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Management of Diabetes Mellitus (DM) and it's Complications: A Literature Review

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disease that occurs when insulin is either absent and/or has impaired action (insulin resistance). Diabetes mellitus (DM) is accompanied by several complications including macrovascular and microvascular complications. Appropriate management plays an important role in reducing morbidity and mortality rates due to complications of diabetes mellitus.

Keywords: Diabetes Mellitus; Treatment; Management; Complications

1. Introduction

1.1. Definition of Diabetes Mellitus (DM)

Diabetes mellitus (DM) is a chronic metabolic disease, involving improperly elevated blood glucose levels. Diabetes mellitus (DM) occurs when there is an imbalance between insulin produced by the beta cells of the pancreas and glucagon produced by the alpha cells of the pancreas, causing imbalanced glucose levels. In the case of DM, insulin is either absent and/or has impaired action (insulin resistance), and thus leads to hyperglycemia (Sapra and Bhandari, 2023). According to American Diabetes Association (2023), the diagnostic criteria for diabetes mellitus are determined if A1C ≥6,5% or fasting blood glucose ≥126 mg/dL or two-hour blood glucose ≥200 mg/dL or in patients with severe diabetes symptoms, random plasma glucose ≥200 mg/dL.

1.1.1. Types of Diabetes Mellitus (DM)

Type I

Type I DM occurs due to destruction of pancreatic beta cells caused by autoimmune disease which occurs in 90% of individuals (Solis-Herrera et al., 2018). Pancreatic destruction occurs because the body's immune system, which is tasked to fighting foreign susbstances, has mistaken the pancreas for a foreign substance and harms the body, so the immune system attacks pancreatic cells (Burrack, Martinov and Fife, 2017). In this type of DM, there is an absolute insulin deficiency which can be determined by the level of c-peptide protein which is small or not detected at all (American Diabetes Association, 2019). This type of diabetes can occur at any age, especially in children and adolescents. Younger people usually have a rapid rate of beta-cell destruction and develop ketoacidosis, whereas adults often prevent ketoacidosis for years due to adequate insulin secretory defenses (Los and Wilt, 2022).

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Type II

Type II diabetes is caused by insulin resistance and, at least initially, a relative deficiency of insulin secretion. In absolute terms, plasma insulin concentrations are insufficient to maintain normal glucose homeostasis even though compensation has occured by plasma insulin concentrations (fasting and eating) which are usually relatively increased. However, as time goes by, progressive beta cell failure occurs and increasingly severe insulin deficiency occurs (Solis-Herrera et al., 2018). According to the American Diabetes Association, in 2010 type II DM was the most common form of diabetes mellitus and accounted for 90-95% of diabetes cases (American Diabetes Association, 2012). Family history of diabetes, unhealthy lifestyle, old age, obesity, lack of physical activity, genetics and certain races or ethnicities are risk factors for type II diabetes mellitus (Deshpande, Harris-Hayes and Schootman, 2018). According to several studies that have been carried out previously, a large number of genes play a role in being risk factors for type II DM, but these genes explain the low percentage of heritability of the disease (Solis-Herrera et al., 2018).

Gestational Diabetes

Gestational diabetes mellitus (GDM) is defined when glucose intolerance is first recognized during pregnancy. The incidence of gestational diabetes mellitus (GDM) mostly appears in the third trimester of pregnancy. At least 6 weeks after the pregnancy ends, the woman should undergo an oral glucose tolerance test and be reclassified as having diabetes, normal glucose tolerance, impaired glucose tolerance, or impaired fasting glucose. Gestational diabetes compllicates approximately 8-9% of all pregnancies, although this figure may be double in populations at high risk of developing type II diabetes (Solis-Herrera et al., 2018).

1.1.2. Sign and Symptoms of Diabetes Mellitus (DM)

People ignore the signs and symptoms of diabetes mellitus because of the chronic development of the disease and lack of awareness of the consequences of hyperglycemia. People are not aware that damage can occur years before symptoms become noticeable. Even though early symptoms can help to get the DM under control before complications occur (Ramachandran, 2014).

