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Diabetes Mellitus: Pathophysiology, Classification, Complications, and Therapeutic Approaches

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ABSTRACT

Diabetes mellitus is a metabolic disorder with abnormally high blood glucose levels that are mainly classified into type 1, type 2 and gestational diabetes. The present study aimed to evaluate the type 1 and type 2 diabetes and special focus on the disease Pathophysiology, Classification, Complications, and Therapeutic Approaches. This review helps to understand the importance of different types of herbal medications, oral hypoglycemic agents, and low dose radiations that are used for the treatment of diabetes mellitus. Traditionally, a variety of medical plants have been used to treat diabetes mellitus, among the most commonly used plants are *Momordica charantia*, and *Carica papaya*. These plants have anti diabetic qualities i.e., to increase insulin secretion, improve glucose uptake, and inhibit glucose absorption. In the recent years, many new classes of oral hypoglycemic agents are used the treatment for both type1 and type2 diabetes, such as (DPP-4) inhibitors, (SGLT2) inhibitors and GLP-1

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receptors. These agents works through various mechanisms that improve glycemic control, which includes insulin secretion, improving insulin sensitivity, reducing hepatic glucose production, and increases glucose uptake in peripheral tissues. Various low dose radiations are also used for the treatment of diabetes mellitus that includes LIL or LLP), which have therapeutic effect on skin wound healing in diabetic patients. Certain other therapies like newer insulin, insulin delivery devices, islet cell transplantation, stem cell technology, artificial pancreas systems were made for glucose management. Some conventional therapeutic approaches like exercise and weight control, medical nutrient therapy, oral glucose drugs, insulin injections are made for the control of diabetes.

Keywords: Diabetes Mellitus, Gestational Diabetes, *Momordica Charantia*, DPP-4 Inhibitors, Hypoglycemic Agents.

Introduction

Diabetes mellitus (DM) is a complex and non-transmissible endocrine disease that has become a global clinical problem. Insulin is released from beta cells in the pancreas to remove glucose from the blood, allowing it to be absorbed and metabolized by muscle and liver [1]. But when there is disturbance or resistance in the secretion of insulin from the beta cells then it gives rise to a metabolic disorder which is commonly known as diabetes mellitus.

Increase the glucose and cholesterol levels in the blood, combined with oxidative stress, can lead to chronic issues affecting various organs such as the kidneys, eyes, nerves, and blood vessels. According to the World Health Organization (WHO), diabetes is a deadly outbreak that causes widespread illness. This condition affects around 387 million people worldwide and is expected to reach over 640 million by 2040 [2]. Diabetes is a leading cause of death worldwide, posing a significant risk to humanity. Approximately 387 million individuals worldwide are affected by the condition, with an 8.3% prevalence rate and 46.3% remaining undiagnosed [3]. China has the highest number of diabetes cases (98.4 million), followed by India with 65.1 million [4]. Asian Indians have a higher risk of diabetes and coronary artery disease due to factors such as insulin resistance [5-7]. Choosing and implementing a glucose-lowering therapy depends on factors such as hyperglycemia severity, hepatic and renal function, hypoglycemia risks, body mass index, self-monitoring ability, and medication cost [8]. In 2017, the International Diabetes Federation (IDF) reported that 425 million people have diabetes mellitus, with over 90% being adults. Additionally, 352 million have impaired glucose tolerance (IGT) [9]. According to the International Diabetes Federation, in 2021, the global prevalence of DM in the adult population was approximately 10.5% (537 million), and this number is expected to increase to 643 million by 2030 [10].

Diabetes prevalence has continuing to rise sharply on a global scale. As of 2011, 366 million individuals worldwide were estimated to have DM, with type 2 accounting for almost 90% of cases [11-12]. Type 2 diabetes is becoming more prevalent worldwide, with 80% of those who have the disease residing in low- and middle-income nations. Research on the prevalence of type 2 diabetes in Africa as a whole has revealed a dearth of information. Research looking at data patterns in Africa shows that

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prevalence has dramatically increased in both rural and urban areas, affecting both genders proportionately [13]. The 2008 World Fact Book report states that the prevalence of diabetes mellitus in Africa was 3.2%, with 40,895 persons (2.0) was in Ethopia [14].The World Health Organization (WHO) states that the number of people with diabetes has increased from 108 million in 1980 to 422 million in 2014.The prevalence of this disease continues to increase rapidly in low and less income countries, are not behaving in the same way in the high income countries [15-16]. It was estimated that in 2019 the disease was the main cause of 1.5 million deaths and in 2012, 2.2 million people died because of diabetes. This study will cover the various types of diabetes, their classification, complications, and current treatments to alleviate symptoms and cure diabetes.

Types of Diabetes

Type 1 diabetes

In type 1 diabetes, the autoimmune destruction of beta cells results in a nearly complete lack of insulin production. As a result, glucose accumulates in the bloodstream, leading to hyperglycemia [17]. In contrast, type 2 diabetes is marked by insulin resistance, which arises when body cells become less responsive to insulin's glucose-lowering effects [18]. This causes a compensatory increase in insulin production, but eventually the pancreas is unable to keep up with the demand, leading in hyperglycemia. Insulin resistance is frequently accompanied by poor insulin secretion, worsening the metabolic abnormalities. The pathophysiology of diabetes includes the action of glucagon, a pancreatic hormone that elevates blood glucose levels. Diabetes frequently results in high glucagon levels, which contribute to hyperglycemia [19].

Type I diabetes causes decreased insulin secretion due to autoantibodies destroying pancreatic β-cells. This leads to hyperglycemia and acidosis from low blood insulin levels. Pancreatic β-cells are destroyed when the immune system loses tolerance and attacks them as alien. T cells govern this process. Identifying and modifying the pathways that lead to β-cell assault by specific antibodies and immune cells can prevent the establishment of diabetes [20]. Immune cells have been linked to type I diabetes in patients with particular HLA system antigens and high blood sugar levels. Research on the human genome found HLA class II as a hereditary risk factor for type I diabetes, accounting for 50% of cases. This shows that the immune system's presentation of a specific peptide plays a role in the disease's development [21]. Type I diabetes is typically associated with a polygenic syndrome, however it can also occur in isolated cases. For example, the Autoimmune Regulator gene is linked to autoimmune poly glandular syndrome type 1 [22]. Autoimmunity can be indicated by the presence of antibodies against insulin, glutamate decarboxylase, insulinoma antigen 2, or zinc transporter 8 in the patient's plasma, which can be measured and correlated with disease severity. CD4+ and CD8+ T cells, found in peripheral blood, pancreatic tissue, and per pancreatic lymph nodes, may influence the synthesis of autoantibodies. However, in patients with type I diabetes, these cells have activity against β cells [23-24]. The presence of auto reactive species in peripheral blood is low, comparable to healthy individuals, the only CD 8+ cells exhibit abnormal activity in the periphery due to activation-related changes (25). These CD8+ cells

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exhibit unique functional characteristics, including low epitope affinity for HLA complexes and minimal interaction with antigen-presenting cells. T receptor alterations that interact with the HLA-epitope complex may not trigger a widespread immune response. These issues stem from inadequate thymic maturation during development [26-28].

Type 2 diabetes

The pathophysiology of type 2 diabetes mellitus is distinguished by insulin deficiency and insulin resistance, which have been linked to inflammatory cytokines in the plasma and high fatty acid levels, resulting in insufficient glucose transport into target cells, increased fat breakdown, and increased hepatic glucose production [29].Hyperglycemia results from excessive glucagon secretion and insulin insufficiency by the glucagon-secreting alpha cell and the insulin-secreting beta cell, respectively. Type 2 diabetes mellitus is diagnosed when patients are unable to increase insulin secretion to compensate for insulin resistance, resulting in an elevated glycemic value [30]. One of the main reasons of this occurrence is β-cell malfunction, which results in insufficient secretion compared to the necessity to maintain a stable glucose level. Insulin resistance occurs when certain receptors are unable to respond to stimuli, resulting in increased glucose production in the liver but decreased utilization in muscle and adipose tissue [31].Insulin is synthesized in pancreatic β cells by structural modifications of pro-insulin and stored in vesicles for secretion when needed. Glucose stimulates its release from blood cells through the glucose transporter, a cation transport protein that alters the ATP/ADP ratio and closes potassium channels. This causes an increase in ATP concentration and intracellular calcium buildup, causing insulin granules to migrate to the cell membrane and be removed through exocytosis [32]

If Excessive food consumption can cause chronic inflammation and damage to pancreatic islet tissue, including oxidative, amyloid, and metabolic stress [33]. Obesity and metabolic stress can trigger lipotoxicity, glucotoxicity, and glycoprotein toxicity by activating the cellular apoptotic unfolded protein response (UPR) at the β-cell level [34]. Increased fatty acid levels can block the sarcoplasmic reticulum, leading to decreased intracellular calcium mobilization. Persistent diabetes can cause β-cells to produce more proinsulin and islet amyloid polypeptides (IAAPs), resulting in proinsulin misfolding in three dimensions. As it accumulates in the cytoplasm, it causes oxidative stress, resulting in tissue damage and persistent inflammation [35].

Another con Hyperglycemia and glucotoxicity can cause an increase in reactive oxygen species (ROS), leading to inflammation and oxidative stress. Excess ROS inactivated mitochondria, rendering them incapable of metabolizing superoxide ions. They play a direct role in diabetes pathogenesis, leading to the formation of advanced glycation end products (AGEs) through the polyol pathway. Thus, a series of changes occur and Normal cell physiology changes, such as increased expression of AGE receptors and activation of protein kinase C isoforms [36-37].

Reduced Physical activity increases the risk of obesity and type II diabetes. Metabolic inflammation, characterized by the production of cytokines such IL-6, TNFα, and IL-1 into the bloodstream, can occur to varying degrees [38].

Elevated IL-1 levels cause pancreatic β-cells to produce NF-KB, leading to decreased

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insulin release and death. Losing weight can increase insulin sensitivity, improve glycemic control, and lower cardiovascular risk. The mechanism for this is the release of anti-inflammatory cytokines like IL-1 and TNF-α Antioxidants, including glutathione, can neutralize free radicals caused by abnormal metabolic pathways [39-41].

Gestational diabetes

Gestational diabetes mellitus is the type of diabetes that occurs during pregnancy. The changes in hormones level can lead to insulin resistance, reducing the body's ability to respond to insulin [42]. Those women who have developed diabetes during pregnancy and those women who are diagnosed with unrecognized, asymptomatic type 2 diabetes during pregnancy are both classified as having gestational diabetes [43]. Gestational diabetes is associated with significant maternal and intrauterine fetal death or stillbirth, including fetal neonatal hypoglycemia, fetal macrosomia and it increases the risk of delivery complications such as birth trauma, shoulder dystocia and C-section delivery [44-45]. Women with gestational diabetes have a high rate of chance to develop diabetes type 2 later in life, with 30-60% of women diagnosed with type 2 diabetes within 20 years after the delivery [46-47]. Pregnancy-related glucose intolerance can cause hyperglycemia of varying severity [48]. GDM, or impaired glucose intolerance, affects 14% of pregnant women or 135,000 women annually in the United States. It is a risk factor for type 2 diabetes in mothers [49-50]. The reported risk of GDM and type 2 diabetes varies by ethnicity, selection criteria, and testing [51]. To reduce maternal and fetal problems, recent guidelines suggest maintaining sufficient glycemic management. Most women with gestational diabetes can manage their blood sugar via diet and exercise, but some may require oral diabetes medication or insulin.

