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Diabetes: The next epidemic?

Mehra Varsha [1*], Mishra Smita [2], Gupta Nomita [3] and Khatri Manisha [1]

[*1]Assistant Professor, Department of Biomedical Sciences, Shaheed Rajguru College of Applied Sciences, University of Delhi
[2]PhD fellow, Department of Biomedical Sciences, Shaheed Rajguru College of Applied Sciences, University of Delhi
[3]Project trainee in Department of Biomedical Sciences, Shaheed Rajguru College of Applied Sciences, University of Delhi
Email: varsha.mehra@rajguru.du.ac.in| Tel: 91-11-9971703464

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Since the evolution of mankind, numerous disease have arisen and many got eradicated. Some of the deadly diseases became history and some became epidemic. Diabetes is one of those diseases which has arisen almost with advent of the human civilization and continues to persist in our society. Existence of diabetes goes back to Vedic and Greek period, where diagnosis was done by tasting urine. Although, it is neither caused by any microbial infection nor is it contagious, yet the disease is rampant in the society and rapidly spreading across the globe. The disease is characterized by hyperglycemia and glycosuria. Although it can be managed by using commercially available drugs, the treatment is often lifelong and requires lifestyle management. If undiagnosed, the disease could lead to severe late stage complications such as neuropathy, retinopathy and nephropathy. These late stage complications are often fatal, contributing to mortality associated with the disease. Around 422 million people are afflicted with diabetes worldwide. India is perhaps one of the highest contributors to diabetes population. The present review is an attempt towards understanding the disease, its mechanism and complications, diagnosis, treatment and looking at the alternative natural plant based therapies.

Keywords: Hyperglycemia, Glycosuria, AGES, Metformin, Plant based drug approach and Diabetes co-infection

INTRODUCTION

Diabetes is the combination of miscellaneous disorders commonly presenting with the hyperglycemia and glucose intolerance due to lack of insulin, defective insulin activity or both. These complications emerge due to the interruption or disturbance in the regulatory systems for the storage and mobilization of metabolic macro-molecules. Classification of diabetes is based on its etiology and clinical manifestations. There are two main types of diabetes viz; Type 1 (inadequate production of insulin) and Type 2 (inadequate utilization of insulin by the cells). Type 1 Diabetes, also known as Insulin Dependent Diabetes Mellitus (IDDM), is the major type of the

diabetes in younger population, but it accounts for a smaller proportion of population (approximately 10%) out of the total burden(Olkoba *et al.,* 2012).

The incidence is increasing across the globe. It is an auto-immune disorder in which the self-immune system is activated to destroy the beta cells of Islets of Langerhans of Pancreas. Further research is required to know exactly what activates the autoimmune system against pancreatic beta cells. It cannot be cured or prevented but can be effectively managed by making certain life style modifications. Symptoms include excessive thirst, polyuria, feeling tired and lethargic, polyphagia, slow wound healing, skin infections, blurred vision, weight loss, mood swings, headaches and many more. A person suffering from type 1 diabetes depends upon every day supply of insulin to replace the insulin which is not adequately produced by the body. Without insulin, body starts catabolizing its own fats and proteins resulting in development of diabetic ketoacidosis (Ramchandran, 2014). Type 2 Diabetes, also known as Non-Insulin Dependent Diabetes Mellitus(NIDDM) is relatively higher in prevalence : approximately 90% in developed countries and of dominance in developing countries. It is a chronic metabolic defect which arises due to inadequate responsiveness of insulin by the target cells and tissues. In normal condition, insulin keeps a check on blood and metabolic glucose levels. However, in NIDDM the cells are not responsive to insulin and therefore the downstream signalling pathways affected by Insulin are blocked. As a result of this non-responsiveness, the blood glucose shows poor or no uptake by the peripheral tissues of the body. The blood glucose levels keep rising with cells starving for glucose at the same time. Poor dietary habits, sedentary life style and obesity are the major factor in development of the disease The genetic cause could be linked to almost 36 genes which contribute directly or indirectly to development of NIDDM. Studies have shown that identical twins have more chance of developing the disease, if one of the twins is afflicted with it; than non-identical twins, pointing at the heredity factors that may be associated with the disease (Taylor, 2013).

