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Various Pathogenesis involved in the Development of Type-II Diabetes Mellitus and its Management Processes

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ABSTRACT

Diabetes Mellitus is a chronic metabolic disorder in which beta cells of the pancreas cannot secrete completely, or enough insulin is required for the body to maintain the blood glucose level in the body. There are several causes of the disorder which mainly include dietary factors and lack of physical activity. Obesity and genetic factors also contribute in leading to the state of diabetes. There are various secondary complications of the disease, such as diabetic nephropathy, neuropathy, and retinopathy. This is one of the multisystem diseases which destroys multiple other systems in the body, including the cardiovascular system, nervous system. This is one of the global burdens for the modern world as the proper treatment of the disease is still unavailable. The only available for the disease is the management of the disease. Type I diabetes mellitus can only be managed by regular insulin therapy in which patients take an insulin injection as per the dosage required by the body. There are various oral hypoglycemic agents for the management of Type II diabetes mellitus. As the proper treatment of the disease is undiscovered, still multiple approaches are made for the treatment. There are various other herbal and natural products which are used for the management of the disease, although these natural products do not have any good results. One of the approaches is to permanent reversal of the disease called reverse diabetes. The process of reverse diabetes involves the regeneration of the beta cells of the pancreas, due to which the amount of insulin required for the body can be secreted, and the blood glucose level can be maintained. Some of the other approaches for the reversal of diabetes include bariatric surgery, pancreas transplantation, and transplantation of islets of the pancreas.

1. Introduction

Glucose serves as a significant source of energy in our body for the proper functioning of the body's metabolism (Piero MN *et al.,* 2015). An increase of glucose levels (*hyperglycemia*) in the body may be due to the malfunction of hormones, insulin, or any other dietary factors leading to the state called 'Diabetes Mellitus' (Yaribeygi H *et al.,* 2020). During 81-133 AD, Araetus of Cappodocia introduced the word "Diabetes." After that, the word Mellitus meant honey-sweet, which was then added by Thomas Willis (Britain) in 1675 after finding the sweetness in urine as bees were seen flying over the urine(Ahmed *et al.,* 2002). Diabetes is one of the groups of many diseases involving excess glucose in the human body due to lack of insulin secretion or lack of utilization of synthesized insulin in the body or both (Galicia-Garcia U *et al.,* 2020). It occurs due to the intake of glucose, so that the insulin cannot function properly in our body. Diabetes can be classified as, Type-I (due to β-cells destruction), Type-II (due to insulin resistance and impaired insulin efficacy), and Gestational diabetes (diabetes which occurs during pregnancy due to glucose intolerance) (Peterscmann A *et al.,* 2018). In this review, we are focusing on Type -II Diabetes Mellitus and its treatment approach.

'The ominous octet,' which includes eight reasons for causing diabetes, is known. These include a decrease in the quantity of insulin secretion, increased glucose reabsorption, decrease in the effect of incretin, an increase of lipolysis, a decrease of the amount of glucose uptake, increased glucagon secretion, neurotransmitter dysfunction, and substantial production of hepatic glucose (Thrasher J *et al.,*

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2017).

Table 1: Ominous octet of diabetes Mellitus

SI No.	Parameters	Quantity (Increased/Decreased)
1.	Insulin secretion	Decrease
2.	Glucose reabsorption	Increase
3.	Effect of incretin	Decrease
4.	Lipolysis	Increase
5.	Glucose uptake	Decrease
6.	Glucagon secretion	Increase
7.	Neurotransmitter dysfunction	Increase
8.	Production of hepatic glucose	Increase

People having Type II diabetes are most probably at high risk for both microvascular complications (including neuropathy, retinopathy, and nephropathy) and macrovascular complications (like cardiovascular comorbidities and cerebrovascular diseases), due to hyperglycaemia and individual components of insulin resistance (metabolic) syndrome (Defronzo RA *et al.,* 2015). The major symptoms include increased thirst, frequent urination, weight loss, and fatigue (Ginter E *et al.,* 2013).