Classification of diabetes

Insulin dependent diabetes (IDDM)

Diabetes or juvenile onset or type 1, affects 5-10% of patients and is caused by autoimmune destruction of pancreatic cells. The condition can affect individuals of various ages, but typically affects children and young adults. Regular insulin injections are necessary to maintain blood glucose levels under control. The rate of β cell breakdown varies, with newborns and children experiencing faster deterioration than adults. Ketoacidosis symptoms are common in children and young adults, although mild fasting hyperglycemia can progress to severe hyperglycemia or ketoacidosis in response to stress or infection [52]. These patients are more likely to develop other autoimmune disorders, such as Graves' disease, vitiligo, coeliac spur, autoimmune hepatitis, myasthenia gravis, Hashimoto's thyroiditis, Addison's disease, and pernicious anemia [52].

Idiopathic Diabetes

A small percentage of patients with type 1 diabetes, primarily of Asian and African descent, have no known cause. These are susceptible to ketoacidosis and have persistent insulin deficiency. Ketoacidosis occurs in episodes, with fluctuating insulin shortage levels. Idiopathic diabetes is genetically predisposed and requires insulin

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replacement therapy based on the patient's condition [52].

Noninsulin dependent diabetes mellitus (NIDDM)

Adult-onset diabetes makes up 90-95% of all diabetes cases. Obesity, insulin resistance, and dyslipidemia are major metabolic disorders that contribute to the epidemic of type 2 diabetes [53]. This kind of diabetes is treated with oral hypoglycemic medications, which are dietary. Insulin resistance and decreased insulin production lead to disease development. Type 2 diabetes is the fourth greatest cause of death in developed nations, with a twofold increase in mortality and a fourfold increase in the risk of coronary heart disease and stroke [54].

Catamenial Hyperglycemia

Diabetic ketoacidosis (DKA) can be caused by infection, low insulin, poor insulin compliance, severe pancreatitis, stroke, medications, metabolic changes, or treatment neglect [55]. Catamenial diabetic ketoacidosis or Catamenial hyperglycemia refers to uncontrolled hyperglycemia in females that occurs before their menstrual cycle. Uncontrolled hyperglycemia required up to four times more insulin. The situation worsens even with continuous insulin infusion, causing vomiting, acidosis, ketonuria, and hyperglycemia. Several tests, including inflammatory indicators, blood count, renal function, ECG, chest radiograph, thyroid function, and urine/blood cultures, were normal.

Pathophysiology of diabetes mellitus

Diabetes is a chronic metabolic disorder characterized by hyperglycemia, which causes significantly elevated blood sugar levels. Hyperglycemia can be produced by insulin production, action, or a combination of both, leading to long-term dysfunctions in carbohydrate, protein, and lipid metabolism [56]. Long-term effects of diabetes include diabetic retinopathy (risk of blindness), nephropathy (kidney failure), and neuropathy (foot ulcers, Charcot's joints, and amputations), autonomic neuropathy (which causes gastrointestinal issues), sexual dysfunction, and cardiovascular abnormalities. Individuals with DM frequently have hypertension and poor lipoprotein metabolism. As a result, they are more prone to peripheral arterial, cerebrovascular, cardiovascular, and atherosclerosis diseases [52]. T1DM causes the autoimmune destruction of insulin-producing cells in the pancreas. The immune system's CD4+ and CD8+ T cells destroy these cells, while macrophages harm the pancreatic islets. T1DM is characterized by insufficient insulin secretion due to autoimmune death of pancreatic β-cells, which can cause metabolic problems [57]. In type 2 diabetes, the processes that maintain normal physiological glucose levels breakdown causes two key pathophysiological defects: decreased insulin secretion due to pancreatic β-cell malfunction and impaired insulin action due to IR [58]. Diabetes significantly increases the risk of CVD diseases such as CAD, stroke, atrial fibrillation, and heart failure. CVD remains the leading cause of death among diabetics [59]. Understanding the complex pathophysiology of diabetes is crucial for managing its effects.

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Pathophysiology Type 1 diabetes mellitus

T1DM is a genetic immune system disorder affecting individuals of all ages, including preadolescents, young adults, and the elderly. T1DM develops due to the loss of pancreatic β cells, which is largely caused by T-lymphocytes [60]. Insulates occurs when immune cells invade pancreatic islets, causing inflammation. Islet infiltration is likely caused by β-cells, as insulates is only found in β-cell islets [61]. T-cells cause inflammation and destroy β cells in islets [61]. Specific genes can impair the immune system's ability to distinguish between self and others.

Autoimmune disorders, such as T1DM, can result from non-self-interactions [60]. The genes linked to T1DM are known as human leucocyte antigens (HLA) and belong to the MHC region. HLA complex polymorphism alleles account for 40-50% of the hereditary risk of T1DM. HLA gene loci are classified as Class I and Class II. T1DM-associated HLA alleles are Class II and play a significant role in antigen presentation to T helper cells. Substitutions in the peptide-binding areas of Class II alleles can change the binding affinity for auto antigens, either reducing or increasing the autoimmune response. Several investigations have found alterations in the makeup of leukocytes linked with T1DM.

These comprise NKT cells, dendritic cells, CD45R-subpopulations, CD4 and CD8 T-cells. However, the causes and effects on disease progression are still being investigated [61]. Insulin insufficiency can cause major effects on protein, carbohydrate, and lipid metabolism. Insulin shortage disrupts glucose metabolism, causing metabolic diseases such as glycosuria, polydipsia, and polyphagia. Uncontrolled T1DM leads to high levels of free fatty acids (FFA) in the plasma due to rapid triglyceride mobilization. Insulin insufficiency causes hypertriglyceridemia and increases the risk of proteolysis, raising plasma amino acid concentrations. Additionally, hyperglycemia in T1DM is exacerbated by hepatic and renal gluconeogenesis of glycogenic amino acids [58].

Pathophysiology Type 2 diabetes mellitus

T2DM causes elevated plasma glucose levels due to impaired insulin production and action [62]. Understanding the etiology of this multifactorial disease has proven challenging. However, T2DM can be categorized as a hereditary disorder. Various genes regulate insulin secretion, action, and β-cell activity. These genes are vital for producing enzymes. Genetic impairments can lead to a series of metabolic reactions, including insulin resistance, increased liver glucose production, impaired fatty acid and glucose uptake, and increased TG breakdown. [60].

Insulin secretion degradation, including hyperglycemia and lipo-toxicity, can lead to a decrease in β-cell mass if not addressed, as shown in animal studies. The progression worsens the long-term regulation of blood glucose levels [63]. Glucolipotoxicity and amyloid accumulation lead to β-cell death through oxidative and endoplasmic reticulum stress [64].

Other organs have an important part in the pathogenesis of Type 2 Diabetes [62]. The liver produces excess glucose due to insulin resistance, higher glucagon levels, and enhanced glucagon sensitivity. Furthermore, insulin is capable of crossing the blood brain barrier (BBB) suppresses hunger by modulating neuropeptides that control food intake. Excess FFAs can cause adipocytes to resist insulin's anti-lipolytic impact.

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Chronic high levels of FFAs disrupt metabolism, leading to gluconeogenesis, IR in skeletal muscle and liver, and decreased insulin secretion [65]. Nonalcoholic fatty liver disease (NAFLD), which is often linked to T2DM, causes an increase in FFA buildup in the liver due to insulin resistance. This accumulation not only worsens NAFLD by causing chronic liver cell stress, but also sets off a cycle of increased lipid accumulation. Obesity, a risk factor for T2DM, lowers adiponectin levels, which normally suppress proinflammatory cytokines Examples include TNF-α and IL-6. Reduced adiponectin levels promote cytokine production, causing inflammation in adipocytes and increasing insulin resistance [66]. Obesity-induced inflammation is linked to IR via the IKKβ/NF-KB pathway. Diabetes management recommendations urge a minimum 5% weight decrease for overweight and obese patients. To effectively manage diabetes, a personalized diet, increased physical activity, and behavioral therapy are recommended [67].

Metabolic pathways and complications

Hyperglycemia causes tissue damage via multiple interrelated metabolic mechanisms. These include the polyol pathway, hexamine biosynthetic pathway, activation of protein kinase C, and increased development of advanced glycation end-products (AGEs). The polyol pathway converts excess glucose to sorbitol and then fructose, depleting NADPH and glutathione and increasing oxidative stress. The hexamine route converts excess glucose into Nacetylglucosamine, which influences transcription factors and gene expression. Protein kinase C activation impacts vascular permeability and blood flow AGEs crosslink proteins, disrupting normal function and causing inflammation. These pathways produce reactive oxygen species, leading to a cycle of oxidative stress that can cause tissue damage even after hyperglycemia is under control [68].

Diabetic retinopathy

Diabetic retinopathy (DR) is a prevalent condition that affects the blood vessels of the retina, affecting 93 million people globally [69]. The condition is typically diagnosed 5 years after symptoms appear and, if untreated, can result in vision loss [70]. Hyperglycemia causes long-term damage to retinal capillaries, leading to endothelial dysfunction, including microangiopathy and arterial stiffness. There are two stages of diabetic retinopathy: non-proliferative (NPDR) and proliferative (PDR). NPDR is an early stage of DR marked by increased vascular permeability, balloon-like capillaries in the retina, and disruption of the blood-retinal barrier (BRB). PDR is the advanced stage where new blood vessels form to compensate for swollen capillaries that cannot bring blood to all retinal cells. Breaking these new arteries can lead to vitreous haemorrhage and retinal detachment, resulting in visual loss [71]. Diabetes management is the primary treatment for DR, however advanced cases may require laser therapy or surgery [71].

Diabetic neuropathy

Diabetic neuropathy is one of the most devastating consequences of diabetes mellitus, which can cause death. Hyperglycemia can cause neuronal damage, affecting numerous. The polyol and hexamine pathways in neurons [72]. In example, peripheral

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neuropathy affects 30-50% of diabetics and is typically classed as multifocal neuropathy. Symptoms include leg discomfort and numbness. Arms are affected as a result of autonomic small fiber injury. It is commonly detected by thermal threshold testing measures a person's sensitivity to temperature fluctuations. Patients with DN typically have a decreased ability to sense those changes [73-74]. A useful technique for identifying patients with peripheral neuropathy is the neuropath test assesses plantar sweat production. Abnormal results may indicate sudomotor dysfunction linked to peripheral neuropathy [74]. Early diagnosis of DN is useful to immediately start treatment and prevent damage of the large nerve fibers that can be deadly.

Diabetic Nephropathy

Diabetic nephropathy is another common type 1 and type 2 diabetes complication. This condition causes kidney function loss and contributes to CKD and ESRD [75]. Diabetic nephropathy is classified into four stages based on the severity of vascular, interstitial, and glomerular abnormalities. Diabetic nephropathy is typically treated with anti-diabetic medications. It is linked to an increased risk of death, especially from cardiovascular disease.

Diabetic Ketoacidosis

Although it is more frequently linked to type 1 diabetes, diabetic ketoacidosis (DKA) can happen to any diabetic patient when their body is under a lot of stress. "A lack of insulin can cause harmful substances called ketones to build up in the blood," according to clinical resources. Increased lipolysis and cytogenesis result from the pathophysiology of insulin insufficiency coupled with high levels of counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). When paired with fluid losses from osmotic diuresis, the ensuing metabolic acidosis poses a serious risk to life and necessitates prompt medical attention. Polyuria, polydipsia, nausea, vomiting, stomach pain, and in extreme situations, Kussmaul respirations and altered mental status are among the clinical symptoms [76].