Global impact of Diabetes

Prevalence of diabetes gives us an insight about an alarming rise in population suffering from the disease in both developed and developing countries. According to World Health Organization (WHO) in 2014, it has been reported that approximately 422 million individuals are suffering from diabetes globally and half of the diabetics live in India, China and USA (WHO Diabetes report 2016). Out of them atleast 90% are suffering from Type 2 Diabetes. One of the reports by International Diabetes Federation showed that approximately 46.3% diabetic cases remain undiagnosed. From the above data, it can be estimated that 1 out 2 people are suffering from diabetes unknowingly (WHO Diabetes report 2016). (Figure 1).
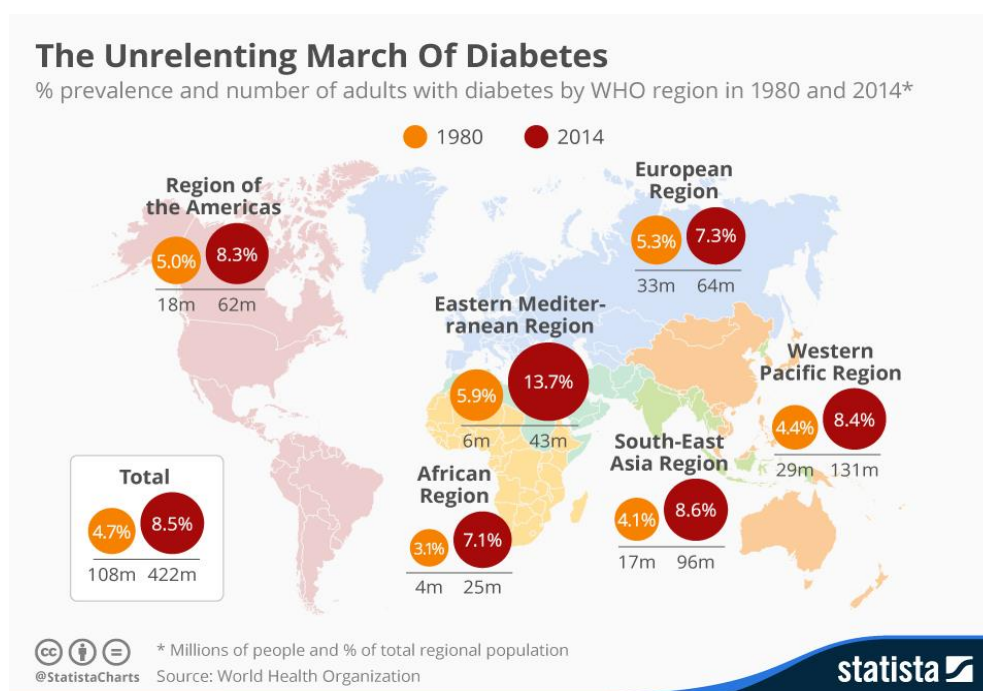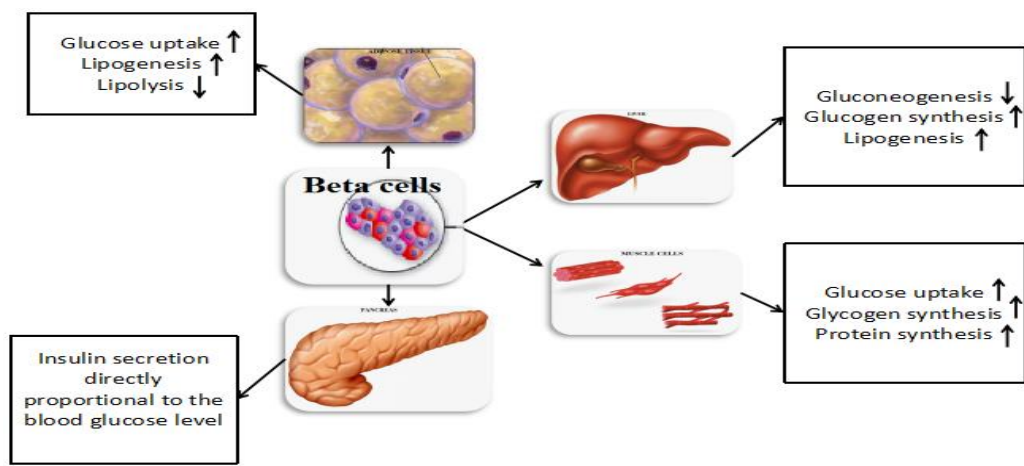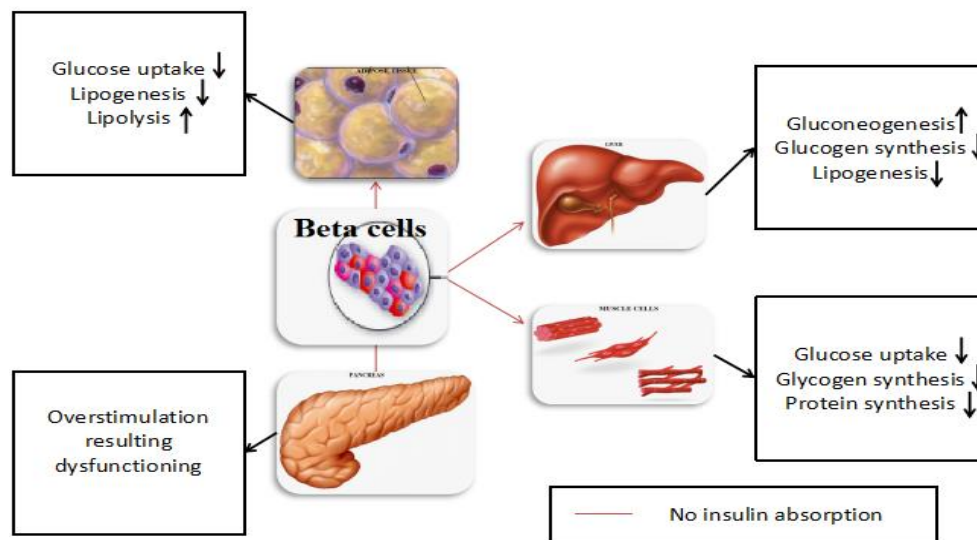

Figure 1: Worldwide prevalence of Diabetes Mellitus (McCarthy N, 2016**)**

(A) Role of Insulin as a promoter for different metabolic functions in Non-diabetic individuals

(B) Role of Insulin as a promoter for different metabolic actions in Diabetic individuals

Figure 2:- Diagrammatical representation of the changes occurring in the system due to the absence of Insulin hormone. Picture (A) gives insights in a healthy, Non-diabetic individual where insulin uptake reduces Gluconeogenesis and Lipolysis and promoting Glycogenesis; whereas picture (B) depicts the changes occurring in a Diabetic individual where unsuccessful insulin absorption causes high blood sugar and increased Gluconeogenesis and Lipolysis.

One of the major causes of rapid increase in diabetes is 'nutrition transition'; a shift to high fat, high sugar diet. Rapid urbanization, erratic working habits and an increasingly sedentary lifestyle are major contributors to such a shift.(McCarthy N, 2016) Out of the all the countries China is considered to be the epicenter for global diabetes epidemic, whereas diabetic incidence is also increasing in African Nations(Hu FB, 2011). India is one of the countries sharing major burden of people suffering from diabetes. More than 62 million of the adult Indian population(7.1%) is afflicted with the disease. This number has been predicted to rise by another 10.9 million by 2030 (Yang *et al.,* 2010).

Diabetes Mellitus:Mechanism of Action
A regular energy source is required for the normal cellular functioning in the human body. Glucose is the primary energy source which circulates in the body via blood as a mobility fuel source. Insulin is one of the pancreatic hormones responsible for regulation of blood glucose level. This hormone binds to its receptor present on the surface of the cells and permits the glucose entry into the respiring cells. Insulin initiates the glucose catabolism through Glycolysis. The energy released from glycolysis upregulates the glycogenesis of excessive glucose and lipogenesis via increasing the production of more insulin from β cells of pancreas. Rest of the glucose

get absorbed by blood, especially RBCs. For normal metabolism, homeostasis is to be maintained between blood and cellular glucose level. This balance is maintained by Insulin and Glucagon(Insulin antagonist) (Yang *et al.,* 2010; Kaveeshwar and Cornwall, 2014) (figure 2).