Main Symptoms (Hasanah et al., 2017)

- Frequent urination
- Easily to feel hungry
- Often feel thirsty

Additional Symptoms (Ramachandran, 2014)

- Unexplained weight loss
- Frequent fatigue
- Irritability
- Reapeated Infections
- Dry mouth
- Decreased vision
- Itching
- Burning or numbness on feet
- Impotence or erectile dysfunction

2. Management of Diabetes Mellitus (DM)

2.1. Oral Anti-Diabetic Drug

2.1.1. Sulfonylureas (Glipizide, Glyburide, Gliclazide, Glimepiride)

Sulfonylureas operate by inhibiting adenosine triphosphate-sensitive potassium channels (K-ATP channels). They form bonds with these channels in pancreatic beta cells, modifying the resting membrane potential of the cells. This alteration leads to an influx of calcium, consequently stimulating the secretion of insulin (de Wet and Proks, 2015). Sulfonylureas is contraindicated to use in people who have a history of hypersensitivity to the drug or sulfonamide derivatives, diabetic ketoacidosis, and type I diabetes mellitus (DM). Sulfonylureas can cause adverse effects such as dizziness, hypoglycemia, nervousness, vomitting, and syncope (Kavitha Ganesan and Senan Sultan, 2019).

2.1.2. Metformin

Metformin act through the mechanism of reducing hepatic gluconeogenesis and lipogenesis and increasing insulin-mediated glucose uptake in muscle by increasing hepatic adenosine monophosphate-activated protein kinase activity (Rena, Hardie and Pearson, 2017). Metformin is contraindicated to use in people who have hypersensitivity to the drug, severe renal dysfunction (eGFR less than 30 mL/minute/1.73 m2), and metabolic acidosis, including diabetic ketoacidosis. Metformin can cause adverse effects such as diarrhea, nausea, vomiting, headache, chest discomfort, vit B 12 deficiency, and skin rash (Kavitha Ganesan and Senan Sultan, 2019).

2.1.3. Alpha-Glucosidase Inhibitors (Acarbose, Miglitol, Voglibose)

Alpha-glucosidase inhibitors act through the mechanism of inhibit the alpha-glucosidase enzyme in intestinal border cells that figest food starch, thereby inhibiting the reabsorption of polysaccharides and the metabolism of sucrose into glucose and fructose (Akmal and Wadhwa, 2020). Alpha-glucosidase is contraindicated to use in people who have hypersensitivity to acarbose, cirrhosis, diabetic ketoacidosis, inflammatory bowel disease, partial intestinal obstruction, and ulcers of the intestine. Alpha-glucosidase can cause adverse effects such as flatulence, diarrhea, and abdominal pain (Kavitha Ganesan and Senan Sultan, 2019).

2.1.4. Thiazolidinediones (Rosiglitazone, Pioglitazone)

Thiazolidinediones act through the mechanism of activating peroxisome proliferator-activated receptor gamma (PPAR-γ) which results in increased insulin sensitivity and peripheral glucose uptake as well as increased levels of adiponectin, a cytokine secreted by fat tissue (Chiarelli and Marzio, 2008). This causes an increase in the amount of insulin-sensitive adipocytes and also stimulate fatty acid oxidation. Thiazolidinediones is contraindicated to use in people who have history of hypersensitivity to the drug, heart failure from Class III or IV of New York Heart Association classification, serious hepatic impairment, bladder cancer, and pregnancy. Thiazolidinediones can cause adverse effects such as edema, cardiac failure, headache, myalgia, and cardiac failure (Kavitha Ganesan and Senan Sultan, 2019).

2.1.5. Meglitinides (Repaglinide and Nateglinide)

Meglitinides act through the mechanism of regulating adenosine triphospate-sensitive pottasium channels in pancreatic beta cells, thereby causing increased insulin secretion. Meglitinides can cause adverse effects such as weight gain, headache, upper respiratory tract infection, and hypoglycemia (Kavitha Ganesan and Senan Sultan, 2019).

2.1.6. DPP-4 Inhibitors (Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin, Alogliptin)

DPP-4 inhibitors act by having the effect of reducing glucagon release, increasing insulin release, and increasing satiety through the process of deactivating insulinotropic polypeptide (GIP) by inhibiting the enzyme dipeptidyl peptidase 4 (DPP-4) (Makrilakis, 2019). Dose of saxagliptin should be adjusted for people who have eGFR less than 45 mL/min/1.73 m^2 with the dose of 2.5 mg once daily. Dose of sitagliptin should be given in a low dose of 25 mg daily for people who have creatinine clearance of less than 30 ml/min/1.73 m^2 and is contraindicated in patients on hemodialysis or peritoneal dialysis. DPP- 4 inhibitors can cause adverse effects such as hypoglycemia, nasopharyngitis, and acute pancreatitis (Kavitha Ganesan and Senan Sultan, 2019).