It can also be due to genetic factors and serenity lifestyle, or both. Obesity is another reason for impaired glucose metabolism leading to the deposition of calories and fat in adipose tissue, causing hypoxia of fatty tissue, destroying the adipocytes causing Type II diabetes mellitus (Xu L *et al.,* 2018). Environmental toxins such as arsenic, cadmium, mercury play a role in developing Diabetes Mellitus (Kuo CC *et al.,* 2013). The generation of reactive oxygen species due to oxidative stress also leads to diabetes (Ighodaro OM *et al.,* 2018). Diabetes insipidus is one of the rare disorders occurring when a person's kidneys begin to secrete urine in large volumes abnormally, which is generally odorless. Diabetes insipidus, as well as diabetes mellitus, may include both Type I and Type II diabetes which may be unrelated. Still, in both cases, it causes the frequent desire for urination as well as constant thirst. People had diabetes insipidus have blood glucose levels on average; although, the kidneys may not be able to balance liquid and fluids in the body (12). Diabetes can be determined if the blood glucose level is more than 200 mg/dl of glucose after 2 hours of food intake. Levels between 140-199 mg/dl can be indicated as pre-diabetes (Preiss D *et al.,* 2011). Insulin is generally used for the treatment of Type-1 diabetes. Short-acting insulin (insulin aspart and insulin lispro), insulin for more extended action (insulin glargine, insulin ultra-lente), and regular insulin are the types of insulin available for the management of Type-1 diabetes (Jacob S *et al.,* 2018).

1. a. Management of Diabetes Mellitus

As specific treatment of the disorder is still unavailable in the market only management techniques and medicaments are available. Some of them are discussed below.

Table No.2 Drugs available in the market for the management of type II diabetes mellitus

Sl No.	Drug category	Examples	Mechanism of Action
1	Sulfonylureas	Glipizide, glibenclamide	Decreases blood glucose level by increasing the sensitivity of beta cells towards glucose (Akkati S *et al.,* 2019).
2	Biguanides	Metformin and phenformin	Decreasing the glucose production by unknown mechanism (Forouhi NG *et al.,* 2019).
3	Thiazolidinediones	Pioglitazone, rosiglitazone	Enhances insulin sensitivity and promotes glucose uptake (Forouhi NG *et al.,* 2019).
4	Glucosidase Inhibitors	Acarbose	Reduction of carbohydrate digestion which leads to decrease in glucose in the body by interfering with glucosidase activity (Defario M *et al.,* 2013).
5	Meglitinide	Repaglinide	Increases sensitivity of beta cells towards glucose (Defario M *et al.,* 2013).
6	Dipeptidyl peptidase IV inhibitors	Sitagliptin	Inhibits glucagon release (Mukherjee J *et al.,* 2016).

1.b.Epidemology

World Health Organisation categorized diabetes as one of the four major non-communicable diseases which requires immediate action. In recent years, it is primarily found an increase in the prevalence of diabetes virtually all around the globe. The number of people who have diabetes is enormous in today's date. The lack of regular diagnosis of diabetes and lack of standard measurement procedures of diabetes-related problems leads to more barriers in evaluating the trends worldwide (Harding JL *et al.,* 2019). In 1964, the earliest known survey, the diabetic population was found to be 30 million throughout the world (Entmacher PS *et al.,* 1965). People having Type I diabetes are estimated to be around 7 to 15%, and the remaining number of approximately 87-91% is estimated to be of Type II diabetes. The remaining digits are of gestational diabetes and other kinds of diabetes. Prevalence of Type-II diabetes was found highest in North Africa, the Caribbean, Western Pacific, Middle East, and North America and lowest in sub-Saharan Africa when categorized on the basis of age (Koye DN *et al.,* 2018). The number increased to 143 million in 1997 (Seidal JC *et al.,* 2000) and 171 million in 2000 and

Table No. 3 : Some of the herbal medications for the management of Diabetes Mellitus are enlisted below:

