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Evolving Trends in Type 2 Diabetes Management: Therapeutic Approaches for the Patients

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ABSTRACT

Diabetes is increasing all around the world like an epidemic. It is creating an alarming situation and dragging countries into a threatening economic crisis in the world. The treatment and management of Diabetes Type 2 have remained challenging, even in this scientifically developed era, despite being known for a long period. At the current time, only half the patients can achieve recommended A1c hemoglobin target level. Variable therapeutic maneuvers have been discussed in this review paper that is under examination process in the management of diabetes. The production of new drugs like biguanides, thiazolidinediones, sulphonylureas, and alpha-glucosidase inhibitors has shown significant positive results in the control of hyperglycemia. A new category of therapeutics has been found with the latest approaches in drug discovery like Amylin analogs, Incretin mimetics, activated receptors of Peroxisome proliferator, GIP analogs, and dipeptidyl peptidase-4 inhibitors are used as recent progressive drugs for the management and treatment of diabetes. Similarly, recent advancements in the investigation, identification, and extraction of substances from plant sources have positively revolutionized the trends in diabetes management. This review paper emphasizes the statistical prevalence, positive and negative impacts of commercial drugs, and multiple prospects of stem cell technology, nanotechnology, and statins for diabetes therapeutic management.

Key words: Diabetes, Therapeutics, Drugs, Approach, Strategy, Insulin, Treatment

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INTRODUCTION

Diabetes is often cited as a silent killer. It poses an alarming threat to humankind. As per a survey, 462 million people are currently affected by Type 2 Diabetes with a 9% prevalence ratio and 47% of them remain undiagnosed. Furthermore, the greater ratio of Type 2 Diabetes affected people is from underdeveloped and developing countries that have a maximum 35 to 50 age group population. An estimated survey has revealed that Asian people are more susceptible to coronary artery diseases and diabetes including increasing abdominal adiposity and insulin resistance. The following Figure 1 represents the approaches for management and general trends of occurrence of diabetes.

Several factors are considered before selecting the type of therapy for lowering the blood glucose level in diabetic patients. For instance, the severity of hyperglycemia, risks of hypoglycemia, functional health of the renal and hepatic system, body mass index, cost of medicines, and the ability of the patients to self-monitoring [1]. Multiple treatment approaches are available for

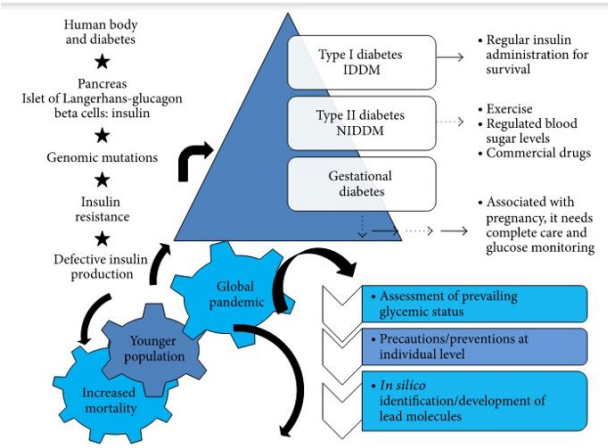

Figure 1: Schematic representation of general diabetes occurrence and approaches for its management.

Type 2 Diabetes. Many conventional therapeutics like troglitazone that rises insulin action in muscle and fat, sulfonylureas and repaglinide that increases the insulin production, metformin which enhances insulin mode of action in liver tissues, and miglitol along with acarbose that triggers a process of delayed carbohydrate absorption from the ingested food [2,3].

However, the medicines used for the treatment of Type 2 Diabetes come with certain limitations as they have multiple side effects. Another approach for treatment is the use of a combination of different drugs, like insulin combination with sulfonylureas that significantly lowers the per day insulin need [4] and FDA approved combination of insulin and metformin. Such combinations are found helpful in maintaining glucose levels and decreasing insulin requirements.