Macro Vascular Complications

Diabetes has several macro vascular complications [77]. Diabetes mellitus is an independent risk factor for heart failure, making it a prevalent consequence. The Framingham study found that diabetes increases the risk of heart failure by two times in men and five times in women compared to non-diabetics [78]. Diabetes complications are 30-40% more common in people with heart failure [79], indicating a strong link between the two conditions. Diabetes and heart failure are linked to metabolic illnesses such glucose toxicity and lipotoxicity, as well as complications from ischemic heart disease. The diagnosis is based on insulin resistance, vascular endothelial dysfunction, microcirculation disease, and capillary failure. Several mechanisms are involved. Diabetic cardiomyopathy refers to cardiac dysfunction that occurs without severe coronary artery disease, hypertension, or valvular heart disease [80-83]. However, its existence has been contested for years [84-85]. The 2013 ACC/AHA Heart Failure Guidelines provide information on diabetic cardiomyopathy [86].

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Cardiovascular disease

Diabetes has resulted in the deaths of 1.6 million people, primarily from cardiovascular disorders [87]. Diabetes patients with no myocardial infarction are equally likely to develop acute coronary syndrome as nondiabetics with myocardial infarction. Diabetes individuals have twice the death rate following myocardial infarction compared to non-diabetic patients [88]. Diabetes patients are at risk for cardiovascular disease due to insulin resistance, hyperglycemia, and excess free fatty acids. These factors increase oxidative stress and disrupt PKC signaling, leading to vascular swelling, constriction, thrombosis, and atherogenesis [88]. Hypoglycemia is linked to higher risk.

Cerebrovascular disease

Diabetes increases the likelihood of developing cerebrovascular disorders, with 20% of diabetics dying from stroke [89-90]. The study examined the relationship between HbA1c, fasting glucose levels, insulin resistance, and beta cell function with various types of cerebrovascular diseases. High HbA1c levels, insulin resistance, and beta cell dysfunction raise the risk of big and small artery ischaemic strokes. Hb1Ac levels are linked to carotid atherosclerosis, fractional anisotropy, and white matter and brain atrophy markers, indicating a link between diabetes and cerebrovascular disease [91].

Peripheral artery disease

Peripheral artery disease (PAD) causes reduced blood flow to the extremities due to atherosclerosis and plaque formation in vessel walls [92]. Diabetes induces vascular dysfunction, inflammation, and atherosclerotic plaque deposition in the arteries, making PAD more frequent in diabetics than non-diabetics [93]. Patients with PAD and diabetes are more likely to develop foot ulcers and require lower extremity amputations [94]. Minority populations, including Native Americans, African Americans, and rural inhabitants, have been found to be at increased risk of lower extremities amputation compared with whites, suggesting that a difficult socioeconomic environment influences the availability of appropriate health care tools favoring drastic and irreversible medical interventions, such as leg amputation [95].

Therapeutic approaches

Therapeutic approaches towards cardiovascular diseases (CVD)

Macro albuminuria and micro albuminuria are strongly associated with a heightened risk of cardiovascular disease (CVD) [96].According to the MICRO-HOPE trial, the use of ramipril, an ACE inhibitor, notably reduces the chances of diabetic nephropathy, stroke, death due to cardiovascular causes, need for revascularization procedures, and overall mortality. Similarly, findings from the LIFE study revealed that losartan, an angiotensin receptor blocker (ARB), significantly lowers the risk of cardiovascular death, stroke, and myocardial infarction (MI). The risk of cardiovascular-related death or hospitalization due to heart failure was reduced by 23% [97].

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Pharmacological approaches to reduce cardio metabolic risk in obese diabetic patients

Obesity greatly contributes to increased mortality and health complications in individuals with both diabetes mellitus (DM) and cardiovascular disease (CVD) [98]. People with diabetes often have a broader waist circumference compared to non-diabetics [99]. In addition to the heart-protective benefits of traditional oral hypoglycemic agents (OHAs) like metformin and TZDs[100], newer treatments such as GLP-1 receptor agonists and SGLT-2 inhibitors are showing encouraging results in managing cardiovascular risks in obese diabetic patients[101-102]. The Diabetes Prevention Study emphasized the role of weight reduction in decreasing the risk of CVD events. Both GLP-1 and SGLT-2 agents contribute to weight loss, further proving their effectiveness in lowering CVD-related mortality [103]. A meta-analysis confirmed that SGLT2 notably reduced the likelihood of such events [104-105]. Additionally, GLP-1 significantly decreased the occurrence of cardiovascular complications and deaths by 10% and 13%, respectively, among patients with type 2 diabetes (T2DM) [106].

Therapeutic strategies for managing hypertension

High blood pressure is a key contributor to the widespread occurrence of cardiovascular diseases (CVDs), which are a leading cause of death in individuals with diabetes. Medications such as ACE inhibitors have been shown to lower the risk of hypertensive individuals developing diabetes by 11–34% [107-108], emphasizing their crucial role in reducing CVD among diabetic patients. The Hypertension Optimal Treatment (HOT) trial suggests keeping diastolic blood pressure (DBP) under 85 mm Hg, which may help in decreasing CVD risk [171]. In diabetic patients, β-blockers have shown positive outcomes [109-110], particularly atenolol, which significantly reduces complications and death from CVD, as confirmed by the UKPDS study [111]. Moreover, the calcium channel blocker fenoldopam, used as a first-line therapy in the HOT trial, was found effective in minimizing CVD events by controlling DBP in diabetic individuals [112].

Strategies for treating hyperlipidemia (Dyslipidemia)

Targeting dyslipidemia is expected to notably decrease the occurrence of issues like CVD among diabetics, as it is a major risk factor [113]. Dyslipidemia in diabetes is typically marked by elevated triglycerides, lower HDL levels, and a higher concentration of LDL particles. These lipid abnormalities play a key role in CVD development [114-115].

Herbal plants that are used for treatment of diabetes mellitus:

Momordica Charantia

It is a member of the Cucurbitaceae family and is frequently referred to as bitter melon (karela).Momordica 1 and Momordica 2, as well as cucurbitacin B, are the active ingredients of Momordica charantia. It is employed to treat diabetes. It contains lectin, which functions similarly to insulin. A nonprotein called lectin is connected to insulin receptors. By affecting peripheral tissues, this lectin lowers blood sugar level [116]. *M. charantia* fruit extract has hypoglycemic action at 200mg/kg.

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Carica papaya

The papaya , a member of the Caricaceae family , has been shown to lower blood sugar levels , reduce body lipids , and promote wound healing in alloxan induced diabetic rats when its seeds and leaves are extracted [117].

Allium sativum

Allium sativum is known locally as garlic since it is a member of the Liliaceae family, which includes Alium sativum. Garlic ethanol extract (10 ml/kg/day) frequently exhibits hypoglycemic effects [118]. Garlic extract outperformed the antidiabetic medication glibenclamide. In rats given STZ, ethanol, petroleum ether extract, and ethyl acetate few found to exhibit anti diabetic effects. Garlic has a number of medicinal benefit, including antimicrobia, antiplatelet, blood pressure, and cholesterol reduction [118].

Aloe borbadensis

Borbadensis aloe it is a member of the Lilicaeae family and is called Ghikanvar. With its green blade – shaped, heavily narrowing, hairy leaves that are packed with clear viscid gel, it resembles a cactus plant. Blood glucose levels are considerably reduced when aloe vera aqueous extract is taken orally at a dose of 150 mg/kg of body weight [119]. Aloe vera gel has several medicinal benefits, including anti – diabetic and antioxidant properties. It also quadruples levels in diabetic rats [120].

Mangifera indica:

It belongs to the Anacardiaceae family and is frequently referred to as a mango. In rats with alloxan – induced diabetes, oral treatment of an aqueous extract did not alter blood glucose levels, whereas leaves extract (250 mg/kg) demonstrated anti – diabetic action [121].

Eugenia jambolana

It is a member of the Myretaceae family and is called jamun. It has mature Eugenia jambolana fruits and dry seeds. Ferulic acid and malvidin 3-laminaribioside are its active constituents. Patients with diabetes are treated with a dried seed extract (200 mg/kg) [122].

Effects of chemicals on diabetes mellitus:

DDP-4 inhibitors

DDP-4 inhibitors, such as saxagliptin and sitagliptin, function by preventing the breakdown of GLP-1 by the enzyme DDP-4. GLP-1 is raised as a result, which promotes the release of insulin and inhibits the release of glucagon [123].

SGLT2 inhibitors

SGLT2 inhibitors, including canagliflozin and dapagliflozi, enhance the excretion of glucose in the urine by preventing the kidneys from reabsorbing glucose [124].

GLP-1 receptor

Exenatide are examples of GLP-1 receptor agonists that function by imitating GLP-1s

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actions and promoting the release of glucagon and insulin [125].

Thiazolidindion

For the treatment of type 2 diabetes mellitus, thiazolidindion, commonly referred to as glitazones, are regarded as a well – established class of anti – diabetic drugs and a physiologically active scaffold. By increasing peripheral glucose synthesis and disposal, thiazolidinediones lower insulin resistance. These compounds activate one of subtype of PPARs, the peroxisome proliferated activated receptor (PPARy). A variety of its hybrids have also demonstrated antidiabetic and other therapeutic properties [126].

Sulfonylureas

Due to its rising frequency and debilitating effects, diabetes mellitus (DM) is a rapidly expanding epidemic and a global public health concern. Oral glucose-lowering medications known as sulfonylureas (SUs) are used as second line treatments for type 2 diabetes (T2D) because of their effective glycaemic control, and renal advantages. Despite certain adverse effects, SUs immediately insulin production by the pancreas. It plays a role in the onset and advancement of hypoglycemia. It is used in place of or in addition to metformin. Elderly weak people who are at increased risk of hypoglycemia. It is used in place of or in addition to metformin. Elderly weak people who are at increased risk of hypoglycemia should avoid SUs [127].

Biguanides

Because of their positive safety profiles and ability to decrease blood sugar, biguanides, like metformin, have long been considered the first choice drugs for the treatment of type 2 diabetes. However, there has been a lot of discussion and investigation due to worries about the possibility of lactic acidosis linked to biguanide use. The goal of this study is to present a thorough examination of the connection between lactic acidosis and biguanides, specifically metformin. We examine the fundamental processes, epidemiological data, risk factors, clinical presentations, diagnostic issues, and treatment approaches associated with lactic acidosis brought on by biguanides. We also examine current research findings, debates, and potential paths forward in this crucial field of clinical practice and pharmacovigilance [128].

Radiation on diabetes mellitus

There is sample evidence that low-dose radiation (LDR) can induce hormesis and adaptive response. LDR-induced adaptive response was cross-resistance to other non-radiation stressors, like chemicals, in addition to being resistant to damage from a subsequent high-dose radiation. Induced or up-regulated production of defensive proteins, including as heart shock proteins and antidioxidants, is one mechanism by which LDR produces the protective effect against tissue damage caused by radiation or chemicals.

This review will provide an overview of the available data, with a focus on the preventive effect of LDR on the development of diabetes and the therapeutic effect of LDR on diabetic cardiovascular complications, as oxidative damage to tissues is a major pathogenesis of many human diseases including diabetes. According to the

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information provided, pre-exposure of mice to LDR delayed the onset of hyperglycemia in diabetes-prone non-obese diabetic mice and decreased the incidence of alloxan-induced diabetes. Low-intensity or power laser (LIL or LPL) radiation has been in animals experiments to have a therapeutic effect on skin wound healing. This has led to the clinical use of LIL to treat diabetes patient's skin ulcers.