Si No.	Scientific Name	Family	Part Of The Plant	Common Name	Availability	Mechanism Of Action
1.	*Urtica dioica*	Urticaceae	Leaves	Stinging needle	Europe, Northern Africa, Asia.	Improves cells function and helps in rebuilding stimulating insulin secretion (Xie W *et al.,* 2011)
2.	*Trigonella foenumgraecum*	Fabaceae	Seeds	Fenugreek	India	Helps in insulin secretion (Kavshankar GB *et al.,* 2011)
3.	*Ferula asafoetida*	Apiaceae	Gum	Asafoetida	Iran and Afghanistan	It helps in the reduction of free radicals and stimulates the secretion of insulin (Abu-zation AS *et al.,* 2010)
4.	*Combretum micranthum*	Combretaceae	Leaves	Kinkeliba in Benin and Geza in Hausa	Africa	Stimulates hyperplasia of remaining - cells and stimulates insulin secretion (Islam D *et al.,* 2018)
5.	*Liriope spicata*	Liliaceae	Leaves	Monkey grass	East Asia and China	Increases insulin secretion and absorption of glucose (Chen X *et al.,* 2009)
6.	*Caesalpinia bonducella*	Caesalpiniaceae	Seeds	Gray nicker	India	Increases insulin secretion (Kannur DM *et al.,* 2006)
7.	*Ginseng*	Araliaceae	Roots,stalks, leaves, berries	Asian ginseng	North America and Eastern Asia	Protects pancreatic cells and stimulates glucose uptake (Gui QF *et al.,* 2016)
8.	*Momordica charantia*	Cucurbitaceae	Fruit pulp, seeds, leaves	Bitter gourd	Asia, Africa, and The Caribbean	It inhibits protein tyrosine phosphatase and activates AMPK, which enhances insulin effects (Ooi CP *et al.,* 2012)
9.	*Dendobium Chrysotoxum*	Orchidaceae	Aerial parts	Golden-bow Dendrobium	Native to southeast asia	Increases mRNA expression Retina treating retinopathy (Gong CY *et al.,* 2014)
10.	*Zingiber zerumbet*	Zingiberaceae	Roots	Bitter ginger	Asia and India	Increases expression of MAPK in the retina (Tzeng TF et al 2013.,)
11.	*Kaempferia parviflora*	Zingiberaceae	Roots	(KP) or krachaidum or thai ginseng	Thailand	Increases cost of energy leading to more glucose uptake (Akase T *et al.,* 2011)
12.	*Allium sativum*	Amaryllidaceae	Seeds	Garlic	China and common worldwide in seasons	Inhibition of intestinal glucose absorption (Ashraf R *et al.,* 2011)
13.	*Symplocos coccinea*	Symplocaceae	Seeds and Leaves		Mexico	Restores glycogen and protein in muscle (Moradi B *et al.,* 2018)
14.	*Opuntia megacantha*	Cactaceae	Leaves	Culinary	South Africa and south America	Increases plasma urea concentration and reduces plasma ions concentration (Buititi P *et al.,* 2000)
15.	*Perilla*	Lamiaceae	Leaves	Perilla	America, Asia and Japan	Improves glucose tolerance (Ha TJ *et al.,* 2012)
16.	*Cinnamomum verum*	Lauraceae	Whole plant	Cinnamon	Asia and Africa	Promotes insulin secretion(Qin B *et al.,* 2010)
17.	*Gymnema sylvestre*	Asclepiadaceae	Leaves	Cowplant	Central India and Srilanka	Prevents absorption of glucose by intestine leading to reduction in glucose level (Thakur GS *et al.,* 2019)

220 million in 2004 (Susan Van D *et al.,* 2010); in 2009, an estimation of 285 million people having diabetes was expected, increasing to 366 million by 2011 (Whiting DR *et al.,* 2011). The number of people suffering from diabetes increased in such a way till 2013; it reached 382 million (Ogurtsova K *et al.,* 2017). The process of increase in people having diabetes increased simultaneously to 415 million in 2015, and death by diabetes in 2015 was calculated as

an increase of up to 5 million and other 425 million people suffering from diabetes till 2017 (Saeedi P *et al.,* 2019). The projected estimation for the new and previous patients may lead to 642 million by 2040, according to the surveys performed to date. The major problem, along with the increase in the number of patients, is the economic burden. The global financial pressure and responsibility is estimated to grow from the U.S. $1.3 trillion by 2015 and to $2.2 trillion in 2030 throughout the world (Bommer C *et al.,* 2018). The number of diabetes people was found 31.1 million in 2000, and it is estimated to increase up to 79.4 million by 2030 in India, which is the highest throughout the world. Similarly, people having diabetes was 20.8 million in China and 17.7 million in the USA in 2000, and this is considered an increase of 42.3 million by 2025 and 30.3 by 2030, respectively (Baynes HW *et al.,* 2015). The increase in the number of diabetic people and the economic burden might be due to its unstoppable nature as the number increases geometrically after each decade. This number can only be controlled by the proper management of diabetes and provide available knowledge as well as awareness (Animaw W *et al.,* 2017).

1.c. Pathogenesis

The process of diabetes begins after the lack of proper uptake of glucose in the cells, which can be stated as hyperglycaemia. The occurrence of hyperglycaemia causes damage to various organs and tissues. Especially in the pancreatic islets, improper insulin secretion results from damage in cells. In the liver, glucose production increases as a result of increased hepatic gluconeogenesis (Petersen KF *et al.,* 2006).