Multiple reasons lead to the development of Diabetes. Secondary forms of this disease may occur owing to genomic changes. Gene mutation in the sequence MODY1-hepatocyte nuclear factor 4 alpha (HNFα); MODY2- glucokinase; MODY3 hepatocyte nuclear factor-1-alpha (HNF1A); MODY4 insulin promoting factor (IPF1); MODY5 hepatic transcription factor-2; Neurogenic differentiation 1 (NEUROD1) -MODY6; MODY7-Krupple like factor 11 (KLF11); MODY8 and MODY9, carboxyl ester lipase (CEL) and paired box gene (PAX4) respectively.

However, Type 2 Diabetes with its severity and rapidly increasing ratio has demanded immediate actions to be taken by devising a well-planned strategy. The primary focus of the medical scientific field is upon achieving complete glycemic regulation at a normal level by appropriate evaluation of present glycemic status, and assessment of linked disorders with this disease to minimize its long-term negative impacts [5]. New generation drugs like metformin and sulphonylureas are found to be involved in issues like weight gain and hypoglycemia, gastrointestinal effects like diarrhea, nausea, and lactic acidosis. These drugs are of special concern as maximum type 2 diabetic patients are already obese [6,7]. Despite using new generation drugs in combination form with oral agents and insulin, the attainment of full glycemic control has remained a challenging task.

To talk about this epidemic issue, this review paper has encompassed evolving trends in the field of medicine for the management of diabetes and its statistical prevalence. Furthermore, the advantages of these emerging trends as well as their limitations are also being discussed here. The present era has foreseen the increased investigation and development of statins, stem cells, and nanotechnology, and next-generation drugs, all these prospects also throw light upon the use of natural products and defines a positive role in the management of this disease.

The unfocused side: Understanding the diabetic mechanism

Amylin proteins and pancreatic β-cell function

Amylin is a β-cell peptide hormone that is secreted by the pancreas along with insulin and is extremely important in glucose regulation. It acts as a satiety agent by slowing down gastric emptying and inhibits glucagon secretion. The postrema is the amylin's production site and it focuses on declining the total demand for insulin. Amylin is a destructive agent for β-cell, important in T2Dm glucose homeostasis, where it forms fibers and amyloid aggregates. Histopathology studies have revealed that the accumulation of certain amyloid proteins and their association with the endocrine system has a significant role in the progression, pathology, and physiology of Type 2 Diabetes [7-9].

α-Cells

In type 2 diabetes, alpha cells play a crucial role. Glucagon is secreted from α-cells which in turn is controlled by glucose hormones. An anomaly in its secretion reveals the disturbance in glucose homeostasis. Similarly, in type 2 diabetes the abnormality in α-cells exists, and according to a bi-hormonal hypothesis, this is owing to excess glucagon production and insulin deficiency. This leads to hyperglycemia. On the other hand, when insulin level is normal, α-cells do not show such behavior. Hypoglycemia is another condition, which reflects the deficiency of glucagon secretion also linked with declined functioning of α-cells [10,11].

Moreover, in islet allotransplantation the retard functioning of α-cells remains the same, no improvement has been observed in them which depicts that even this procedure is not 100% effective in curing type 2 diabetes [12-14].

δ-Cells, SsT, and pancreatic PP cells (F-Cells)

δ-Cells, SsT, and Pancreatic PP Cells (F-Cells)

are present in the stomach, intestine, and neuroendocrine and pancreatic region. SsT is secreted when the body encounters fluctuations in glucose levels. α-cells and β-cells act as receptors for SsT which inhibits the secretion of glucagon and insulin in the blood. Moreover, it is also involved in making islets responsive to cholinergic activation, nutrient-induced glucagon secretion inhibition and changing the normal feedback loops and glucose homeostasis.

When it comes to F cells, it has been found that after food intake these are released which imparts delaying effects on gastric emptying, peristalsis, hepatic glucose secretion, pancreatic secretion, and gallbladder squeezing. These functions collectively affect energy metabolism. The route of PP cell administration leaves different effects, for instance, its intraperitoneal route reduces body weight and lowers food intake and rises energy utilization. So, high PP levels are incriminated in treating obesity and diabetes [15,16].