In diabetic conditions, due to lack of Insulin/insulin non responsiveness, the blood glucose levels cease to be regulated. Body tries to maintain its homeostasis to a certain extent,yet, if the blood sugar level increases abnormally, excess sugar is excreted in the urine, leading to a condition of polyuria and glycosuria. Release of insulin by beta cells of Islets of Langerhans involves two phases. First phase involves rapid release of insulin in response to increased level of blood sugar level. As the affinity of GLUT-2 receptors present on beta cells, for glucose is low, there has to be a certain threshold level of glucose inside the Langerhans cells in order to spur Insulin release.The Insulin release starts soon after the entry of food in stomach and continues for 10-15 minutes. It suppresses the lipolysis, proteolysis and gluconeogenesis occurring in liver and encourages cell to use free glucose present in blood. Increased glucose level further promotes Insulin synthesis which is released slowly and in a sustained manner in blood till it attains glucose homeostasis: this is known as Second phase Insulin secretion.Insulin released in blood binds to Insulin Receptor(IR; Receptor Tyrosine Kinase) causing tyrosine phosphorylation on cytosolic chain of IR, leading to a cascade of chain reaction : activation of MAP-Kinase and PI_3 Kinase pathways. The activation of MAP-Kinase encourages cell growth while PI_3 Kinase pathway promotes transportation of GLUT-4 transmembrane proteins on plasma membrane, which has high affinity for glucose molecules, and hence promotes glucose uptake by cells(Sonksen & Sonksen, 2000). It also promotes glycogenesis, lipogenesis and protein synthesis. Thus, Insulin's role is to act as a promoter for the glucose utilization in the cells. (figure 3).
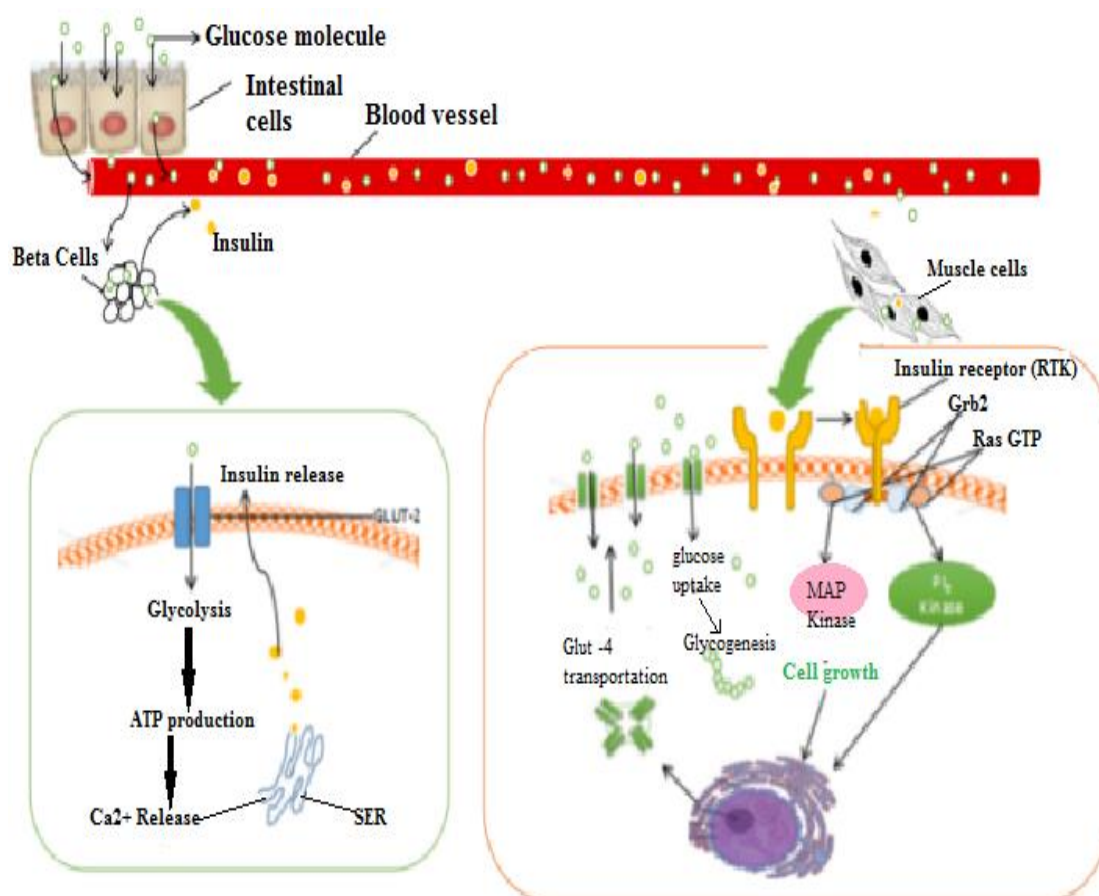

Figure 3: Cellular signalling pathway and mechanism involved in Insulin secretion and its functioning.

Table 1:- Diabetes leading to organ specific adverse consequences

S. No.	Organs	Adverse consequences
1	Heart	Stroke, angina pectoris, chronic heart disease
2	Muscle	Fatigue
3	Liver	Cirrhosis, ammonia toxicity, cancer, hepatitis, jaundice, excess ketone body production
4	Pancreas	Beta-cell destruction, dysfunction, pancreatitis, cancer
5	Kidney	Stones, nephropathy
6	Brain	Dementia, Alzheimer
7	Eyes	Retinopathy, cataract
8	Blood	Hyper-osmolarity, advanced glycated end products, atherosclerosis, anemia, acidosis, immune suppression
9	Urinary bladder	Glycosuria, polyuria, ketonuria
10	Skin	Digital scelerosis, scleroderma, diabeticorum vitiligo (skin patches), acanthosis nigricans
11	Uterus	Gestational diabetes, infertility (both males and females), intrauterine fetal death, PCOD
12	Limbs (specially foot)	Numbness, delayed wound healing, amputation

In diabetes patients, dysfunctioning of Insulin (lack of secretion or insulin resistance) makes glucose unavailable for the body to use, leading to hyperglycemic condition and Glucose toxicity. The nonavailability of glucose to cells of the body leads to the body looking for alternative sources to generate energy. Consequently, upregulation of gluconeogenesis (use of stored glucose), lipolysis and proteolysis (using stored fats and proteins) takes over in liver, muscles and adipose tissues. It also takes a toll on pancreas to produce more and more Insulin (as a result of sensing cell starvation) which causes β cell dysfunctioning with time (Yang *et al.,* 2010; Kaveeshwar and Cornwall, 2014). To maintain blood osmolarity, excess glucose is excreted out through urine leading to polyuria and glycosuria. Sometimes, excess of glucose is absorbed by RBC, leading to formation of Gluco-Haemoglobin. This causes an increase in blood viscosity; making the blood flow sluggish. This also reduces the efficiency of RBC and leads to Anemia. Glucose also get deposited on lipids and proteins, forming 'glycated proteins'(Advanced Glycation End products; AGES) which worsens diabetes and causes other complications like Atherosclerosis, Heart Stroke, Nephropathy, Neuropathy etc. (Sonksen & Sonksen, 2000)(Refer table 1). Fats and proteins, used as substitute fuel for metabolism, cause excess of ketone bodies formation and accumulation of ammonia leading to Ketoacidosis, Nephropathy, Liver cirrhosis etc. Diabetes also suppresses immune system, especially humoral immunity, encouraging opportunistic infections. It also results in hormone disregulation: high androgen production and Poly Cystic Ovarian Disease/Syndrome (PCOD/PCOS) etc. (Figure 4)(Sonksen & Sonksen, 2000).

Diabetes Mellitus: Complications
To overcome the hyperglycemic condition, blood often deposits the excessive glucose in the blood vessels and capillaries, blocking the blood flow. This is the root cause of various complications like Retinopathy, Nephropathy and Neuropathy. Diabetic Retinopathy is a major complication of various Diabetic eye diseases like Diabetic Macular Edema (DME), Cataract, and Glaucoma; all potential causes of blindness. In Retinopathy, blockage of retinal blood vessels (branches from central retinal artery) takes place due to thickening of blood vessels caused by high glucose level. Lower blood supply leads to Ischemia(Sonksen & Sonksen, 2000). In some cases, retinal cells become oversensitive to light(Solar and Radiation retinopathy), damaging the light cells via oxidative damage. Diabetes compromised with other diseases like Sickle cell Anemia, leads to Hperviscosity Syndrome, causing Central Artery Thrombosis, directly blocking the blood flow and death of retinal cells. The tissue damage/cell death may remain confined to an area(Non-proliferative Retinopathy), or it may spread in due course of time (Ramchandran, 2014; Taylor, 2013). To prevent cell death, in some cases, blood vessel proliferation(Angiogenesis and Neovascularization) occurs. These vessels are often leaky, leech out debris

and are prone to hemorrhage, leading to loss of vision and blindness. Retinal blood vessel bleeding can also cause the appearance of "floating" spots in vision which sometimes clear on their own. This condition occurs due to fluid accumulation in retinal macula leading to DME. Without proper treatment, bleeding recurs, increasing the risk of permanent vision loss (Taylor, 2013).