a. Normal Glucose Homeostasis

Glucose is one of the significant sources of energy in our bodies. An increase in the concentration of glucose levels in adipose tissue and hepatic cells causes damage to the islet cells of the pancreas. Pancreatic β-cells are very susceptible to the attention of glucose levels in the blood and lead to differences in its homeostasis by slight changes in its function and population dynamics. Prolonged exposure to abnormally high blood glucose has various effects on insulin secretion and the survival of cells (Khodabandehloo H *et al.,* 2016). Glucagon is a hormone responsible for the regulation of glucose homeostasis in the body. Improper insulin secretion is found in people with Type II diabetes. The process of insulin resistance and glucose tolerance remains the same due to the compensatory insulin secreted in the body (Defronzo RA *et al.,* 2004). A point of view came forward a few years ago that insulin resistance causes the β-cell failure through exhaustion, which means continued stimulation of a normal beta-cell eventually causes it to become permanently dysfunctional, which is not validated (Leahy JL *et al.,* 2005). Insulin secretion is a very complex mechanism and a multiple point regulation processes. β-cells of the pancreas are primarily responsible for transcription of the gene encoding insulin and the processing and synthesis of insulin in response to an increase in extracellular glucose concentrations in the blood, which leads to hyperglycemia (Puddu A *et al.,* 2013). In people having type II diabetes, the decrease in β-cell function is related to the loss of glucose-stimulated insulin secretion as well as the reduction of β-cells number (Shulman G *et al.,* 2000).

b. Peripheral Insulin Resistance

It is one of the characterizing mechanisms for the state of Type-II Diabetes Mellitus. When the sensitive potassium (K^+) channel gets closed, and the activation of Protein Kinase-C signaling pathway, the glucose-stimulated insulin secretion from β-cells occurs due to an increase in calcium (Ca^{2+}) influx into the cells (Cooper ME *et al.,* 2012). The reduction in the usage and transportation to the insulin-sensitive parts and tissues in the body, such as adipose tissue, skeletal muscle, leads to the state of insulin resistance and then hyperglycaemia in the body (Olefsky JM *et al.,* 2010). The process of insulin resistance begins when translocation of the enzyme protein kinase C- takes place due to activation of serine and threonine kinase pathways causing phosphorylation of insulin receptor substrate-1 (Morino K *et al.,* 2013). The impairing of IRS-1 may also be due to irregular levels of triacylglycerols, diacylglycerol due to increased diet containing fat, carbohydrates which cause downstream of insulin cascade signalling (Galbo T *et al.,* 2013, Camell CD *et al.,* 2014, Iqbal J *et al.,* 2018). The negative feedback in the tissues begins, which takes part in normal insulin signaling. The insulin-sensitive tissues fail to function correctly, leading to the pancreatic β-cells increasing insulin secretion (Donath MY *et al.,* 2011). This increase in insulin secretion through activation of the PKC pathway and an increase in the cAMP pathway activates protein kinase A, influencing Ca^{2+} influx (Heit JJ *et al.,* 2006). The increased secretion of insulin is continued to fulfill the higher demand. Still, this process cannot be continued by cells for a longer duration as the cells are exhausted, leading to the condition of insulin resistance in the body (Chawla A *et al.,* 2011, Kalupahana NS *et al.,* 2021). This phenomenon of insulin resistance and impaired secretion of insulin leads to a state of improper glucose metabolism, and the free availability of glucose in the body causes hyperglycaemia and ultimately to a form of diabetes Mellitus, principally Type-II Diabetes Mellitus (Alam U *et al.,* 2014).

c. β-Cells Dysfunction

β-cells of the pancreas are responsible for the secretion of insulin in the body for the proper metabolism of glucose. These generally synthesize insulin according to a specific limit. Stress on the β-cells due to over insulin secretion for long-duration leads to dysfunction of cells (Ighodaro OM *et al.,* 2018). The dysfunction of cells can be known by a decrease in glucose-induced insulin secretion (Porte D *et al.,* 2001). One of the significant reasons of - cells dysfunction is the generation of Reactive Oxygen Species in Mitochondria of β- cells. The age of ROS occurs due to the presence of complexes I and III in the mitochondrial membrane leading to the generation of highly reactive species superoxide (O_2-) ions (Pacher D *et al.,* 2007). This superoxide is generally converted into less reactive H_2O_2 by the presence of isoenzymes such as superoxide dismutase. Once those molecules of H_2O_2 cross the membrane, these become highly reactive (OH^-) hydroxyl ions. The other main path for ROS formation is via the glucose transporter pathway (McCulloch LJ *et al.,* 2011). In the following pathway, the phosphorylation of glucose occurs in the presence of hexokinase and glucokinase, which causes activation of glycolytic efflux. The increase in glycolytic flux leads to the increase in the Tricarboxylic Acid (TCA) cycle leading to the rise in the production of ATP in mitochondria (Thorens B *et*

al., 2015). This process further supports ATP- sensitive K^+ channels, leading to a decrease in hyperpolarizing outward K^+ flux. The following processing finally causes an increase in intracellular Ca^{2+} leading to an adequate amount of insulin secretion (Rutler GA *et al.,* 1992). These increased amounts of glycolytic efflux and TCA cycle flux are required for the increased secretion of insulin to respond to the high glucose level in the body (Rharass T *et al.,* 2014, Starkov AA *et al.,* 2002). However, as soon as glucose clearance becomes insufficient due to peripheral insulin resistance and the simultaneous increase in both the TCA cycle and glycolytic flux, the generation of ROS production continues leading to damage of the –cells (Sarre A *et al.,* 2012, Hou N *et al.,* 2008).