Although the exact mechanisms by which LDR prevents diabetes are unknown, they may involve immunomodulation to maintain pancreatic antioxidants to shield cells from oxidative damage. The mechanisms underlying LIL's therapeutic effect on diabetic wound healing may include immunomodulation, beta cell proliferation stimulation, antioxidant action, and enhancement of systemic and wound regional microcirculation. Therefore, numerous research have shown that LDR, specifically LIL, is a therapeutically effective treatment for diabetic wound healing, even though there are only a handful that show LDR prevents the development of diabetes. These early findings are very motivating for us to investigate the clinical implications of LDT in areas connected to diabetes [128].

Emerging trends

Improving glycaemic control, lowering complications, and improving patient quality of life are the driving patient quality of life are the driving forces behind emerging trends in diabetes management

Incretin mimetics

Insulin mimetic are drugs, which include GLP-1 analogues, increases the secretion of insulin, prevent the release of glucagon, and postpone the empting of the stomach [128].

Dipeptidyl peptidase-4 (DPP-4) Inhibitors

Medications such as saxagliptin and sitagliptin prevent GLP-1 from being broken down, which raises insulin output and leaves glucagon levels [128].

Sodium glucose cotransporter 2 (SGLT2) inhibitors

Drugs like canagliflozin and dapagliflozin increases glucose excretion and improve glycaemic management by decreasing the kidney ability to reabsorb glucose [128].

Newer insulins

Insulin glargine, detemir, and degludec are examples of long acting insulins that offer more consistent and long lasting glucose management [128].

Insulin delivery devices

Insulin administration and glucose control have been enhanced by developments in insulin pens, jets, and continuous subcutaneous insulin infusion pumps [128].

Islet cell transplantation

To restore insulin production, donor beta cells are transplanted into the host's portal vein in this promising treatment [128].

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Stem cell technology

The ability of stem cells to enhance insulin action and regenerate beta cells is being investigated by researchers [128].

Artificial pancreas systems

Systems of artificial pancreas by combining continuous glucose monitoring with insulin delivery, these systems seek automate glucose management [128].

Conventional therapeutic approaches for diabetes management

Exercise and weight control

It has been demonstrated that exercise helps patients with glycemic blood levels [129-130] found that aerobic, resistance, and combined training methods are effective in lowering HbA 1c levels. They also found that a diet high in proteins, low in carbohydrates, and low in glycemic index (similar to the Mediterraneon diet) lowers blood sugar levels in diabetic patients who are at high risk of cardiovascular disease [129-130]. In 50% of patients with long-duration type 2 diabetes, this regimen is more effective than all antidiabetic treatments at achieving non-diabetic fasting glucose levels [131]. Diabetes remission is linked to intensive weight loss interventions based on physical activity, food, and social support [132-133], underscoring the significance of weight control in the treatment of diabetes.

Oral glucose drugs

Biguanides, sulfonylureas, meglitinides, and thiazolidinediones are the primary classes of oral medications used to treat diabetes [134-141]. One of those medications, pioglitazone, a thiazolidinedione, has raised some health issues in a number of studies. It effectively lowers fasting blood glucose and HbA1c levels, but it can also result in edema and an increase in body weight [134]. However, the medication is utilized by those who have cardiovascular disease, diabetes, and dyslipidemia. A lower risk of heart attack, diabetes complications, and death is linked to sulfonylureas and metformin [134-141]. Despite their beneficial medicinal effects, sulfonylureas, such metformin and glyburide, have been associated with a higher risk of hypoglycemia than pioglitazone [141].

Insulin injections

Patients with type 1 diabetes who are unable to make insulin spontaneously are treated mostly with insulin injections [142]. Patients with type 2 diabetes are less likely to need insulin therapy, and when diet, exercise, weight loss, and oral antidiabetic medications fail to lower blood glucose levels as intended, insulin therapy is employed [143]. After at least two months of dual oral therapy, insulin therapy is initiated when HbA1c levels are above 7%. If this doesn't happen, insulin is gradually administered along with other drugs to guarantee optimal blood glucose control. To reach and maintain HbA1c levels below 7%, several insulin injections must be given daily as one is typically insufficient [144]. The two potential adverse effects of insulin therapy are weight gain and hypoglycemia. For insulin therapy to be effective, patients must restrict their food consumption and check their blood sugar levels at least four times a day, before each meal. Patients with type 1 diabetes can ensure a

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long, healthy life if they adhere to this medication, which lowers hypoglycemic and hyperglycemic episodes [145].

Oral glucose drugs

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Future perspective

Combination therapies using peptide hormones

Several hypothalamic-pituitary endocrine axis, which control the activity of the thyroid, pancreatic islets, gonadal and adrenal glands, and other organs, are influenced by the adipocyte-secreted hormone leptin, a protein encoded by the obese (ob) genes. Additionally, the hormone has pleiotropic effects on wound healing, osteogenesis, angiogenesis, and the immune system [155-156]. When used to treat a rare form of human obesity brought on by particular ob gene mutations, several clinical trials have demonstrated that recombinant human leptin has favorable effects on energy balance and obesity-related endocrinopathies [158]. In addition to its effects on body weight and food intake, leptin possesses strong anti-diabetic properties. Specifically, it can reverse type 1 and type 2 diabetes in animal models. Furthermore, individuals with severe insulin resistance benefit greatly from long-term leptin replacement therapy, which is well tolerated and significantly improves triglyceride levels, insulin sensitivity, and glycemic management [157]. These findings have prompted the development of novel anti-diabetic and anti-obesity therapies that include the use of mimetics, synthetic peptide analogs, and leptin receptor antagonists [157]. Obese mice's glucose and lipid metabolism has improved when those leptin analogs are combined with GLP-1 receptor agonists [156].

Incretions combination therapy

In rodent models of obesity, a new peptide with agonist action at three peptide hormone receptors—GLP-1, glucose dependent insulin tropic polypeptide (GIP), and glucagon receptors—has demonstrated positive effects on body weight and the prevention of diabetic complications [159]. In diabetic animal models, dual co-agonists or best mono-agonists are less effective in reducing body weight, improving glycemic control, or reversing steatosis. Genetic, pharmacological, and selective chemical loss-of-function studies have confirmed the role of each of those molecules in metabolic changes in vivo. A synergistic combination of glucagon, GLP-1, and GIP contributes to the metabolic efficacy of this type of treatment by increasing energy expenditure, decreasing caloric intake, and mitigating the diabetogenic effects of

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glucagon, respectively, improving glucose control [159]. Simultaneously, scientists have created a peptide that strongly co-agonistically interacts with both GLP-1 and GIP receptors, which are Incretin hormones. This unimolecular dual Incretin peptide has a significantly better ant hyperglycemic and insulin tropic effect than other GLP-1 agonists, both in patients with diabetes and in rodent and primate (cynomolgus monkey) models of obesity and diabetes (diabetic (db/db)mice and Zucker diabetic fatty (ZDF)rats). Unlike selective GIP agonists, which have minimal impact on weight loss, dual Incretin co-agonists effectively reduce fat mass in obese rats. Polyethylene Glycol (PEG) ylation, or site-specific limitation, of the proteins results in a longer duration of action and, thus, lower dosage, preventing the negative gastrointestinal effects brought on by the administration of large doses of selective GLP-1 agonists. In any case, more research is required to validate the powerful benefits of dual Incretin agonists in the treatment of type 2 diabetes [160].

Gene therapy

A novel approach to treatment, gene therapy aims to change the patient's genes or cells in order to accomplish the intended outcome. Both in vivo and ex vivo gene therapy are possible. The idea behind ex vivo therapy is to remove the patient's cells from their body, alter their genetic makeup, and then put them back into the patient. Instead, the goal of in vivo therapy is to alter the patient's cells without taking them out of the body.

Ex vivo therapy

The ability of cells other than beta cells to produce insulin has been investigated in some of the earliest research in the field of ex vivo gene therapy, with the aim of implanting these cells in the human body as an extra source of the hormone [161-164]. Rat liver cells, or hepatocytes, were used in those experiments. After being cultured with the insulin promoter factor 1, those cells—which were separated from rodent cells—were able to respond to glucose and sulfonylureas by producing and releasing insulin. These cells were able to lower the no fasting glucose levels in diabetic mice after being transplanted in them [164]. The expression of the pancreatic duodenal home box 1 (Pdx1) gene, a crucial transcription factor in pancreatic development and insulin expression in beta cells, can also elicit the differentiation of fetal human progenitor liver cells (FH) into cells that produce insulin. The ability of those FH cells to respond to glucose by producing and releasing insulin and maintaining euglycemia for extended periods of time in diabetic mice suggests that this method may be a novel source of cells for transplantation into T1DM patients [164]. Cells used in ex vivo gene therapy must be appropriately engineered to respond to glucose in order to prevent episodes of hypoglycemia and hyperglycemia, not trigger the immune response that could result in rejection from the human body, and adjust to physiological changes that occur in the body, such as aging, weight fluctuations, and the body's response to exercise [163].

In Vivo therapy

Since hepatocytes can be made to differentiate into islets and used to replace damaged beta cells in the pancreas, the liver is a target organ for gene therapy. Adenoviruses

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have been employed as vectors to transfer the proinsulin gene into the liver of T1DM-carrying mice as part of an in vivo gene therapy strategy. Upon appropriate stimulation following the infection, those cells were able to produce [165-168]. These findings have demonstrated that, despite their lack of innate capacity to manufacture the hormone, hepatocytes can be utilized as an extra source of insulin following genetic modification. Genetically modifying the enzyme in diabetic rats has been shown to reduce blood glucose levels by 38% and raise blood insulin levels by 67%. However, it also had a significant impact on fat metabolism, raising levels of triglycerides by 190% and free fatty acids by 310%. According to those findings, genetically modifying hepatic GCK is currently not regarded as a reliable method of treating diabetes. Conversely, pdx 1 expression [169] in diabetes mouse hepatocytes has been shown to raise plasmatic insulin levels by 300%, indicating that genetic modification of this transcription factor may be taken into consideration to develop novel anti-diabetic treatments [170].

Stem cell Therapy

Stem cell therapy is one of the newest and most sophisticated methods for treating major metabolic diseases like diabetes [170-178]. Stem cells are rapidly proliferating cells that can develop into any kind of cell in the body, including muscle, pancreas, and brain cells. When nonmyeloablative hematopoietic stem cell transplantation (AHST) was utilized to treat type 1 diabetes in individuals on immunosuppressive medications, the results of stem cell therapy were assessed [178]. Over several months, patients received intravenous injections of stem cells. C peptide levels rose six months after the transplant, indicating increased insulin production. However, there was a decrease in anti-glutamic acid decarboxylases (GAD) plasmatic levels, which are typically elevated in type 1 diabetic patients and suggest immune-mediated beta cell death. Patients who no longer needed intense insulin therapy showed better beta cell activity, as evidenced by lower blood glucose levels and A HbA1c concentration below 7% [178]. Although it has been shown to improve beta cell function, stem cell transplantation is not advised for individuals with diabetic ketoacidosis. Even though stem cell therapy has been shown to be successful in reversing hyper glycaemia, most patients need insulin or traditional anti-diabetic therapy a few months after the transplant because beta cell mass decreases over time for immune system activation [175]. If the patient's stem cells are derived from the same patient rather than from donors, the immune-mediated loss of beta cells can be prevented. According to this viewpoint, the main goal of stem cell therapy is to reprogrammed diabetic patients' fibroblasts into induced pluripotent stem cells (iPS) that are intended to differentiate into beta cells, which are subsequently replanted in the patient's highly vascularized body tissues [176].