If the blood capillaries of kidneys get blocked/damaged due to high blood sugar, cholesterol or hypertension, constriction of afferent and efferent arterioles of nephrons occur (Taylor , 2013). It causes hyperfiltration which gradually change to hypofiltration over time. Consequently, changes within glomerulus: basement membrane thickening, widening of slits between podocytes and then increase in mesangial cells and matrix. All these conditions, ceases glomerulus filtration causing albuminuria and Nephrosclerosis. If detected at early stage(by checking proteinuria blood test and serum creatinine level), it can be cured by using ACE (Angiotensin Converting Enzyme) inhibitors, otherwise it may complicate the situation to partial or full kidney damage(Taylor, 2013; Sonksen & Sonksen, 2000).

As these blood capillaries also supply neurons(Vasa nervorum), their blockage damage the peripheral nervous system: sensory and motor neurons as well as autonomic nervous system(Kaveeshwar and Cornwall, 2014). Therefore, afflicting almost all organs and systems. Neural disease is closely related and interlaced with vascular problems. Development of blood vessel abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to lower blood supply hence causing Neuronal Ischemia, a hallmark of Diabetic Neuropathy, which in turn affect blood vessel functioning as they are controlled by normal nerve functioning. Presence of AGES damage the neurons by binding to myelin sheath, making them susceptible to phagocytosis, eventually contributing to peripheral segmental demyelination. Symptoms of Diabetic Neuropathy are sensitivity/loss of sense of touch, numbness or pain in the extremities, muscle weakness or wasting, nausea, indigestion, diarrhea, dizziness, excessive sweating and vaginal dryness in women and erectile dysfunction in men(Taylor, 2013; Kaveeshwar and Cornwall, 2014; Sonksen & Sonksen, 2000).
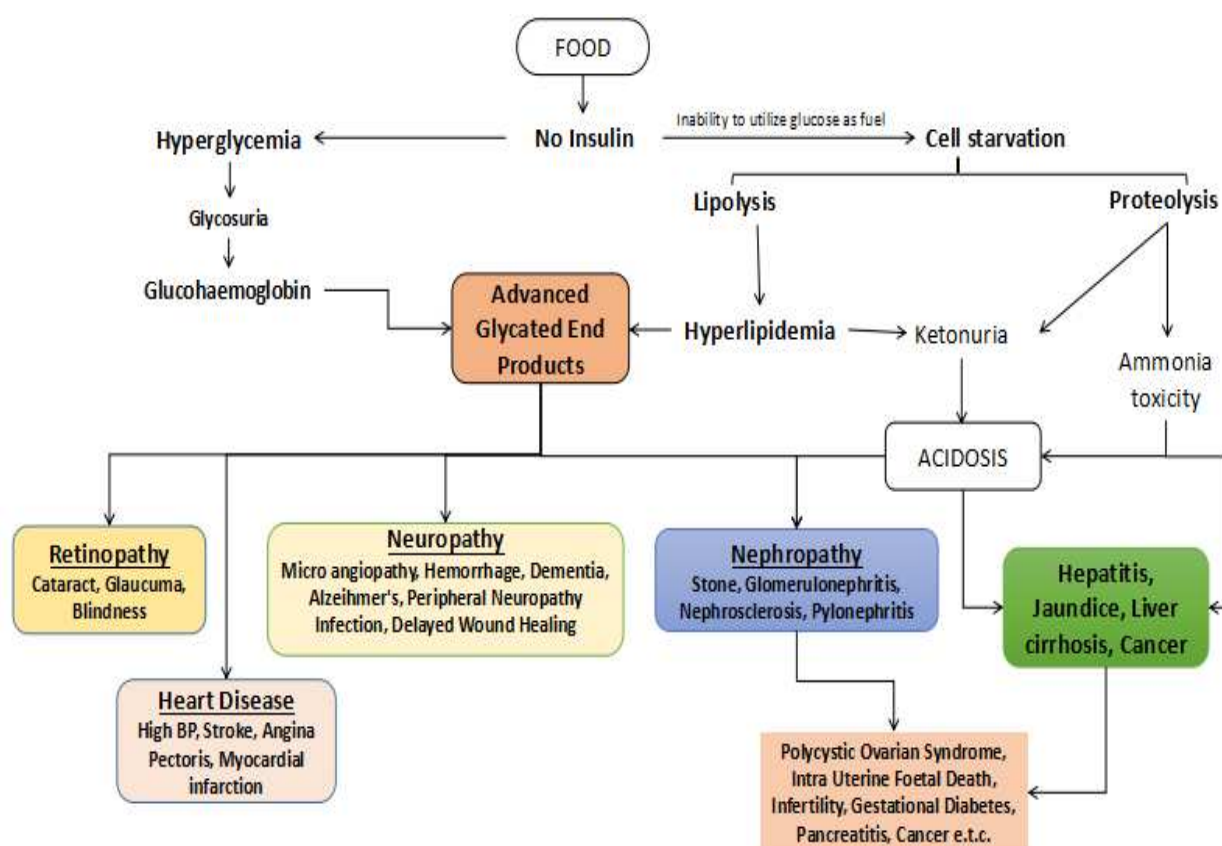

Figure 4: Complications arising in Diabetes Mellitus
Table 2:- Diagnostic Tests for Diabetes detection(Berg *et al.,* 2002)

Table 2:- Diagnostic Tests for Diabetes detection(Berg *et al.,* 2002)

Test Name	Description	Diagnosis criteria		
		Normal	**Pre-diabetes**	**Diabetes**
HbA1c test	For pre-diabetes and diabetes. This test is convenient because no fasting is required.	<5.7%	5.7-6.4%	6.5% or greater
FPG test	8 hours fasting is required prior to test. The laboratory procedures are followed to determine the amount of glucose in the plasma, as measured in mg/dL.	< 100 mg/dL	100-125 mg/dL	126 mg/dL or greater
OGTT – 2 hr. post glucose - rich beverage	This test measures how well the body handles a standard amount of glucose. The patient is allowed to drink large premeasured glucose drink. Two hours after the administration blood is withdrawn and blood sugar levels are compared before-and-after glucose ingestion to see how well the body processed the sugar. These levels are measured in mg/dL.	< 140 mg/dL	140-199 mg/dL	200 mg/dL or greater
Random plasma glucose test	A plasma glucose test is a measure of how much sugar/glucose is circulating in blood. "Random" implies that blood can be drawn in the laboratory at any time and is irrespective of fasting.			200 mg/dL or greater

Several studies were done to focus on mechanisms of insulin signalling in order to define the pathogenesis of insulin resistance. Insulin action is mediated through a protein tyrosine kinase receptor, in which tyrosine autophosphorylation occurs, initiating the cascades of reactions causing the plieotropic actions of insulin. However, due to extrinsic or intrinsic factors, instead of tyrosine, serine phosphorylation may occur (presumably mediated by serine/threonine kinase) on the insulin receptor, which has actions antagonistic to that of tyrosine phosphorylation[2]. In a non-diabetic person, serine phosphorylation occurs at a much lower rate, but in diabetes patients, around 50% of Insulin receptors undergo serine phosphorylation. Hence, it may be an important factor which causes Insulin Resistance(IR) in diabetics. It is believed that the defect in insulin action is limited to glucose metabolism, other biologic actions of insulin - including those involved in steroidogenesis - are not impaired.