2.1.7. SGLT2 Inhibitors (Dapagliflozin and Canagliflozin)

SGLT2 inhibitors reduce plasma glucose levels through inhibiting sodium-glucose co-transporter 2 (SGLT-2) which has an impact on inhibiting glucose reabsorption by 90% and resulting in glycosuria. SGLT2 inhibitors is contraindicated to use in people who have history of serious hypersensitivity to the drug, end-stage renal disease (ESRD), and patients on dialysis. SGLT2 inhibitors can cause adverse effects such as renal impairment, fungal vaginosis, urinary tract infection, and hyperphosphatemia (Kavitha Ganesan and Senan Sultan, 2019).

2.2. Insulin Injections

Insulin injections act by binding directly to its receptor on the plasma membrane of cells with maximum density in liver cells and adipocytes. The binding of insulin to the alpha subunit will cause the activation of tyrosine kinase in the beta subunit resulting in translocation of the glucose transporter from the cytoplasm to the se surface. These glucose transporters allow the entry of glucose from the blood into cells, thereby reducing blood glucose levels (Thota and Akbar, 2023).

2.2.1. Rapid Acting Insulins

Rapid acting insulins such as lispro and aspart initiate their effects within 5 to 15 minutes, reaching their maximum impact in 30 minutes. Their effectiveness lasts for a duration of 3 to 5 hours. Typically administered before meals, these insulins are consistently paired with either short-acting or long-acting insulins to manage blood sugar levels throughout the day (Thota and Akbar, 2023).

2.2.2. Short Acting Insulins

Regular insulin, classified as short-acting, commences its effects within 30 to 40 minutes and reaches its peak in 90 to 120 minutes. Its duration of action spans 6 to 8 hours. Patients are advised to administer these agents prior to meals, and it is crucial to consume food within 30 minutes after administration to prevent hypoglycemia (Thota and Akbar, 2023).

2.2.3. Intermediate Acting Insulins

Intermediate acting insulins, such as NPH, initiate their effects within 1 to 4 hours and reach their peak in 4 to 8 hours. Typically administered twice a day, these insulins contribute to the maintenance of blood sugar levels throughout the day (Thota and Akbar, 2023).

2.2.4. Long Acting Insulins

Long acting insulins, exemplified by glargine and detemir, initiate their effects within 1 to 2 hours. They offer a sustained plateau effect that lasts for 12 to 24 hours. Typically administered after meals, the dosing regimen is commonly during nighttime. The extended duration of action contributes to a reduction in the frequency of dosing throughout the day (Thota and Akbar, 2023).

2.2.5. Nanotechnology

Nanotechnology has played a pivotal role in advancing diabetic management by introducing innovative techniques for glucose measurement and insulin delivery, contributing to improved outcomes. Novel nanotechnology-based approaches encompass non-invasive insulin delivery methods and the development of more effective vaccines, including cell-based and gene-based therapies for type 1 diabetes (T1DM). The significance of nanotechnology in diabetes extends to inventive diagnosis, detection of immune cell activity, assessment of beta-cell mass, glucose level monitoring, and non- invasive insulin delivery (Aloke et al., 2022).

The mass of beta cells is indicative of their functionality in insulin secretion, and the progressive loss of these cells leads to T1DM. Early detection of beta-cell loss stages using nanotechnology, such as magnetic nanoparticles (MNPs), with unique properties for magnetic resonance imaging (MRI), facilitates timely clinical interventions (Aloke et al., 2022).

Nanomedicine addresses challenges in continuous glucose monitoring (CGM), where glucose- sensing devices involve a detector, a transducer, and a reporter. Nanoparticles, predominantly composed of glucose oxidase, glucose-binding proteins, and glucose-binding small molecules, serve as effective transducers, ensuring accurate and patient-friendly glucose detection (Aloke et al., 2022).

In the management of both type 1 (T1DM) and type 2 diabetes (T2DM), insulin shots remain essential. Conventional needle injections, despite improvements for pain reduction, still pose a psychological barrier, impacting patient compliance. To address this, microcomputer closed-loop or nano pumps are being developed to provide timely insulin delivery linked to plasma glucose concentration, minimizing the risk of glucose fluctuations and enhancing patient adherence (Aloke et al., 2022).