Conclusion

Diabetes mellitus is a most common endocrine disorder, which has affected millions of people in the world. It is a type of disease which is caused by hyperglycemia resulting from imperfections in insulin secretion, insulin action or both. The available drugs for the diabetes mellitus that are present have many side effects and problems like unwanted hypoglycemia that are the turning point of the research to shift towards

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traditionally available medicines which have low side effect and wide range of bio activity and seems highly attractive. From this review article, it is useful for the health professionals, scholars and scientists to develop alternative medicines on the basis of available evidence to cure different kinds of diabetic problems using herbal preparations substances and extracts like *momordica charantia*, *carica papaya*, *allium sativum*, *aloe bobsdensis*, *Mangifera indica*, *Eugenia jambolana*. These plants extracts for use for the treatment of diabetes mellitus and they shows significant role in controlling hyperglycemia that are isolated from different plants plays very important role to design medicines and treat hyperglycemic problems. Studies have demonstrated the effectives of new classes of medicastions, like GLP-1 receptor agonists SGL2 inhibitors, Sulfonylureas, DPP-4 inhibitors, Biguanides, Thiazolidinediones these chemicals were used in enhancing glycemic control and lowering the cardiovascular risk. Additionally, advances insulin delivery devices and emerging trends such as artificial pancreas system and stem cell technology, hold promise for further improving diabetes management. The exact mechanisms by which LDR prevents diabetes are unknown, they may involve immunomodulation to maintain of pancreatic function and the activation of pancreatic antioxidants to shield beta cells from oxidative damage. The mechanisms underlying LIL's therapeutic effect on diabetic wound healing may include immunomodulation, cell proliferation stimulation, antioxidant action, and enhancement of systemic and wound regional microcirculation. Therefore, numerous research have shown that LDR, specifically LIL, is a therapeutically effective treatment for diabetic wound healing, even though there are only a handful that show LDR prevents the development of diabetes. These early findings are motivating for us development of diabetes. Certain other therapies like newer insulin, insulin delivery devices, islet cell transplantation, stem cell technology, artificial pancreas systems were made for glucose management. Some conventional therapeutic approaches like exercise and weight control, medical nutrient therapy, oral glucose drugs like biguanides, sulfonylureas, meglitinides and thiazolidinediones are the primary classes of oral medications used for the glucose management. Patients with type 1 diabetes who are unable to make insulin spontaneously are treated with some insulin injections which are made for the control of diabetes. Some gene therapies and stem cell therapies both in vivo and in vitro are made to replace the damaged beta cells in the pancreas, and the liver is a target organ for gene therapy. When nonmyloablative hematopoietic stem cell transplantation was utilized to treat type 1 diabetes in individuals on immunosuppressive medications, the results of stem cell therapy were assessed. Over several months patients were received intravenous injections of stem cells. C peptide levels rose six months after the transplant, including increased increase insulin production.

References

Inzucchi, Silvio E., Richard M. Bergenstal, John B. Buse, Michaela Diamant, Ele Ferrannini, Michael Nauck, Anne L. Peters, Apostolos Tsapas, Richard Wender, and David R. Matthews. "Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Stuy of Diabetes (EASD)." *Diabetes Spectrum* 25, no. 3 (2012): 154-171.

Online ISSN 3007-3197
Print ISSN 3007-3189

Giovannini, P.; Howes, M.J.R.; Edwards, S.E. Medicinal plants used in the traditional management of diabetes and its sequelae in Central America: A review. J. Ethnopharmacol. 2016, 184, 58–71.

International Diabetes Federation, 2014, http://www.idf.org/ diabetesatlas.

Madras Diabetes Research Foundation (India), 2014, http:// mdrf.in/.

S. R. Joshi, "Metabolic syndrome—emerging clusters of the Indian phenotype," *Journal of Association of Physicians of India*, vol. 51, pp. 445–446, 2003.

R. Deepa, S. Sandeep, V. Mohan et al., "Abdominal obesity, visceral fat and type 2 diabetes—Asian Indian phenotype," in *Type 2 Diabetes in South Asians: Epidemiology, Risk Factors and Prevention*, V. Mohan and G. H. R. Rao, Eds., pp. 138–152, Jaypee Brothers Medical Publishers, New Delhi, India, 2006.

M. Chandalia, N. Abate, A. Garg, J. Stray-Gundersen, and S. M. Grundy, "Relationship between generalized and upper body Obesity to insulin resistance in Asian Indian men," *The Journal of Clinical Endocrinology & Metabolism*, vol. 84, no. 7, pp. 2329– 2335, 1999.

A. Ramachandran, C. Snehalatha, V. Viswanathan, M. Viswanathan, and S. M. Haffner, "Risk of noninsulin dependent diabetes mellitus conferred by obesity and central adiposity in different ethnic groups: a comparative analysis between Asian Indians, Mexican Americans and Whites," *Diabetes Research and Clinical Practice*, vol. 36, no. 2, pp. 121–125, 1997.

International Diabetes Federation. Data from: IFD Diabetes Altas Globally. IDF Diabetes Atlas, 8thed, 2017. Available online: https://diabetesatlas.org/upload/resources/previous/files/8/IDF_DA_8e-EN-final.pdf (accessed on 11 May 2022).

International Diabetes Federation. IDF Diabetes Atlas. 2021. Available online: https://www.idf.org/aboutdiabetes/what-isdiabetes/facts-figures.html (accessed on 11 February 2019).

Jumpup (2007) Williams Textbook of endocrinology (12thed.). Elsevier/ Saunders, Philadelphia, USA 1371–1435.

Chen L, Magliano DJ, Zimmet PZ (2014) The worldwide epidemiology of type 2 diabetes mellitus: present and future perspectives. Nature reviews endocrinology.

DMICC (2014) Genetic basis of type 1 and type2 diabetes, obesity, and their complications. Advances and emerging opportunities in diabetes research: a Strategic Planning report of the DMICC.

Central Intelligence Agency (2008) The World Fact book: CIA.

Bansal, M. (2020). Cardiovascular disease and COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14(3), 247-250. https://doi.org/10.1016/j.dsx.2020.03.013 19.

Cigarroa, R. G., Lange, R. A., Williams, R. H., & Hillis, D. (1989). Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. The American journal of medicine, 86(6), 649-652. https://doi.org/10.1016/0002-9343(89)90437-3

17 Roep BO, Thomaidou S, van Tienhoven R and Zaldumbide A. (2021). Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?). Nat Rev Endocrinol. 17(3):150-161.

Online ISSN 3007-3197
Print ISSN 3007-3189

Borse SP, Chhipa AS, Sharma V, Singh DP and Nivsarkar M. (2021). Management of Type 2 Diabetes: Current Strategies, Unfocussed Aspects, Challenges, and Alternatives. Medical principles and practice: international journal of the Kuwait University, Health Science Centre. 30(2): 109–121.

Sugandh F, Chandio M, Raveena F, Kumar L, Karishma F, Khuwaja S, Memon UA,

Bai K, Kashif M, Varrassi G, Khatri M and Kumar S. (2023). Advances in the Management of Diabetes Mellitus: A Focus on Personalized Medicine. Cureus. 15(8):e43697. Doi: 10.7759/cureus.43697.

Warshauer JT, Bluestone JA, Anderson MS. New Frontiers in the Treatment of Type 1 Diabetes. *Cell Metab*. 2020; 31(1):46-61. doi:10.1016/j.cmet.2019.11.017

Barrett JC, Clayton DG, Concannon P, et al. Genomewide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet*. 2009; 41(6):703-707. doi:10.1038/ng.381

Hansen MP, Matheis N, Kahaly GJ. Type 1 diabetes and polyglandular autoimmune syndrome: A review. *World J Diabetes*. 2015; 6(1):67-79. doi:10.4239/wjd.v6.i1.67

Velthuis JH, Unger WW, van der Slik AR, et al. Accumulation of autoreactive effector T cells and allospecific regulatory T cells in the pancreas allograft of a type 1 diabetic recipient. *Diabetologia*. 2009; 52(3): 494-503. Doi: 10.1007/s00125-008-1237-z

Michels AW, Landry LG, McDaniel KA, et al. IsletDerived CD4 T Cells Targeting Proinsulin in Human Autoimmune Diabetes. *Diabetes*. 2017; 66(3):722-734. Doi: 10.2337/db16-1025

Kuric E, Seiron P, Krogvold L, et al. Demonstration of Tissue Resident Memory CD8 T Cells in Insulitic Lesions in Adult Patients with Recent-Onset Type 1 Diabetes. *Am J Pathol*. 2017; 187(3):581-588. Doi: 10.1016/j.ajpath.2016.11.002

Abreu JR, Martina S, Verrijn Stuart AA, et al. CD8 T cell autoreactivity to preproinsulin epitopes with very low human leucocyte antigen class I binding affinity. *Clin Exp Immunol*. 2012; 170(1):57-65. Doi: 10.1111/j.1365-2249.2012.04635.x

Unger WW, Velthuis J, Abreu JR, et al. Discovery of low-affinity preproinsulin epitopes and detection of autoreactive CD8 T-cells using combinatorial MHC multimers. *J Autoimmun*. 2011; 37(3):151-159. Doi: 10.1016/j.jaut.2011.05.012.

Beringer DX, Kleijwegt FS, Wiede F, et al. T cell receptor reversed polarity recognition of a self-antigen major histocompatibility complex. *Nat Immunol*. 2015; 16(11):1153-1161.doi:10.1038/ni.3271

R. Khardori. Type 2 Diabetes Mellitus: Practice Essentials, Background, PathophysiologyEMedicine (2022)

Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet*. 2005; 365(9467):1333-1346. Doi: 10.1016/S0140-6736(05)61032-X

Cerf ME. Beta cell dysfunction and insulin resistance. *Front Endocrinol (Lausanne).* 2013; 4:37. Published 2013 Mar 27. doi:10.3389/fendo.2013.00037

Rorsman P, Ashcroft FM. Pancreatic β-Cell Electrical Activity and Insulin Secretion:

Online ISSN 3007-3197
Print ISSN 3007-3189

Of Mice and Men. *Physiol Rev*. 2018; 98(1):117-214. doi:10.1152/physrev.00008.2017.

Christensen AA, Gannon M. The Beta Cell in Type 2 Diabetes. *Curr Diab Rep*. 2019; 19(9):81. Published 2019 Aug 9. Doi: 10.1007/s11892-019-1196-4

Yamamoto WR, Bone RN, Sohn P, et al. Endoplasmic reticulum stress alters ryanodine receptor function in the murine pancreatic β cell. *J Biol Chem*. 2019; 294(1):168-181. doi:10.1074/jbc.RA118.005683

Halban PA, Polonsky KS, Bowden DW, et al. β-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. *Diabetes Care*. 2014; 37(6):1751-1758. Doi: 10.2337/dc14-0396

Dali-Youcef N, Mecili M, and Ricci R, Andrès E. Metabolic inflammation: connecting obesity and insulin resistance. *Ann Med*. 2013; 45(3):242-253. Doi: 10.3109/07853890.2012.705015

Roca-Rivada A, Castelao C, Senin LL, et al. FNDC5/irisin is not only a myokine but also an adipokine. *PLoS One*. 2013; 8(4):e60563. Published 2013 Aprdoi:10.1371/journal.pone.0060563

Bunney PE, Zink AN, Holm AA, Billington CJ, Kotz CM. Orexin activation counteracts decreases in nonexercise activity thermogenesis (NEAT) caused by high-fat diet. *Physiol Behav*. 2017; 176:139-148. doi:10.1016/j.physbeh.2017.03.040

American Diabetes Association. 3. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes Care*. 2019; 42(Suppl: S29-S33. doi: 10.2337/dc19S003

Shamsuzzaman AS, Winnicki M, Wolk R, et al. Independent association between plasma leptin and Creactive protein in healthy humans. *Circulation*. 2004; 109(18):2181-2185. doi:10.1161/01.CIR.0000127960.28627.75

Leeuwenburgh C, Fiebig R, Chandwaney R, Ji LL. Aging and exercise training in skeletal muscle: responses of glutathione and antioxidant enzyme systems. *Am J Physiol*. 1994; 267(2 Pt 2):R439-R445. doi:10.1152/ajpregu.1994.267.2.R439

Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005; 28(4):956-62.