It has been estimated that by 2030 the global prevalence of diabetes will reach 552 million(WHO Diabetes report, 2016). The disease is probably the biggest factor for blindness, heart stroke and kidney failure in adults. The above factors makes diabetes a global threat and presumably the next epidemic.

Diagnosis of Diabetes Mellitus
Early stages of diabetes are asymptomatic, therefore, blood tests are the most reliable technique for the diagnosis. Laboratory analysis of blood is needed to ensure accurate results. Glucose measuring devices such as finger-prick device do not measure blood accurately and can be used as quick indicator only. A persistently high fasting blood glucose levels alongwith HB1Ac and abnormal OGTT are some of the positive indicators for Diabetes. The tests recommended are listed in table 2.

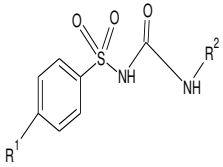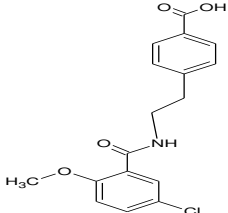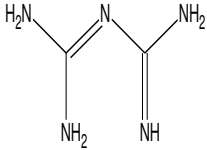**Diabetes Mellitus: Treatment and Side effects**
Diabetes is one of the common diseases which requires appropriate health care system and management. Diet and exercise are the key regimes for NIDDM. If they fail to attain a desired glycemic levels, pharmacological interventions are often required.
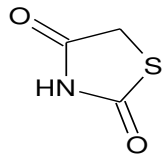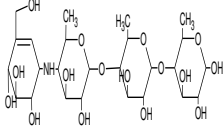
The treatment and management of IDDM has changed drastically in the last 60 years.In 1936, the first commercially available, extended-action insulin, PZI (protamine zinc insulin) was made. This formulation consisted of an amorphous combination of protamine, zinc, and insulin. After that different sustained action insulin(s) have been developed until the animal source insulin came in 1983(Diabetes Care, 2014; White JR, 2014). In 1996, first recombinant rapid-acting human

insulin analog,i.e lispro, was approved which was followed with a succession of additional insulin analogs, which included the rapid-acting insulin - aspart and glulisine and also the long-acting basal analogs like glargine and detemir. Insulin is the most effective anti-hyperglycemic agent used in treating diabetes. In case when insulin is unable to control the glycemic level(insulin resistance cases), pharmacological intervention is needed(Owens, 2012; Nobel *et al.,* 1998; Aspart insulin (rDNA origin) injection, 2017). Metformin and sulfonylurea (tends to cause initial weight gain) are the first line drugs used in the treatment of NIDDM. Metformin is considered as most preferred drug for the treatment of overweight patients because it causes less weight gain and associated with lower rate of hypoglycemia(Apidra insulin glulisine (rDNA origin) injection, 2017). Many other drugs are also formulated for the treatment i.e. glucosidase inhibitors, Non-sulfonylurea insulin secretagogues (for patients with irregular meal times)(Brunetti and Kalabalik , 2012). Table-3 enlists various class of drugs used in diabetes treatment and their mechanism of action.

Table 3:- Oral hypoglycemic Drug used in the treatment of Diabetes mellitus

Name of the drug	Structure	Mechanism of action	Side effects	Examples	Reference
Sulfonylureas		It increases pancreatic insulin secretion by depolarizing the cell membrane, hence increases Ca^{2+} influx. Sensitizes β cells to glucose, limiting glucose production in liver.	Hypoglycemic attacks, Upset stomach, skin rash, itching, weight gain	Glimepiride, Glipizide, Glyburide	Karter *et al.,* 2005
Meglitinide		Mechanism is similar to Sulfonylureas, but weaker affinity to K^+ channels, hence quicker decrease in glycemic levels.	Weight gain and low blood glucose	Nateglinide	Luna and Feinglos, 2001
Biguanide		Suppresses glucose production, decreases gluconeogenesis and its absorption, increases the insulin sensitivity. It does not increases the Insulin output but the Insulin sensitivity by transporter linked system.	Kidney complications, upset stomach, tiredness, metal taste	Metformin	Luna and Feinglos, 2001; American Diabetes Association, 2015
Thiazolidinedione		It increases the insulin sensitivity by increasing transcription of certain genes like aP2; decreasing FFA,TNF-α and leptin levels.	Weight gain, risk of liver disease, anemia risk and swelling of legs	Pioglitazone, Actos	Bydureon – exenatide, NIM, 2017
Alpha-glucosidase inhibitors		It decreases the postprandial hyperglycemia by reducing gastrointestinal carbohydrate absorption	Gas, bloating and diarrhoea	Acarbose	Byetta exenatide injection, 2017; Diabetes treatment, 2017; Type 1 Diabetes, 2017

When glucose can no longer be controlled with single oral agent, a combination of two or more drugs are given to achieve the target glucose levels. One of the best oral agent combination is metformin and sulfonylurea. Other combinations used commonly are sulfonylurea with either alpha glucosidase inhibitors or thiazolidinediones. A new class of antidiabetogenic drugs that provide comparable efficacy to current treatments is Dipeptidyl peptidase IV(DPP- 4) inhibitors. They rapidly inactivate GLP-1 (glucagon like peptide) and GIP (gastric inhibitory polypeptide) which increases the activity of these hormones and improves the islet function resulting in glycemic controls (in NIDDM). They are effective as mono-therapy in patients with uncontrolled glycemic levels (Chaudhary *et al.,* 2017; Kuritzky, 2006; Sena *et al.,* 2010).

Patients who fail to achieve the adequate glycemic levels with oral drug combinations are shifted to treatment with extraneous insulin. Different types of insulin formulations are available which directly targets the glucose metabolism. Sometimes Insulin therapy is combined with oral drug therapy to achieve better target. For example,a combination of glargine with sulfonylurea or Metformin is used to control the glycemic level . Although, side effects from the usage of commercial insulin is very rare, in some cases it may cause Type-1 Hypersensitivity response due to the preservatives added in commercial insulin injection. Mild skin irritation, pricking and pain around injection site can be observed(Sena *et al.,* 2010; Karter *et al.,* 2005).