Adipose tissue and resistin

Adipose tissue plays a significant role in the release of certain hormones like resistin, plasminogen activator inhibitor-1, rennin-angiotensin, and many more, and it also works in collaboration with certain other hormones and CNS- Central Nervous System. Normally, these adipose tissues are storage houses for fats from where free fatty acids are released when the body went through abnormal conditions. These adipose tissues show less response towards insulin and excessive release of free fatty acids when the body is consistently subjected to abnormal β-cell functioning. These lead to obesity in type 2 diabetes. Resistin released by these adipose tissues is the inhibitory hormone that develops resistance against insulin. Its expression has also been observed in the hypothalamus, pancreatic islets, and pituitary glands. Moreover, it is also a product of macrophages where the recruitment of pro-inflammatory factors and immune cells are favored by resistin. This hormone is found largely associated with hyperglycemia, obesity, and reversal of immunity neutralization [17,18].

Genetics

'The genetic's nightmare', is what type 2 diabetes is often cited as in the medical field. Multiple gene alterations have been observed owing to the contribution of both genetic and various environmental parameters. These factors either directly or indirectly contribute and leave an influence upon the genetic makeup that leads to the development of type 2 diabetes. Innervations, alteration in parental imprinting, and pancreatic angiogenesis are some common defects. Both paternal and maternal sensitivity and resistance towards insulin define the makeup in the offspring. β-cell dysfunctioning, genetic failure of its predisposition, heterozygous mutations, and autosomal dominancy in its transcription are the most prominent reasons that lead to the early stage of type 2 diabetes. HNF-4α HNF-1α and HNF-1β are the well-known genes responsible for the early development of type 2 diabetes. Moreover, during pregnancy diabetes is developed in some females which is due to gene expression like PI3K as p85a its subunit and GLUT-4 which became the reason behind the rise in placental GLUT-1 mRNA insulin resistance expression. On the other hand, offsprings carrying genotypes in a combination of AA and GA+ AA are more prone to the development of type 2 diabetes. Importantly, some genetic alterations lead to changes in the multiple synthesis process that can cause the decline in levels of glycemia, microalbuminuria, riboflavin, variation in uric acid levels, and poor vitamin D synthesis that enhances insulin resistance [19].

Gut microflora

The gastrointestinal tract has different types of microflora whose population increases down the track. The concentration of this microflora in the upper intestine is less than 10 cfu/mL while in the mid ileum it becomes 10 cfu/ mL and is highly concentrated in the colon. The most common microflora in the human body is Acinetobacter, Bacteroidetes, Firmicutes, Proteobacteria, and Yeast. No doubt that obesity is a prominent factor leading to type 2 diabetes, interestingly, the population of good bacteria (Bifidobacteria: Bacteroides) decreases in this disease, and harmful bacteria like *E. coli, Enterobacteriaceae,* and *Faecalibacterium* increases. Changes in the population of these bacteria lead to metabolic syndrome and insulin resistance. Inflammation of the intestine is common in diabetic patients, which reveals that microbiota from the gut can easily leak into the body's circulation system and activates inflammasome production. Moreover, chronic hyperglycemia, injury to interstitial cells of gastroparesis and Cajal are common

in diabetic patients along with vagal control. Peristalsis movement is disturbed with the increase in intestinal weight, mucosal surface area, and per villus more goblet cell production. These changes altogether contribute to excessive bacterial growth and compromise the intestinal barrier and giving microbial access to the other parts of the body. Gut microbiota is involved in influencing the immune system, metabolic activities, nutrient absorption, obesity, cellular uptake, altered bile acid, de novo lipogenesis, FFa oxidation decline, delayed digestion, changes in tissue composition, chronic inflammation by endotoxin, and varied intestinal functional barriers [20,21].

Evolving trends in type 2 diabetes management

Nanotechnology

For insulin administration and glucose measurement, nanotechnology has provided novel strategies. In this category, glucose sensors and closed-loop insulin provision are used for the treatment of both type 1 and type 2 diabetes. For drug administration, microcapsules have been designed with numerous micro pores that allow the passage of tiny molecules like insulin, oxygen, and glucose. Moreover, the pores on microcapsules are small enough to permit the movement of bigger molecules like virus graft-borne particles and immunoglobulins around them. These capsules can be placed under the epidermis layer in patients which can temporarily maintain the normal body's glucose feedback control loop without making the patient prone to serious risk infections, as these do not require strong immunosuppressants for their activities.