2.2.6. Gene Therapy

Gene therapy involves addressing symptoms of a condition caused by a faulty gene by introducing a normal gene from an external source. This approach encompasses three primary intervention methods:

(i) introducing a new gene into the body, (ii) replacing the abnormal gene with a functional one, and (iii) deactivating malfunctioning genes responsible for the condition (Aloke et al., 2022).

Managing T1DM is challenging, particularly with conventional drugs, making gene therapy an emerging and promising therapeutic option. The etiology of T1DM is multifactorial, involving both environmental and genetic factors.

Researchers have identified numerous genes associated with T1DM evolution, making gene therapy a potential avenue for more effective management or even a cure (Aloke et al., 2022).

While gene therapy for diabetes mellitus (DM) primarily focuses on T1DM, various genes have been explored as potential treatments for type 2 diabetes (T2DM), given its strong genetic susceptibility. Through genetic linkage studies, around 75 independent genetic loci have been identified for T2DM, leading to the discovery of novel therapeutic targets. Genetic loci can significantly influence drug response, and numerous loci show promise for T2DM gene therapy. For instance, inhibiting nucleotide- binding oligomerization domain-like receptor protein 3 (NLRP3) has shown anti-inflammatory effects, protects against apoptosis of pancreatic beta cells, and prevents T2DM development in mice. In theory, genes associated with the initiation, progression, and deterioration of T2DM are potential targets (Aloke et al., 2022).

3. Complications of Diabetes Mellitus (DM)

3.1. Macrovascular Complications of Diabetes Mellitus

3.1.1. Cerebrovascular Disease

Diabetes is a significant and standalone indicator of the likelihood of experiencing a stroke and cerebrovascular disease, similar to its association with coronary artery disease. Individuals diagnosed with type 2 diabetes face a considerably heightened risk of stroke, with an elevated risk ranging from 150% to 400%. Moreover, there is an increased likelihood of stroke-related dementia, recurrence, and mortality in individuals with diabetes (Fowler, 2008). Diabetes constitutes an autonomous risk factor for stroke across all age groups, with a 2 to 4 times higher risk, particularly pronounced in individuals of Caucasian descent and women. Moreover, diabetes introduces an increased susceptibility to sudden and eventual fatality resulting from a stroke. Individuals with diabetes who experience a stroke exhibit more profound neurological deficits and disability, a less favorable long-term prognosis, and a heightened incidence of stroke recurrence compared to those without diabetes (Cade, 2008)

Similar to its impact on cardiovascular disease (CVD), the presence of diabetes detrimentally affects cerebrovascular circulation by elevating the risk of atherosclerosis in both intracranial and extracranial regions, such as the carotid arteries. Diabetics manifest a heightened occurrence of conventional stroke risk factors, including hypertension, dyslipidemia, heart failure, and atrial fibrillation. Nonetheless, even after accounting for these factors, diabetes continues to emerge as a potent predictor of stroke, underscoring its independent risk despite the coexistence of traditional risk factors (Cade, 2008)

Furthermore, diabetes-related complications such as diabetic retinopathy (DR), proteinuria, microalbuminuria, and hyperuricemia (elevated blood uric acid levels) contribute to an escalated risk of stroke. Lastly, heightened levels of chronic inflammatory markers in the bloodstream are linked to an augmented stroke risk in individuals with diabetes (Cade, 2008).

3.1.2. Peripheral Artery Disease

Presently in the United States, over 3.5 million individuals (with a prevalence order of African Americans > whites > Hispanics) diagnosed with diabetes are affected by peripheral arterial disease (PAD). Peripheral arterial disease is characterized by the occlusion of arteries in the lower extremities, leading to claudication and intermittent pain, particularly during physical exercise and activity, which can result in functional limitations and disability. Individuals with diabetes face a 15-fold higher likelihood of undergoing lower extremity amputation compared to those without diabetes. Mortality among individuals with diabetes and peripheral neuropathy (PN) is frequently linked to cardiovascular disease (CVD). Moreover, instances of lower extremity amputations are more prevalent in individuals with diabetes and PAD compared to those without diabetes but afflicted by PAD. The occurrence of peripheral arterial disease correlates with the duration and severity of diabetes (Cade, 2008).