Mostly, drugs used to lower the blood glucose level or raise insulin sensitivity have mild side effects which can be handled easily. But in some cases, it is found out that treatment of NIDDM using hypoglycemic drugs is counterproductive and worsens Diabetes progression. Some drugs have been declared dangerous for NIDDM treatment, by the FDA. They may increase the risk of heart failure. For example- Saxagliptin, Alogliptin, Avandia, Pioglitazone. Some other drugs like Farxiga, linagliptin, sitagliptin, Alogliptin e.t.c, are known to cause various side effects including disabling joint pain(Byetta exenatide injection, 2017; Diabetes treatment, 2017; Type 1 Diabetes, 2017; Diabetes Medicines, 2016).

Diabetes and Plant based drugs
From the above discussion on various drugs for treating Diabetes, it can be inferred that although, drugs with

insulin therapy are able to keep the glucose level in check, the eradication of the disease and complication arising from it cannot be lowered by drug therapy alone. Since the disease is chronic, the treatment is lifelong and the patient is dependent on medications which cannot be withdrawn. This lifelong medication regime causes myriad of side effects including weight gain, chronic heart, liver and kidney diseases. Thus, the treatment and management of diabetes requires a more robust and holistic approach.

Natural and nature identical compounds have been shown to offer relief from lot of diseases since a long time. Plants have many phytochemicals and bioactive compounds which have diverse function like antimicrobial, anti-tussive, anti-inflammatory analgesic, anti-septic etc(Victoza, NIM, 2018; Singh *et al.,* 2007). They are rich in anti-oxidants which play very important role in cellular defense against diseases. It has been observed that, in diabetes, ROS and other kinds of oxidative stress play an important role in disease progression. Many of the complication in diabetes arise due to oxidative stress(Singh *et al.,* 2007). An anti-oxidant therapy should prove to be effective in slowing down progression and reduce complications arising from diabetes. Since plants are the natural and one of the richest source of anti-oxidants, plant based approach in diabetes should go a long way in effectively managing the disease. Ancient Ayurvedic texts such as Sushrut Samhita, described two types of Diabetes as well as their treatment, long ago. The treatment listed in the text includes specific mineral intake, dietary modification, and medicinal plant remedies (Shirazi *et al.,* 2014). Medicines prepared from plants seemed to ameliorate the disease completely. More than 1000 plants were reported to possess anti-diabetic activity(Elder, 2004). Different plant extracts have been tested and found positive for this activity. Certain plants possessing anti-diabetic activity are mentioned in table 4 with the brief explanation of their mechanism of action.

It is clear from the above discussion that Diabetics have an increased risk of developing numerous health problems. Persistent hyperglycemia and hyperlipidemia, may affect the heart, blood vessels, liver, eyes, kidneys, nerves, skin and teeth. Moreover, it also affects immune system and promotes various kinds of secondary infections. Most common long term complications of diabetes include atherosclerosis/arteriosclerosis, macro-vascular complications and micro-vascular complications, which affects the Heart, kidney, eyes, feet

and brain. Other parts of the body can also be affected by diabetes, including the digestive system, the skin, genital organs, teeth and gums, and the immune system. Studies on Diabetes suggest that it encourages severe infections by crippling our immune system. Diseases like Tuberculosis, Sexual Transmitted Diseases(STD), PCOS, Obesity and various cancer like Colorectal, Liver, Breast cancer e.t.c; are found to be associated with diabetes. In the following section, these threats and their interrelationship with diabetes are discussed briefly.

Table 4:- Selected list of medicinal plants possessing anti-diabetic activity

Plant Name	Part	Effects	References
Momordica charantia	Fruit	Charantin and lectin lowers blood glucose levels. Vicine is a insulin like compound	Manyam, 2004; Welihineda *et al.,* 1986; Baskaran *et al.,* 1990
Trigonella foenum	Seeds	Lowers blood glucose by slowing the digestion and carbohydrate metabolism	Welihineda *et al.,* 1986
Zingiber officinale	Rhizome	Gingerols- increases the uptake of glucose bye muscles	Tripathi and Chandra, 2009
Cinnamomum zeylanicum	Seed, Water extract of seeds.	It decreases the stomach emptying and significantly reduces hyperglycemia after without affecting satiety	Li *et al.,* 2012
Murraya koenigii	Leaves, ethanolic and DCM extract was found to be most active.	Protection of beta cells of pancreas and increases the level of glucose-P dehydrogenase enzyme levels, hence normalizing the hepatic and muscle gluconeogenesis. The levels of post-prandial hyperglycemia reduces due to the pancreatic and intestinal glucosidase inhibitory activity of the extracts.	Ranasinghe *et al.,* 2012
Syzygium cumini	Leaves, fruits and seeds	Jamboline –marked decreased in blood glucose levels.	Tembhurne and Sakarkar, 2010
Actinidia deliciosa	Fruit, methanolic extract	Presence of fructose which is a slow releasing sugar. It also has Inositol, which regulates insulin levels.	Nair and Santhakumari, 1986
Gymnema sylvestre	Leaves	Assists in regeneration of pancreatic beta cells.	Soren *et al.,* 2016
Coccinia indica	Fruit	Abnormal changes in fatty acids composition in diabetes are prevented	Baskaran *et al.,* 1990
Azadirachta indica	Leaves	Prevents diabetic nephropathy	Shibib *et al.,* 1993
Myrtus communis	Ethanolic extract of leaves	Exhibits hypoglycemic effects as well as a good candidate of anti-oxidant. Plant extracts were tested on Streptozotocin induced diabetic mice, and found positive result.	Khosla *et al.,* 2000; Elfellah *et al.,* 1984
Memecylon umbellatum	Ethanolic extract of leaves	Lowers serum glucose level in alloxan induced diabetic mice.	Mohaddese, 2017
Morus indica	Leaves	Fagomine, extracted from the leaf extract was found to be responsible for lowering blood sugar and enhancing Insulin sensitivity. It also lowers lipid content in blood.	Amalraj T and Ignacimuthu, 1998
Ocimum sanctum	Leaves, ethanolic leaf extract	Prominently increases insulin level and decreases the blood glucose level in rats. In-vitro study on isolated pancreatic cells also gave similar results. Mechanism of action is somehow similar to Metformin.	Andallu *et al.,* 2009
Artemisia pallens	Aerial part	Hypoglycemic effects seen in alloxan induced rats.	Chattopadhyay, 1993
Bidens pilosa	Leaves, water extract	It significantly decreases blood glucose levels and increases serum insulin levels in diabetic rats. It also significantly improves glucose tolerance, decreases HbA1C levels and protects islet structure by stimulating insulin secretion via pancreatic islets	Subramonium *et al.,* 1996
Cryptolepis sanguinolenta	Stem, ethanolic water extract	It significantly decreases the glucose transport and absorption and reduces plasma glucose, total cholesterol, triglyceride, and LDL cholesterol in diabetic rats.	Alarcon-Aguilar *et al.,* 2000
Ficus religiosa	Bark, aqueous extract	It significantly increases the serum insulin, body weight and glycogen content in liver and skeletal	

