents, promote B cells repair and regeneration and increase c peptide level. It has antioxidant properties and protects B cells from oxidative stress. It exerts an insulin like action by reducing the glycated haemoglobin levels, normalizing the microalbuminurea and modulating the lipid profile. It minimizes long term diabetic complications.
2. Epinsulin marketed by Swastik formulations, contains epicatechin, a benzopyran, as an active principle. Epicatechin increases the cAMP content of the islet, which is associated with increased insulin release. It plays a role in the conversion of proinsulin to insulin by increasing cathepsin activity. Additionally it has an insulin-mimetic effect on osmotic fragility of human erythrocytes and it inhibits Na/K ATPase activity from patient's erythrocytes. It corrects the neuropathy, retinopathy and disturbed metabolism of glucose and lipids. It maintains the integrity of all organ systems affected by the disease. It is reported to be a curative for diabetes, Non Insulin Dependent Diabetes Mellitus (NIDDM) and a good adjuvant for Insulin Dependent Diabetes Mellitus (IDDM), in order to reduce the amount of needed insulin. It is advised along with existing oral hypoglycemic drugs. And is known to prevent diabetic complication. It has gentle hypoglycemic activity and hence induces no risk of being hypoglycemic.
3. Pancreatic Tonic (ayurvedic herbal supplement): Pancreas Tonic is a botanical mixture of traditional Indian Ayurvedic herbs currently available as a dietary supplement.
4. Bitter gourd powder marketed by Garry and Sun: It lowers blood & urine sugar levels. It increases body's resistance against infections and purifies blood. Bitter Gourd has excellent medicinal virtues. It is antidotal, antipyretic tonic, appetizing, stomachic, antibilious and laxative. The bitter Gourd is also used in native medicines of Asia and Africa. The Bitter gourd is specifically used as a folk medicine for diabetes. It contains compounds like bitter glycosides, saponins, alkaloids, reducing sugars, phenolics, oils, free acids, polypeptides, sterols, 17-amino acids including methionine and a crystalline product named p-insulin. It is reported to have hypoglycemic activity in addition to being antihaemorrhoidal, astringent, stomachic, emmenagogue, hepatic stimulant, anthelmintic and blood purifier.
5. Dia-Care manufactured by Admark Herbals Ltd. is claimed to be effective for both Type 1, Type 2 diabetes within 90 days of treatment and cures within 18 months. Persons taking insulin will eventually be liberated from the dependence on it. The whole treatment completes in 6 phases, each phase being of 90 days. Approx. 5 grams (1 tea spoon) powder is mixed with 1/2 glass of water, stirred properly and kept overnight. Only the water and not the sediment must be taken in the morning on empty stomach. To the remaining medicine fresh water is added and kept for the whole day and is consumed half an hour before dinner. The taste of the drug is very bitter. It is a pure herbal formula without any side effects.
6. Diabetes-Daily Care manufactured by Nature's Health Supply is a Unique, Natural Formula, which effectively and safely Improves Sugar Metabolism. Diabetes Daily Care™ was formulated for type 2 diabetics and contains all natural ingredients in the proportion optimal for the body's use.
7. Gurmar powder manufactured by Garry and Sun is an anti-diabetic drug, which suppresses the intestinal absorption of sacharides, which prevents blood sugar fluctuations. It also correlates the metabolic activities of liver, kidney and muscles. Gurmar stimulates insulin secretion and has blood sugar reducing properties. It blocks sweet taste receptors when applied to tongue in diabetes to remove glycosuria. It deadens taste of sweets and bitter things like quinine (effects lasts for 1 to 2 hours). Besides having these properties, it is a cardiac stimulant and diuretic and corrects metabolic activities of liver, kidney and muscles.
8. DIABETA, a formulation of Ayurvedic Cure, available in the capsule form is an anti-diabetic with combination of proven anti-diabetic fortified with potent immunomodulators, antihyperlipidemics, anti-stress and hepatoprotective of plant origin. The formulation of Diabeta is based on ancient ayurvedic references, further corroborated through modern research and clinical trials. Diabeta acts on different sites in differing ways to effectively control factors

and pathways leading to diabetes mellitus. It attacks the various factors, which precipitate the diabetic condition, and corrects the degenerative complications, which result because of diabetes. Diabeta is safe and effective in managing Diabetes Mellitus as a single agent supplement to synthetic anti-diabetic drugs. Diabeta helps overcome resistance to oral hypoglycemic drugs when used as adjuvant to cases of uncontrolled diabetes. Diabeta confers a sense of well -being in patients and promotes symptomatic relief of complaints like weakness giddiness, pain in legs, body ache, polyuria and pruritis.

9. Syndrex manufactured by Plethico Laboratory contains extracts of germinated fenugreek seed. Fenugreek is used as an ingredient of traditional formulations over 1000 years. We are currently studying the mechanism of this antidiabetic drug using animal model on one hand and cultured islet cells on the other.[22]

CONCLUSION

Many different plants have been used individually or in formulations for treatment of diabetes and its complications. One of the major problems with this herbal formulation is that the active ingredients are not well defined. It is important to know the active component and their molecular interaction, which will help to analyse therapeutic efficacy of the product and also to standardize the product. Efforts are now being made to investigate mechanism of action of some of these plants using model systems.

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