Other factors which contributes to type 2 Diabetes Mellitus include improper food, people taking unhealthy food regularly increases the chances of growth of diabetes (Haak T *et al.,* 2017). Lack of daily exercise and physical activity causes deposition of fat and fatty acids in adipose tissue leading to insulin resistance and simultaneously diabetes (Grant AK *et al.,* 2019). Smoking and stress are some others points that are previously established (Aronson R *et al.,* 2016). The transfer of disease from parents to children is also one of the other reasons for the cause of the disease (Wang Y *et al.,* 2017). There are various others factors, including those for the cause of diabetes in many people, out of which dietary and lack of exercise are the major factors (Haak T *et al.,* 2018).

2. Recent Technological Advancement In The Treatment And Management Of Type-2 Diabetes Mellitus

There are many conventional methods for the management and treatment of Diabetes Mellitus. Some of the few ways available for the direction of the disease are using oral hypoglycaemic medications such as metformin, glipizide, pioglitazone, and many others (Beck RW *et al.,* 2018). Along with those available agents, insulin therapy is also available, which is either intravenous or intramuscular, as insulin is metabolized in the first-pass metabolism. However, those available drugs are not found to be effective, so newer technologies and modifications are proposed (Kooiman TJ *et al.,* 2018).

A. Glucose Meters

These are the diagnosing instruments that help to monitor glucose level as well as the rate of physical and other activities, daily food intake, and time and duration of medication administration. These modern developments help to monitor patients' data from remote areas and at the proper time from certified diabetes personal (Nauck MA *et al.,* 2016). Several primary advantages such as maintaining body weight, weight loss, and reduction in glucose level in our body and blood were seen from the observation for two weeks to 2 years. Similarly, secondary advantages are the self-efficacy of patients, changes in behavior, and acceptance of interventions that are provided by those programs (WHO 2016).

B. Insulin Pump Therapy

During the management of diabetes, oral hypoglycaemic agents are used, and sometimes, even insulin therapies are prescribed. However, these therapies may not be sufficient, and sometimes insulin pump therapy is needed, which can be either single-dose therapy as well as multiple or several dose injections (MDI) are prescribed, or these help in the monitoring of the glucose level. These methods help in the tracking of carbohydrate levels and insulin sensitivity factors and gradually help in the reduction of that levels (Taylor R *et al.,* 2008). This method also shows a reduction in HbA1c levels as these has the ability for the reduction of HbA1c for the minimum duration of 6 months. Those insulin pump therapies provide doses in a more precise form and show various glucose level reductions. This shows the new targeting for diabetes management as HbA1c (Rubino F *et al.,* 2016).

C. Continuous Glucose Monitoring System

These are one of a kind of devices that are used for the measurement of both the glucose level of blood capillaries and glucose level of intestines as well, which is done throughout the full day automatically. Those devices helped in capturing the data and displaying those for both instant and long-term analysis (Rubino F *et al.,* 2002). Patients keep their device for seven days to 10 days according to their feasibility which is seen to have shown improvement and control in normal blood glucose levels. Devices are long to patients during their time of food intake, dosing of their medications, as well as when they perform physical activity (Cohen R *et al.,* 2012).

D. Flash Glucose Monitoring system

These are similar to continuous glucose monitoring system devices. Still, they differ as these devices help to monitor blood glucose levels during fasting, after the meal, and overnight blood glucose levels. This is one of the methods which helps in the identification of unknown patterns for the title of the hyperglycaemic or hypoglycaemic level in the body. These are useful for daily basis monitoring of glucose levels throughout the body (Federico A *et al.,* 2016).

Conclusion

Diabetes Mellitus is a global problem that does not have any available treatment to date. As once a person suffers from the disorder, it is difficult to find a proper cure. The disorder can only be managed by appropriate diet intake and proper physical activity. Economic and health problems throughout the globe are developing daily due to the lack of treatment available. So, it is indispensable to find treatment for the disorder as early as possible.

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