		muscle of STZ-induced diabetic rats and reduces the levels of serum triglyceride and total cholesterol. It also has anti lipid- peroxidative effect in the pancreas of STZ-induced diabetic rats.	Ajayi *et al.,* 2012
Enicostemma littorale	Aerial aqueous extract	It increases glucose induced insulin secretion, which does not get affected by Ca^{2+} channel blockers.	Pandita *et al.,* 2010
Andrographis paniculata	Leaves, ethanolic extract	Lowers fasting glucose serum level but insulin level remains same. Also reduce hepatic glucose phosphatase activity and reduces fasting serum triglyceride levels.	Murli *et al.,* 2002
Capsicum frutescens	Fruit	Increases serum insulin level in STZ-induced diabetic rats.	Zhang and Tan, 2000
Justicia adhatoda	Leaves and roots ethanol extract	Lowers serum glucose , triglycerides and cholesterol levels and increases the insulin levels in alloxan induced diabetic rats.	Islam and Choi, 2008
Morus alba	Leaves, ethanolic extract	Corrects lipid abnormalities and prevents oxidative stress	Roy *et al.,* 2013
Cinnamomum tamala	Leaves, ethanolic extract	polyphenol, exerts insulin potentiating activity in STZ-induced rats.	Mohammadi and Naik, 2008
Asphaltum punjabianum	Tar, gum, mineral like substances	Fulvic acid eradicates free radical damage to pancreatic islet B cells. **Shilajit capsules** improves the function of pancreas to secrete **insulin** and further aids in the expulsion of toxins through urine.	Bisht and Sisodia, 2011
Emblica officinalis	Fruit	Exceptional phytonutrients, **helps to decrease blood glucose levels in diabetics and lowers cholesterol.**	Bhattacharya, 1995
Curcuma longa	Rhizome	Curcumin derivative acts on pancreatic islet cells for their regeneration	Patel and Goyal, 2011
Acacia arabica	Seeds and bark;	Chloroform extract of bark has hypoglycemic, hypolipidemic, and antioxidant properties.	Sharma *et al.,* 2006

Metabolic syndrome, PCOS & Diabetes Mellitus

The concurrence of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution, mild dyslipidemia and hypertension and its association with subsequent development of NIDDM and cardiovascular disease have given rise to the concept of the metabolic syndrome, also known as the IR syndrome. IR is considered the underlying factor in this syndrome. The pathogenesis of this syndrome is still unclear, although environmental factors such as diet and physical activity, coupled with largely unknown genetic factors, interact to produce the syndrome.

PCOS is a set of symptoms arising due to elevated level of androgens in women. PCOS is the most common endocrine disorder among women between the ages of 18 to 44. It affects approximately 2% to 20% of females in this age group. It is one of the leading cause of poor fertility(Patil *et al.,* 2011). PCOS symptoms include irregular periods, amenorrhea, menorrhagia, excess body and facial hair, acne, pelvic pain and patches of thick, darker, velvety skin. PCOS is closely associated with NIDDM, also leads to obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer. Many women with PCOS also have diabetes,

therefore, many researchers are examining to establish relationship between PCOS and the body's ability to produce insulin. There is an increasing amount of evidence that leads to high production of androgen, that worsens the PCOS condition (Patil *et al.,* 2011).

The relationship between hyperandrogenism and hyperglycemia was first observed in 1921. The association between increased insulin resistance and occurrence of PCOS is now well recognized. Insulin resistance(IR) is defined as reduced glucose response to a given amount of insulin. There are several mechanisms contributing to the state of IR: peripheral target tissue resistance, decreased hepatic clearance, or increased pancreatic sensitivity. In IR cases, hyperinsulinaemia causes decreased production of Sex Hormone Binding Globulin(SHBG) in liver, disordering the production of LH/FSH. Elevated level of insulin in blood also leads to rise in level of Ovarian Androgen production. Combined result promotes Hyperandrogenism and Oligo/Anovulation. Studies showed that obese PCOS women had significantly decreased insulin sensitivity compared with non-obese PCOS women. Consistent with the degree of insulin resistance, the manifestation of compensatory hyperinsulinaemia in lean PCOS women

was incipient, being evident only in response to meals. Collectively, these observations indicate that IR is a common finding in women with PCOS independent of obesity and that of IR in obese PCOS is composed of dual contributions, one unique to PCOS and the other obesity-specific. Several groups have focus on mechanisms of insulin signalling in order to define the pathogenesis of insulin resistance in PCOS. A potential mechanism responsible for this appears to be related to excessive serine phosphorylation of insulin receptor, which was observed in at least 50% of PCOS women.(Patil *et al.,* 2011; Wang *et al.,* 2011).

Diabetes and Tuberculosis

Diabetes Mellitus is an independent risk factor for Tuberculosis(TB). The association between diabetes and tuberculosis dates back 1000AD in Greek, where it was noted that tuberculosis gets complicated in diabetics and vice versa. An Indian saint named Yugimahamuni also described the association of Diabetes Mellitus and TB by a combination of symptoms called 'meganoikal'(Cibula *et al.,* 2000). These symptoms included obesity, glycosuria, thirst, incontinence, respiratory symptoms and unconsciousness. Both disease worsen the outcome of the other disease. TB is a specific morbidity often associated with Diabetes Mellitus and is therefore aptly described as a complication of Diabetes. Diabetic patients are more susceptible to infections and may lead to severe illness due to immune suppression. Reactivation of older lesions induced by TB infection may also occur. Just like tuberculosis, prevalence of diabetes is more in developing countries. Being diabetic, increases the TB risk 1.5 to 7.8 folds. Multi-drug resistant TB was found to be associated with Diabetes Mellitus with a ratio of 2.1. Although, NIDDM is more prevalent globally, IDDM carries more TB risk than NIDDM. TB infected individuals show impaired glucose tolerance, which promotes the risk for the development of Diabetes. Usually, this symptom subdues and reverts back to normal after successful treatment for TB, but the risk for development of diabetes persists. Active tuberculosis patients show enlarged pancreas which is a clear indication of pancreatitis, which further points at the role of TB in development of Diabetes Mellitus.

The count of T lymphocytes and neutrophils decreases in diabetes patients, leading to reduced level of Th1 cytokine response, which is vital to control tubercular infection. Also, there is reduced production of TNF-α, IL-1 β and IL-6 in individuals accompanied with TB and diabetes. Due to glucose toxicity, Reactive Oxygen Species are produced, interacting randomly with biomolecules as well as macrophages, causing impaired phagocytic and chemotactic functions of macrophage. These reasons are primarily responsible for susceptibility to TB in diabetics (Cibula *et al.,* 2000; Dooley and Chaisson, 2009).