Low Wang CC, Hess CN, and Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. Circulation. 2016; 133(24):2459-502.

Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010; 375(9733):2215-22.

Cavender MA, Steg PG, Smith SC Jr, Eagle K, Ohman EM, Goto S, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation. 2015; 1 32(10):923-31.

Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, et al.

Online ISSN 3007-3197
Print ISSN 3007-3189

Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. Stroke. 2012; 43(5):1212-7.

Lakshmi SS, Sarella PN, Adarsh K, Padmini PL, Kumar MV. Concurrent Diagnosis of Renal Calculi, Uterine Fibroids and Ovarian Cysts: A Complex Case Study. Journal of Clinical and Pharmaceutical Research. 2023 Oct 24:22-7

Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications, World Health Organization, Department of Non Communicable Disease Surveillance, Geneva, Switzerland, 1999.

American Diabetes Association, "Gestational diabetes mellitus," *Diabetes Care*, vol. 23, pp. 77–79, 2000.

L. Jovanovic and D. J. Pettitt, "Gestational diabetes mellitus, *"The Journal of the American Medical Association*, vol. 286, no. 20, pp. 2516–2518, 2001.

D. Coustan, "Gestational diabetes," in *Diabetes in America*, M. I. Harris, C. C. Cowie, M. P. Stern, E. J. Boyko, G. E. Reiber, and P. H. Bennett, Eds., pp. 703–717, U.S. Government Printing Office, Washington, DC, USA, 2nd edition, 1995.

American Diabetes Association, "Diagnosis and classification of diabetes mellitus," *Diabetes Care*, vol. 33, supplement 1, pp. S62–S69, 2010.

D. E. Moller, "New drug targets for type 2 diabetes and the metabolic syndrome," *Nature*, vol. 414, no. 6865, pp. 821–827, 2001.

J. McKinlay and L. Marceau, "US public health and the 21st century: diabetes mellitus," *The Lancet*, vol. 356, no. 9231, pp. 757–761, 2000.

H. M. Kronenberg, S. Melmed, K. S. Polonsky, and P. R. Larsen, *Williams Textbook of Endocrinology*, Saunders, Philadelphia, Pa, USA, 11th edition, 2008.

Banday, M. Z., Sameer, A. S., & Nissar, S. (2020). Pathophysiology of diabetes: An overview. *Avicenna journal of medicine*, *10*(04), 174-188.

Banday, M. Z., Sameer, A. S., & Nissar, S. (2020). Pathophysiology of diabetes: An overview. *Avicenna journal of medicine*, *10*(04), 174-188.

Baynes HW. Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. Journal of Diabetes and Metabolism. 2015; 6: 1–9.

Ozougwu JC, Obimba KC, Belonwu CD, Unakalamba CB. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. Journal of Physiology and Pathophysiology. 2013; 4: 46–57.

Oktay AA, Akturk HK, Esenboğa K, Javed F, Polin NM, Jahangir E. Pathophysiology and Prevention of Heart Disease in Diabetes Mellitus. Current Problems in Cardiology. 2018; 43: 68–110.

Guthrie RA, Guthrie DW. Pathophysiology of diabetes mellitus. Critical Care Nursing Quarterly. 2004; 27: 113–125.

Roep BO. The role of T-cells in the pathogenesis of Type 1 diabetes: from cause to cure. Diabetologia. 2003; 46: 305–321

Scheen AJ. Pathophysiology of type 2 diabetes. Acta Clinica Belgica. 2003; 58: 335–341.

Kaku KAKU. Pathophysiology of Type 2 Diabetes and Its Treatment Policy. JMAJ. 2010; 53: 41–46.

Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet (London, England). 2014; 383: 1068–1083.

Annual Methodological Archive Research Review
http://amresearchreview.com/index.php/Journal/about
Volume 4, Issue 4 (2026)

Online ISSN 3007-3197
Print ISSN 3007-3189

http://amresearchreview.com/index.php/Journal/about

Cornell S. Continual evolution of type 2 diabetes: an update on pathophysiology and emerging treatment options. Therapeutics and Clinical Risk Management. 2015; 11: 621–632.

Kim J, Lee J. Role of obesity-induced inflammation in the development of insulin resistance and type 2 diabetes: history of the research and remaining questions. Annals of Pediatric Endocrinology & Metabolism. 2021; 26: 1–13.

Almourani R, Chinnakotla B, Patel R, Kurukulasuriya LR, Sow ers J. Diabetes and Cardiovascular Disease: an Update. Current Diabetes Reports. 2019; 19: 161.

Ohiagu, F. O., Chikezie, P. C., & Chikezie, C. M. (2021). Pathophysiology of diabetes mellitus complications: Metabolic events and control. *Biomedical Research and Therapy*, *8*(3), 4243-4257.

Yau, J. W. Y., Rogers, S. L., Kawasaki, R., Lamoureux, E. L., Kowalski, J. W., Bek, T., Chen, S.-J., Dekker, J. M., Fletcher, A., Grauslund, J., Haffner, S., Hamman, R. F., Ikram, M. K., Kayama, T., Klein, B. E. K., Klein, R., Krishnaiah, S., Mayurasakorn, K., O'Hare, J. P., Meta-Analysis for Eye Disease (META-EYE) Study Group. (2012). Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care, 35(3), 556– 564. https://doi.org/10.2337/dc11-1909

Lechner, J., O'Leary, O. E., & Stitt, A. W. (2017). The pathology associated with diabetic retinopathy. Vision Research, 139, 7–14. https://doi.org/10.1016/j.visres.2017.04.003

Moreno, A., Lozano, M., & Salinas, P. (2013). Diabetic retinopathy. Nutricion Hospitalaria, 28 Suppl 2, 53–56. https://doi.org/10.3305/ nh.2013.28.sup 2. 67 14.

Dewanjee, S., Das, S., Das, A. K., Bhattacharjee, N., Dihingia, A., Dua, T. K., Kalita, J., &

Manna, P. (2018). Molecular mechanism of diabetic neuropathy and its pharmacotherapeutic targets. European Journal of Pharmacology, 833, 472–523. https://doi.org/10.1016/j.ejphar.2018.06.034

Feldman, E. L., Callaghan, B. C., Pop-Busui, R., Zochodne, D. W., Wright, D. E., Bennett, D.

L., Bril, V., Russell, J. W., & Viswanathan, V. (2019). Diabetic neuropathy. Nature Reviews. Disease Primers, 5(1), 41. https://doi.org/10.1038/s41572-019-0092-1

Malik, R. A. (2020). Diabetic neuropathy: A focus on small fibres. Diabetes/Metabolism Research and Reviews, 36 Suppl 1, e3255. https://doi.org/10.1002/dmrr.3255

Papadopoulou-Marketou, N., Chrousos, G. P., & Kanaka-Gantenbein, C. (2017). Diabetic nephropahy in type 1 diabetes: a review of early natural history, pathogenesis, and diagnosis. Diabetes/Metabolism Research and Reviews, 33(2). https://doi.org/10.1002/dmrr.2841.

Long B, Lentz S, Koyfman A, Gottlieb M. Euglycemic diabetic ketoacidosis: Etiologies, evaluation, and management. Am J Emerg Med. 2021 Jun; 44: 157-160. Doi: 10.1016/j.ajem.2021.02.015

Viigimaa, M., Sachinidis, A., Toumpourleka, M., Koutsampasopoulos, K., Alliksoo, S., & Titma, T. (2020). Macrovascular Complications of Type 2 Diabetes

Online ISSN 3007-3197
Print ISSN 3007-3189

Mellitus. Current Vascular Pharmacology, 18(2), 110–116. https://doi.org/10.2174/1570161117666190405165151.

Kannel, W.B.; Hjortland, M.; Castelli, W.P. Role of diabetes in congestive heart failure: The Framingham study. Am. J. Cardiol. 1974, 34, 29–34. [Google Scholar] [CrossRef]

Cosentino, F.; Grant, P.J.; Aboyans, V.; Bailey, C.J.; Ceriello, A.; Delgado, V.; Federici, M.; Filippatos, G.; Grobbee, D.E.; Hansen, T.B.; et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur. Heart J. 2020, 41, 255–323. [Google Scholar] [CrossRef] [Green Version]

Wang, Z.V.; Hill, J.A. Diabetic cardiomyopathy: Catabolism driving metabolism. Circulation 2015, 131, 771–773. [Google Scholar] [CrossRef]

Lee, W.S.; Kim, J. Diabetic cardiomyopathy: Where we are and where we are going. Korean J. Intern. Med. 2017, 32, 404–421. [Google Scholar] [CrossRef] [PubMed] [Green Version]

Jia, G.; Hill, M.A.; Sowers, J.R. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. Circ. Res. 2018, 122, 624–638. [Google Scholar] [CrossRef] [PubMed]

Dillmann, W.H. Diabetic Cardiomyopathy. Circ. Res. 2019, 124, 1160–1162. [Google Scholar] [CrossRef] [PubMed

Bando, Y.K.; Murohara, T. Diabetes-related heart failure. Circ. J. 2014, 78, 576–583. [Google Scholar] [CrossRef] [PubMed] [Green Version]

Quinaglia, T.; Oliveira, D.C.; Matos-Souza, J.R.; Sposito, A.C. Diabetic cardiomyopathy: Factual or factoid? Rev. Assoc. Med. Bras. 2019, 65, 61–69. [Google Scholar] [CrossRef]

86.Yancy, C.W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D.E., Jr.; Drazner, M.H.; Fonarow, G.C.; Geraci, S.A.; Horwich, T.; Januzzi, J.L.; et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J. Am. Coll. Cardiol. 2013, 62, e147–e239. [Google Scholar] [CrossRef] [Green Version]

Henning, R. J. (2018). Type-2 diabetes mellitus and cardiovascular disease. Future Cardiology,

14(6), 491–509. https://doi.org/10.2217/fca-2018-0045

Htay, T., Soe, K., Lopez-Perez, A., Doan, A. H., Romagosa, M. A., & Aung, K. (2019). Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. Current Cardiology Reports, 21(6), 45. https://doi.org/10.1007/s11886-019-1133-9.