The nano target approach is very precise, effective, and beneficial with extremely limited side effects. The drug administered through this technology is target-specific, i.e., it hits the required organ, tissue, and tumors. The biggest challenge doctors are facing is nanoparticles' scalability. Potential negative impacts like the appearance of carbon buckyballs and nanotubes have been observed which appear through absorption, ingestion, or inhalation of the drugs [22].

A new perspective: Statin therapy

Statins (HMG-CoA reductase inhibitor) are well known for inhibiting low-density lipoprotein processing in the liver and declining their level in the blood along with improvement in the blood vessels' health. CVD- cardiovascular disease is a high-profile concern linked with type 2 diabetes, statins are considered extremely important here in preventing this disease. Statins are also known as lipid-lowering agents as they limit the step in the formation of cholesterol by converting HMG-CoA into mevalonic acid.

Statins help lower the risk of CVD in people who have a moderate intake of fats. But the other side of the coin does show some disadvantages. Muscle disorders due to myositis, renal dysfunction, and hepatic disorders are well-known side effects of statin therapy, but these are rare. The trial carried out on 6000 plus patients has revealed that many young individuals and those with the absence of disease showed bad concurrence with this therapy. Despite various hurdles, this therapy is under trial and is found quite effective in preventing CVD in diabetic patients [23].

A novel approach: Gene therapy

Cloning and expression of insulin production have been in process since the 1970s which has revolutionized the medical field. The main purpose is the normal regulation of blood sugar level which in turn also reduces the risks of occurrence of other linked diseases. Somatic gene therapy, the first known ex vivo gene therapy, in which therapeutic genes are inserted in tissues that are removed from the body and are then reimplanted. On the other hand, in vivo gene therapy is also utilized where genes are directly placed in the body either by local injections or in intravenous, subcutaneous, or through other intrabronchial routes.

In vivo therapy is more in use because of its effective and easy administration process. Currently, genes which carry the expression of glucose-lowering properties that are insulin independent in nature and administration of blood sugar lowering genes are common. For instance, in the liver glucokinase has been found which has glucose-lowering impacts. This discovery has made possible the genetic transfer of glucokinase for the management of type 2 diabetes. In another therapeutic strategy, the "protein targeting to glycogen" PTG gene was utilized for the conversion of glucose to glycogen for normal regulation of glucose in the liver.

Other areas include the therapy of provoking β cells production in the liver, introduction of

new proteolytic cleavage sites into proinsulin molecules which can, later on, be converted into insulin by a hormone. This introduction of the insulin gene is recognizable by furin and protease found in many tissue systems like of liver. Insulin gene insertion which can encode insulin is also becoming a part of therapy. It has a single chain strand that codifies almost 40% normal activity of mature insulin.

Natural products for diabetes therapy

Medicines from plant sources are gaining immense importance as they are cost-effective with minimum to no side effects. Many bioactive drugs extracted from plant sources are in use. These have anti-diabetic properties due to hypoglycemic effects and these are often more effective than other common oral diabetes drugs like daonil, chlorpropamide and tolbutamide. Anti-diabetic components obtained from plants are usually used directly as drugs. Phytomolecule's chemical structure plays important role in the fight against diabetes. Many plants have been found as an important source of flavonoids, terpenoids, coumarins, phenolics, and other blood sugar level lowering bioactive components. Many plants like *Alliumsativum, Allium cepa, Gymnema sylbestre, Withania somnifera, Murraya koenigii*, and *Spreng* are commonly known for their great anti-diabetic properties [24,25].

CONCLUSION

Fight against diabetes is becoming the major concern of health professionals in the 21st century. Glycemic controlling approaches are required for the management of type 2 diabetes. It is imperative to control the dysfunctioning of β cells which causes the loss of glycemic control. Insulin and conventional drug have been in use for a long time and these are effective, but better and promising strategies are required to get optimum results in the long run with little to no side effects at all. The menace of diabetes also produces many other dangerous diseases. In the present era, new generation therapeutics including gene therapy, plant-based drugs, the combination of conventional drugs, nanotechnology, and statin therapy is gaining immense importance due to their promising results.

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