The mechanisms involved in causing tuberculosis in diabetic individuals are not completely understood. Studies showed that, hyperglycemia, cellular insulinopenia and indirect effects on macrophage and lymphocyte function, leads to diminished ability to control bacilli. Phagocytes (alveolar macrophages and their precursor monocytes) and Lymphocytes are necessary to keep tuberculosis in check as effector cells. It has been observed that diabetes afflict the role of effector cells by affecting chemotaxis, phagocytosis, activation, and antigen presentation by phagocytes in response to *M.tuberculosis*. In diabetic patients, chemotaxis of monocytes is impaired, and this defect does not improve with insulin. Decreased hydrogen peroxide production in macrophage again promotes tuberculosis infection and containment the diabetics. Insulin deficiency leads to impairment of antigen presentation and T cell activation and proliferation which occurs due to the poor phagocyte binding leading to reduced IL-2 production which in turn activates T cells. In NIDDM patients, IL-2 production by monocytes bearing normal number of Fc receptors remained same. However, number of monocytes bearing complement receptor 3 is lower compared to normal, thus leading to diminished adherence and phagocytosis (Cibula *et al.,* 2000; Dooley and Chaisson, 2009; Olmos *et al.,* 1989). Diabetes was shown to inhibit interferon γ production, T-cell growth, function, and proliferation. Diabetes strips over the potency of macrophages (nitric-oxide-dependent intracellular killing) by inhibiting interferon γ.

It has been speculated that hyperglycemia leads to reduced IFN-γ production, lymphocyte proliferation in response to phytohaemagglutinin and lowered IL-12 and nitric oxide concentration in lungs and spleen in Type 2 diabetes (NIDDM). Studies indicate that patients with NIDDM, reverting the glucose level to normal and administration of IL-12 did not increase T-lymphocyte proliferation or expression of IL-12 receptor(Dooley and Chaisson, 2009). All the studies point to depressed immunological function in Type 1 and Type 2 Diabetes that might lead to predisposition to various infectious

diseases. The implications of diabetes-related differences in the immune response to tuberculosis are being investigated. The relative contribution of genetics, vitamin deficiencies, and other factors to increased risk of tuberculosis in diabetic patients remains to be established.

Diabetes and Cancer

Several studies have suggested that diabetes mellitus may increase the risk of developing a variety of cancers, and the inference of the association between diabetes and cancer are also made frequently. Cancer and diabetes are diagnosed within the same individual more frequently than would be expected by chance, even after adjusting for age. The only consistently observed associations between diabetes and cancer are for pancreatic and liver cancer, but relatively few studies of persons with diabetes have examined risk for several cancer sites. In addition, the independent contribution of diabetes as a risk factor for cancer, separate from high body mass, has not been adequately defined by prior studies. It is said that hyperinsulinemia and NIDDM increase the risk of breast cancer through direct effects on breast tissue or indirectly by increasing circulating concentrations of estrogen, testosterone and insulin-like growth factors. In a study, it was found that diabetes was associated with a 13 and 25% increased risk of breast cancer in case–control and cohort studies, respectively. The disease is associated with a 1.2-fold increased risk of bladder cancer, 1.3-fold increased risk of colorectal cancer, 1.7-fold increased risk of pancreatic cancer and 2.5-fold increased risk of hepatocellular carcinoma. In recent epidemiologic studies, insulin-like growth factor 1 (IGF-1) has been associated with increased risk of colorectal cancer. IGF-1 may act as a promoter of colon tumor cell growth (Kim *et al.,* 1995).

The majority of cancer cells express insulin and IGF-1 receptors; the insulin isoform receptor is commonly expressed. This isoform can stimulate insulin-mediated mitogenesis, even in IGF-1 receptor deficient cells. A cascade of multiple signaling pathways are activated after insulin receptors or IGF-1 receptors interact with their ligands (insulin). Phosphorylation of the initial kinase linked to downstream signaling pathways, may stimulate multiple cancer causing factors like proliferation, protection from apoptotic stimuli activation of anti-apoptotic genes), invasion, and metastasis, potentially enhancing the initiation and progression of many types of cancer cells. It is also clear that insulin/IGF may stimulate the transformed

cells(initial stage of cancer - metaplasia, dysplasia) into cancer progression. For example, hyperglycemia allows IGF-1 to stimulate vascular smooth muscle cell proliferation and migration. Although this process has been linked to the patho-physiology of atherosclerosis, abnormal vasculature growth is also a hallmark of cancer. In addition to its metabolic functions, the insulin receptor is also capable of stimulating cancer cell proliferation and metastasis (Kim *et al.,* 1995; Coughlin *et al.,* 2004). Cancer cells uptake glucose constitutively high which is independent of insulin binding to its receptor. Hence, on cancer cells, insulin receptor activation may mostly relate to cell survival and mitogenesis than to enhance glucose uptake. Increases in serum or plasma levels of IGF-1 have been observed in recent epidemiologic studies of prostate and premenopausal breast cancer.

Some indirect factors like abnormal production of cytokines, chemokines and other proteins may also involve in cancer development. IL-6, monocyte chemoattractant protein, plasminogen activator inhibitor-1(PAI-1), adiponectin, leptin, and tumor necrosis factor-α are some of the factors that might play etiologic role in regulating malignant transformation or cancer progression. Recently, it was found out that GLP-1 drugs, known as Exenatide and Liraglutide, may increase progression of pancreatic cancer (Vigneri *et al.,* 2015; Butler *et al.,* 2010). Although the correlation between diabetes and cancer is not very well known, but it cannot be disregarded completely. Association of hyperinsulinaemia and hyperlipidemia with malignancies have been extensively studied and further exploration is needed.

Many sexually transmitted diseases like chlamydia, herpes and HIV/AIDS are found to increase the risk of NIDDM to 82%. Some studies indicate that even intestinal infection may increase the diabetes risk to 88%. The therapy for HIV treatment, known as HAART therapy also increases type 1 diabetes risk(Kalra *et al.,* 2011). Studies show the impairment of insulin function is caused due to the direct involvement of Hepatitis C viruses, leading to Insulin resistance. Hyper-insulinaemia, hyperlipidemia, obesity, viral and bacterial infection, hormonal imbalance, weak immune response, sedentary life style and other factors like heredity, induced mutations, protein dysfunction or errors in downstream intracellular signalling promotes diabetes. Therefore, only one kind of therapy is not enough to combat the disease. Multiple therapeutic approaches

such as hormone therapy, conventional medicines, gene therapy and plant based medicines etc, should be considered for diabetes treatment. In a recent study, knocking off glucagon hormone in insulin impaired mice prevented diabetes. Metformin, a very popular anti-diabetic drug, is used to manage both diabetes and tuberculosis (Singhal *et al.,* 2014). In the same way, properties of other drugs used in treatment of other diseases should get evaluated for anti-diabetic properties.

CONCLUSION

Diabetes, although non-infectious, is one of the most prevalent diseases across the globe. It is a complex multifactorial disease existing in predominantly two forms: IDDM and NIDDM. It is predominantly a disease requiring lifestyle management along with conventional treatment.. Due to it being largely asymptomatic in the early stages, it remains undiagnosed for a long period of time. This leads to loss of homeostasis and complications at later stages. Neuropathy, nephropathy and retinopathy along with hyperinsulinaemia and hyperlipidemia makes the disease difficult to manage. Long term medications and secondary infections are the two other banes of the disease. Recent speculation about probable role of anti-diabetic drugs in enhancing cancer risk only adds to the existing woes accompanying the disease. More than one kind of therapeutic approach is the need of the hour to manage the disease in the best possible way. Plant based drugs are one of the safest alternative and their use as adjunct therapies should be scientifically looked at, more vigorously.

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