Georgakis, M. K., Harshfield, E. L., Malik, R., Franceschini, N., Langenberg, C., Wareham, N. J., Markus, H. S., & Dichgans, M. (2021). Diabetes Mellitus, Glycemic Traits, and Cerebrovascular Disease: A Mendelian Randomization Study. Neurology, 96(13), e1732–e1742. https://doi.org/10.1212/WNL.0000000000011555

Phipps, M. S., Jastreboff, A. M., Furie, K., & Kernan, W. N. (2012). The diagnosis and management of cerebrovascular disease in diabetes. Current Diabetes

Online ISSN 3007-3197
Print ISSN 3007-3189

Reports, 12(3), 314–323. https://doi.org/10.1007/s11892-012-0271-x

van Sloten, T. T., Sedaghat, S., Carnethon, M. R., Launer, L. J., & Stehouwer, C. D. A. (2020). Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. The Lancet. Diabetes & Endocrinology, 8(4), 325–336. https://doi.org/10.1016/S2213-858 7(19)30405-X

American Diabetes Association. (2003). Peripheral arterial disease in people with diabetes. Diabetes Care, 26(12), 3333–3341. https://doi.org/10.2337/diacare.26.12.3333

Barnes, J. A., Eid, M. A., Creager, M. A., & Goodney, P. P. (2020). Epidemiology and Risk of Amputation in Patients with Diabetes Mellitus and Peripheral Artery Disease. Arteriosclerosis, Thrombosis, and Vascular Biology, 40(8), 1808–1817. https://doi.org/10.1161/ATVBAHA.120.314595

Firnhaber, J. M., & Powell, C. S. (2019). Lower Extremity Peripheral Artery Disease: Diagnosis and Treatment. American Family Physician, 99(6), 362–369.

Mascarenhas, J. V, Albayati, M. A., Shearman, C. P., & Jude, E. B. (2014). Peripheral arterial disease. Endocrinology and Metabolism Clinics of North America, 43(1), 149–166. https://doi.org/10.1016/j.ecl.2013.09.003

Berhanu P, Kipnes MS, Khan MA, Perez AT, Kupfer SF, Spanheimer RC, et al. Effects of pioglitazone on lipid and lipoprotein profiles in patients with type 2 diabetes and dyslipidaemia after treatment conversion from rosiglitazone while continuing stable statin therapy. Diabetes & Vascular Disease Research. 2006; 3: 39–44.

Bloomgarden ZT. Cardiovascular disease and diabetes. Diabetes Care. 2003; 26: 230–237.

Flegal KM, Graubard BI, Williamson DF, Gail MH. Causespecific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007; 298: 2028–2037

Balkau B, Deanfield JE, Després JP, Bassand JP, Fox KAA, Smith SC, Jr, et al. International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. Circulation. 2007; 116: 1942– 1951

Sosale A, Saboo B, Sosale B. Saroglitazar for the treatment of hypertrig-lyceridemia in patients with type 2 diabetes: current evidence. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2015; 8: 189–196

Ghosh RK, Ghosh GC, Gupta M, Bandyopadhyay D, Akhtar T, Deedwania P, et al. Sodium Glucose Co-transporter 2 Inhibitors and Heart Failure. The American Journal of Cardiology. 2019; 124: 1790–1796.

Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine. 2016; 375: 1834–1844.

Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006; 29: 2102–2107

Zarich SW, Nesto RW. Implications and treatment of acute hyperglycemia in the setting of acute myocardial infarction. Circulation. 2007; 115: e436–e439.

Online ISSN 3007-3197
Print ISSN 3007-3189

Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet (London, England). 2019; 393: 31–39.

Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. The Lancet. Diabetes & Endocrinology. 2018; 6: 105–113.

Naseri MW, Esmat HA, Bahee MD. Prevalence of hypertension in Type-2 diabetes mellitus. Annals of Medicine and Surgery (2012). 2022; 78: 103758

Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The New England Journal of Medicine. 2000; 342: 145–153.

Patel BM, Mehta AA. Choice of anti-hypertensive agents in diabetic subjects. Diabetes & Vascular Disease Research. 2013; 10: 385–396.

Sowers JR, Haffner S. Treatment of cardiovascular and renal risk factors in the diabetic hypertensive. Hypertension (Dallas, Tex.: 1979). 2002; 40: 781–788.

Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. Hypertension (Dallas, Tex.: 1979). 2001; 37: 1053–1059.

UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospec tive Diabetes Study Group. BMJ (Clinical Research Ed.). 1998; 317: 713–720.

Haile K, Timerga A. Dyslipidemia and Its Associated Risk Factors among Adult Type-2 Diabetic Patients at Jimma University Medical Center, Jimma, Southwest Ethiopia. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2020; 13: 4589–4597.

Taha D. Hyperlipidemia in children with type 2 diabetes mellitus. Journal of Pediatric Endocrinology & Metabolism: JPEM. 2002; 15 Suppl 1: 505–507.

Chahil TJ, Ginsberg HN. Diabetic dyslipidemia. Endocrinology and Metabolism Clinics of North America. 2006; 35: 491– 510, vii–viii.

de Oliveira LLH, de Assis ACR, Giraldez VZR, Scudeler TL, Soares PR. Dyslipidemia: A Narrative Review on Pharmacotherapy. Pharmaceuticals (Basel, Switzerland). 2024; 17: 289.

Khan Y. Aziz I, Bihari B, Kumar H, Roy M, Verma VK. A Review- Phytomedicines Used in Treatment of Diabetes. Asian Journal of Pharmaceutical research; 2014:4–3

Giovannini P, Jayne MR, Howes E, E S. Medicinal plants used in the traditional management of diabetes and its sequelae in Central America: a review. Journal of. Ethno pharmacology; 2016(2).

Malvi R, Jain S, Khatri S, Patel A, Mishra S. A Review on Antidiabetic Medicinal Plants and Marketed Herbal Formulations. International Journal of Pharmaceutical & Biological Archives; 2011(2):1344–1355.

Rahimi M. A Review: Anti Diabetic medicinal plants used for diabetes mellitus. Bulletin of environmental, pharmacology and life. Sciences; 2015(4):163–

Online ISSN 3007-3197
Print ISSN 3007-3189

180.

Gebreyohannes G, Gebreyohannes M. Medicinal values of garlic: A review. International. Journal of Medicine and Medical Sciences; 2013(5):401–408.

Lakshmi MS. Rani KSS, Reddy UKT. A review on diabetes mellitus and the herbal plants used for its treatment. Asian. Journal of pharmaceutical and clinical research; 2012(5):15–21.

Bordoloi R, Dutta KN. A Review on Herbs Used in the Treatment of Diabetes mellitus. Journal of Pharmaceutical, Chemical and Biological. Sciences; 2014(2):86–92.

Aloke C, Egwa CO, Aja PM, Obasi NA, Chukwu J, Akumadu BO, Ogbu PN and Achilonu I. (2022). Current Advances in the Management of Diabetes Mellitus. Biomedicines. 10(10):2436. Doi: 10.3390/biomedicines10102436

Gurvinder Singh, Rajesh Kumar, Desna DS, Manish Chaudhary Kaur Navneet Current Diabetes Reviews 20 (6), 89-109, 2024

Devajit Mohajan, Haradhan Kumar Mohanjan Journal of Innovations in Medical Research 3 (1), 14-19, 2024

S Narade Pharmacol. Discov 4, 18, 2024

GJ Wang, XK Li, K Sakai, L Cai - Human & experimental …, 2008 - journals.sagepub.com

Williams DM, Jones H and Stephens JW. (2022). Personalized Type 2 Diabetes Management: An Update on Recent Advances and Recommendations. Diabetes Metab Syndr Obes.15:281-295.

Ajala, O., English, P., & Pinkney, J. (2013). Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. The American Journal of Clinical Nutrition, 97(3), 505–516. https://doi.org/10.3945/ajcn.112.042457

Boulé, N. G., Haddad, E., Kenny, G. P., Wells, G. A., & Sigal, R. J. (2001). Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA, 286(10), 1218–1227. https://doi.org/10.1001/jama.286.10.1218

Gregg, E. W., Chen, H., Wagenknecht, L. E., Clark, J. M., Delahanty, L. M., Bantle, J., Pownall, H. J., Johnson, K. C., Safford, M. M., Kitabchi, A. E., Pi-Sunyer, F. X., Wing, R. R., Bertoni, A. G., & Look AHEAD Research Group. (2012). Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA, 308(23), 2489– 2496. https://doi.org/10.1001/jama.2012.67929

Snowling, N. J., & Hopkins, W. G. (2006). Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a metaanalysis. Diabetes Care, 29(11), 2518–2527. https://doi.org/10.2337/dc06-1317

Steven, S., & Taylor, R. (2015). Restoring normoglycemia by use of a very low calorie diet in long- and short-duration Type 2 diabetes. Diabetic Medicine : A Journal of the British Diabetic Association, 32(9), 1149–1155. https://doi.org/10.1111/dme.12722

American Diabetes Association. (2020). 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. Diabetes Care,

Online ISSN 3007-3197
Print ISSN 3007-3189

43(Suppl 1), S98–S110. https://doi.org/10.2337/dc20-S009

Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. W. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. The New England Journal of Medicine, 359(15), 1577–1589. https://doi.org/10.1056/NEJMoa0806470

Home, P. D., Pocock, S. J., Beck-Nielsen, H., Curtis, P. S., Gomis, R., Hanefeld, M., Jones, N. P., Komajda, M., McMurray, J. J. V, & RECORD Study Team. (2009). Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet (London, England), 373(9681), 2125–2135. https://doi.org/10.1016/S0140-6736(09)60953-3

Joshi, S. R., Standl, E., Tong, N., Shah, P., Kalra, S., & Rathod, R. (2015). Therapeutic potential of α-glucosidase inhibitors in type 2 diabetes mellitus: an evidence-based review. Expert Opinion on Pharmacotherapy, 16(13), 1959–1981. https://doi.org/10.1517/14656566.2015.1070827

Kajbaf, F., & Lalau, J.-D. (2014). Mortality rate in so-called " metformin-associated lactic acidosis": a review of the data since the 1960s. Pharmacoepidemiology and Drug Safety, 23(11), 1123–1127. https://doi.org/10.1002/pds.3

Leonard, C. E., Han, X., Brensinger, C. M., Bilker, W. B., Cardillo, S., Flory, J. H., & Hennessy, S. (2018). Comparative risk of serious hypoglycemia with oral antidiabetic monotherapy: A retrospective cohort study. Pharmacoepidemiology and Drug Safety, 27(1), 9–18. https://doi.org/10.1002/pds.4337

van de Laar, F. A., Lucassen, P. L., Akkermans, R. P., van de Lisdonk, E. H., Rutten, G. E., & van Weel, C. (2005). Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care, 28(1), 154–163. https://doi.org/10.2337/diacare.28.1.154

Yin, J., Deng, H., Qin, S., Tang, W., Zeng, L., & Zhou, B. (2014). Comparison of repaglinide and metformin versus metformin alone for type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Research and Clinical Practice, 105(3), e10-5. https://doi.org/10.1016/j.diabres.2014.06.009

Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. W. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. The New England Journal of Medicine, 359(15), 1577–1589. https://doi.org/10.1056/NEJMoa0806470

Swinnen, S. G., Hoekstra, J. B., & DeVries, J. H. (2009). Insulin therapy for type 2 diabetes. Diabetes Care, 32 Suppl 2(Suppl 2), S253-9. https://doi.org/10.2337/dc09-S318 Taylor, M. J., Chauhan, K. P., & Sahota, T. S. (2020). Gels for constant and smart delivery of insulin. British Journal of Diabetes, 20(1), 41–51. https://doi.org/10.15277/bjd.2020.248

Hirsch, I. B., Farkas-Hirsch, R., & Skyler, J. S. (1990). Intensive insulin therapy for treatment of type I diabetes. Diabetes Care, 13(12), 1265–1283. https://doi.org/10.2337/diacare.13.12.1265

Silver, B., Ramaiya, K., Andrew, S. B., Fredrick, O., Bajaj, S., Kalra, S., Charlotte, B. M., Claudine, K., & Makhoba, A. (2018). EADSG Guidelines: Insulin

Online ISSN 3007-3197
Print ISSN 3007-3189

Therapy in Diabetes. Diabetes Therapy : Research, Treatment and Education of Diabetes and Related Disorders, 9(2), 449–492. https://doi.org/10.1007/s13300-018-0384-6

Alam, F., Islam, M. A., Mohamed, M., Ahmad, I., Kamal, M. A., Donnelly, R., Idris, I., & Gan, S. H. (2019). Efficacy and Safety of Pioglitazone Monotherapy in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Scientific Reports, 9(1), 5389. https://doi.org/10.1038/s41598-019-41854-2

American Diabetes Association. (2020). 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. Diabetes Care, 43(Suppl 1), S98–S110. https://doi.org/10.2337/dc20-S009

Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. W. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. The New England Journal of Medicine, 359(15), 1577–1589. https://doi.org/10.1056/NEJMoa0806470

Home, P. D., Pocock, S. J., Beck-Nielsen, H., Curtis, P. S., Gomis, R., Hanefeld, M., Jones, N. P., Komajda, M., McMurray, J. J. V, & RECORD Study Team. (2009). Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet (London, England), 373(9681), 2125–2135. https://doi.org/10.1016/S0140-6736(09)60953-3

Joshi, S. R., Standl, E., Tong, N., Shah, P., Kalra, S., & Rathod, R. (2015). Therapeutic potential of α-glucosidase inhibitors in type 2 diabetes mellitus: an evidence-based review. Expert Opinion on Pharmacotherapy, 16(13), 1959–1981. https://doi.org/10.1517/14656566.2015.1070827

Kajbaf, F., & Lalau, J.-D. (2014). Mortality rate in so-called " metformin-associated lactic acidosis": a review of the data since the 1960s. Pharmacoepidemiology and Drug Safety, 23(11), 1123–1127. https://doi.org/10.1002/pds.3689

Leonard, C. E., Han, X., Brensinger, C. M., Bilker, W. B., Cardillo, S., Flory, J. H., & Hennessy, S. (2018). Comparative risk of serious hypoglycemia with oral antidiabetic monotherapy: A retrospective cohort study. Pharmacoepidemiology and Drug Safety, 27(1), 9–18. https://doi.org/10.1002/pds.4337

Van de Laar, F. A., Lucassen, P. L., Akkermans, R. P., van de Lisdonk, E. H., Rutten, G. E., & van Weel, C. (2005). Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care, 28(1), 154–163. https://doi.org/10.2337/diacare.28.1.154

Yin, J., Deng, H., Qin, S., Tang, W., Zeng, L., & Zhou, B. (2014). Comparison of repaglinide and metformin versus metformin alone for type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Research and Clinical Practice, 105(3), e10-5. https://doi.org/10.1016/j.diabres.2014.06.009

Clemmensen, C., Chabenne, J., Finan, B., Sullivan, L., Fischer, K., Küchler, D., Sehrer, L., Ograjsek, T., Hofmann, S. M., Schriever, S. C., Pfluger, P. T., Pinkstaff, J., Tschöp, M. H., Dimarchi, R., & Müller, T. D. (2014). GLP-1/glucagon coagonism restores leptin responsiveness in obese mice

Online ISSN 3007-3197
Print ISSN 3007-3189

chronically maintained on an obesogenic diet. Diabetes, 63(4), 1422–1427. https://doi.org/10.2337/db13-1609

Grasso, P. (2011). Novel approaches to the treatment of obesity and type 2 diabetes mellitus: bioactive leptin-related synthetic peptide analogs. Recent Patents on Endocrine, Metabolic & Immune Drug Discovery, 5(3), 163–175. https://doi.org/10.2174/187221411797265917

Moon, H.-S., Chamberland, J. P., & Mantzoros, C. S. (2012). Amylin and leptin activate overlapping signalling pathways in an additive manner in mouse GT1-7 hypothalamic, C_2C_{12} muscle and AML12 liver cell lines. Diabetologia, 55(1), 215–225. https://doi.org/10.1007/s00125-011-2332-0

Finan, B., Ma, T., Ottaway, N., Müller, T. D., Habegger, K. M., Heppner, K. M., Kirchner, H., Holland, J., Hembree, J., Raver, C., Lockie, S. H., Smiley, D. L., Gelfanov, V., Yang, B., Hofmann, S., Bruemmer, D., Drucker, D. J., Pfluger, P. T., Perez-Tilve, D., … Tschöp, M. H. (2013). Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. Science Translational Medicine, 5(209), 209ra151. https://doi.org/10.1126/scitranslmed.3007218

169. Finan, B., Yang, B., Ottaway, N., Smiley, D. L., Ma, T., Clemmensen, C., Chabenne, J., Zhang, L., Habegger, K. M., Fischer, K., Campbell, J. E., Sandoval, D., Seeley, R. J., Bleicher, K., Uhles, S., Riboulet, W., Funk, J., Hertel, C., Belli, S., … Tschöp, M. H. (2015). A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. Nature Medicine, 21(1), 27–36. https://doi.org/10.1038/nm.3761

Fodor, A., Harel, C., Fodor, L., Armoni, M., Salmon, P., Trono, D., & Karnieli, E. (2007). Adult rat liver cells transdifferentiated with lentiviral IPF1 vectors reverse diabetes in mice: an ex vivo gene therapy approach. Diabetologia, 50(1), 121–130. https://doi.org/10.1007/s00125-006-0509-8

Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. W. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. The New England Journal of Medicine, 359(15), 1577–1589. https://doi.org/10.1056/NEJMoa0806470

Kuroda, M., Bujo, H., Aso, M., & Saito, Y. (2011). Adipocytes as a vehicle for ex vivo gene therapy: Novel replacement therapy for diabetes and other metabolic diseases. Journal of Diabetes Investigation, 2(5), 333–340. https://doi.org/10.1111/j.20401124.2011.00133.x

Zalzman, M., Gupta, S., Giri, R. K., Berkovich, I., Sappal, B. S., Karnieli, O., Zern, M. A., Fleischer, N., & Efrat, S. (2003). Reversal of hyperglycemia in mice by using human expandable insulin-producing cells differentiated from fetal liver progenitor cells. Proceedings of the National Academy of Sciences of the United States of America, 100(12), 7253–7258. https://doi.org/10.1073/pnas.1136854100

Auricchio, A., GAO, G.-P., Yu, Q. C., Raper, S., Rivera, V. M., Clackson, T., & Wilson, J. M. (2002). Constitutive and regulated expression of processed insulin following in vivo hepatic gene transfer. Gene Therapy, 9(14), 963–971. https://doi.org/10.1038/sj.gt.3301746

Chan, L., Fujimiya, M., & Kojima, H. (2003). In vivo gene therapy for diabetes

Online ISSN 3007-3197
Print ISSN 3007-3189

mellitus. Trends in Molecular Medicine, 9(10), 430–435. https://doi.org/10.1016/j.molmed.2003.08.003

Kojima, H., Fujimiya, M., Matsumura, K., Younan, P., Imaeda, H., Maeda, M., & Chan, L. (2003). NeuroD-betacellulin gene therapy induces islet neogenesis in the liver and reverses diabetes in mice. Nature Medicine, 9(5), 596–603. https://doi.org/10.1038/nm867

Morral, N., Mc Evoy, R., Dong, H., Meseck, M., Altomonte, J., Thung, S., & Woo, S. L. C. (2002). Adenovirus-mediated expression of glucokinase in the liver as an adjuvant treatment for type 1 diabetes. Human Gene Therapy, 13(13), 1561–1570. https://doi.org/10.1089/10430340260201653

O'Doherty, R. M., Lehman, D. L., Télémaque-Potts, S., & Newgard, C. B. (1999). Metabolic impact of glucokinase overexpression in liver: lowering of blood glucose in fed rats is accompanied by hyperlipidemia. Diabetes, 48(10), 2022–2027. https://doi.org/10.2337/diabetes.48.10.2022

Ferber, S., Halkin, A., Cohen, H., Ber, I., Einav, Y., Goldberg, I., Barshack, I., Seijffers, R., Kopolovic, J., Kaiser, N., & Karasik, A. (2000). Pancreatic and duodenal homeobox gene 1 induces expression of insulin genes in liver and ameliorates streptozotocin-induced hyperglycemia. Nature Medicine, 6(5), 568–572. https://doi.org/10.1038/75050

Hori, Y. (2009). Insulin-producing cells derived from stem/progenitor cells: therapeutic implications for diabetes mellitus. Medical Molecular Morphology, 42(4), 195–200. https://doi.org/10.1007/s00795-009-0471-x

Maehr, R., Chen, S., Snitow, M., Ludwig, T., Yagasaki, L., Goland, R., Leibel, R. L., & Melton, D. A. (2009). Generation of pluripotent stem cells from patients with type 1 diabetes. Proceedings of the National Academy of Sciences of the United States of America, 106(37), 15768–15773. https://doi.org/10.1073/pnas.0906894106

Meier, J. J., Bhushan, A., & Butler, P. C. (2006). The potential for stem cell therapy in diabetes. Pediatric Research, 59(4 Pt 2), 65R-73R. https://doi.org/10.1203/01.pdr.0000206857.38581.49

Millman, J. R., & Pagliuca, F. W. (2017). Autologous Pluripotent Stem Cell-Derived β-Like Cells for Diabetes Cellular Therapy. Diabetes, 66(5), 1111–1120. https://doi.org/10.2337/db16-16

Pagliuca, F. W., Millman, J. R., Gürtler, M., Segel, M., Van Dervort, A., Ryu, J. H., Peterson, Q. P., Greiner, D., & Melton, D. A. (2014). Generation of functional human pancreatic β cells in vitro. Cell, 159(2), 428–439. https://doi.org/10.1016/j.cell.2014.09.040

Spaggiari, G. M., Abdelrazik, H., Becchetti, F., & Moretta, L. (2009). MSCs inhibit monocytederived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2. Blood, 113(26), 6576– 6583. https://doi.org/10.1182/blood-2009-02-203943

Stock, A. A., Manzoli, V., De Toni, T., Abreu, M. M., Poh, Y.-C., Ye, L., Roose, A., Pagliuca, F. W., Thanos, C., Ricordi, C., & Tomei, A. A. (2020). Conformal Coating of Stem Cell Derived Islets for β Cell Replacement in Type 1 Diabetes. Stem Cell Reports, 14(1), 91– 104.

Online ISSN 3007-3197
Print ISSN 3007-3189

https://doi.org/10.1016/j.stemcr.2019.11.004

Voltarelli, J. C., Couri, C. E. B., Stracieri, A. B. P. L., Oliveira, M. C., Moraes, D. A., Pieroni, F., Coutinho, M., Malmegrim, K. C. R., Foss-Freitas, M. C., Simões, B. P., Foss, M. C., Squiers, E., & Burt, R. K. (2007). Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. JAMA, 297(14), 1568–1576. https://doi.org/10.1001/jama.297.14.1568

Hanna, J., Bteich, M., Tawk, Y., Ramadan, A. H., Dia, B., Asadallah, F. A., Eid, A., Kanj, R., Costantine, J., & Eid, A. A. (2020). Noninvasive, wearable, and tunable electromagnetic multisensing system for continuous glucose monitoring, mimicking vasculature anatomy. Science Advances, 6(24), eaba5320. https://doi.org/10.1126/sciadv.aba5320