3.2. Microvascular Complications of Diabetes Mellitus

3.2.1. Diabetic Retinopathy

Diabetic retinopathy (DR) is a microvascular complication that can impact the peripheral retina, macula, or both, constituting a significant cause of visual impairment and blindness among individuals with diabetes. The prevalence of DR rises with advancing age and prolonged diabetes duration. In a study encompassing individuals with both type 1 and type 2 diabetes, it was observed that after 30 years of diabetes, a majority of patients exhibited some form of DR,

with over half manifesting proliferative DR. Notably, individuals with type 1 diabetes who use insulin displayed the highest prevalence of DR, whereas those with type 2 diabetes diagnosed after the age of 30 exhibited the lowest prevalence. Recent findings indicate that diabetic retinopathy is also present in approximately 10% of individuals with insulin resistance (prediabetes) and is correlated with the presence of hypertension and an elevated body mass index (Cade, 2008).

Aldose reductase serves as the primary enzyme in the intracellular polyol pathway, which entails the conversion of glucose to glucose alcohol, specifically sorbitol. Elevated levels of glucose intensify the flow of sugar molecules through the polyol pathway, resulting in the intracellular accumulation of sorbitol. The osmotic stress arising from the accumulation of sorbitol has been proposed as a fundamental mechanism contributing to microvascular complications associated with diabetes, including diabetic retinopathy (Fowler, 2008).

3.2.2. Diabetic Neuropathy

Approximately half of individuals with diabetes exhibit some variant of peripheral neuropathy (PN), encompassing both polydiabetic and monodiabetic neuropathies. The exact nature of peripheral nerve damage resulting from hyperglycemia remains uncertain, but it is probably linked to mechanisms such as the accumulation of polyols, injury from Advanced Glycation End-products (AGEs), and oxidative stress (Cade, 2008).

Diabetic neuropathy can present in various manifestations, encompassing sensory, focal/multifocal, and autonomic neuropathy. Notably, over 80% of amputations are associated with foot ulceration or injury, often attributed to diabetic neuropathy (Fowler, 2008). Moreover, individuals with diabetes commonly experience autonomic neuropathy, specifically cardiovascular autonomic dysfunction, characterized by irregularities in heart rate (HR) and vascular function regulation. Physical therapists frequently encounter diabetes-related PN in their assessment and treatment of balance and movement impairments, as these issues often impact lower extremity sensation and can induce lower extremity pain in individuals with diabetes. The combination of diminished sensation in the lower extremities and impaired peripheral vascular function may contribute to the development of ulcers, primarily affecting the legs (Cade, 2008).

Similar to diabetic retinopathy (DR), risk factors for PN involve suboptimal glycemic control, reflected in elevated glycated hemoglobin levels and impaired glucose tolerance, as well as factors such as age, diabetes duration, tobacco use, dyslipidemia, and hypertension, especially diastolic hypertension. Additional independent risk factors for PN encompass increased height, body mass, the presence of cardiovascular disease (CVD), severe ketoacidosis (indicated by elevated byproducts of fat metabolism in the blood), and the presence of microalbuminuria (indicative of early renal dysfunction). In contrast to DR, the pathogenesis of PN appears to be associated with both vascular and nonvascular metabolic mechanisms, although this theory remains contentious (Cade, 2008).

Cardiac autonomic neuropathy linked to diabetes is frequently underdiagnosed and presents clinical abnormalities such as resting tachycardia, exercise intolerance, variability in resting HR, delayed HR recovery post-exercise, orthostasis, "silent" myocardial infarction, and an increased risk of mortality. The prevalence of diabetes-related cardiac autonomic neuropathy remains uncertain, with reported figures ranging from 1% to 90%, contingent on various outcome variables. Risk factors for diabetes-related cardiac neuropathy include age, obesity, smoking, suboptimal glycemic control, and hypertension (Cade, 2008).

3.2.3. Diabetic Nephropathy

Diabetic nephropathy (DN) is a severe and progressive complication associated with both type 1 diabetes mellitus (DM) and type 2 DM. Typically, the initial indication of DN is microalbuminuria, which advances to overt albuminuria (i.e., elevated levels of albumin in urine, indicative of more pronounced renal dysfunction), ultimately culminating in kidney failure. This progression is the primary cause of end-stage renal disease (ESRD). Approximately a quarter of individuals with type 2 diabetes experience either microalbuminuria or advanced DN, with a deterioration rate of 2% to 3% annually. Other distinctive characteristics of DN encompass the thickening of the glomerular basement membrane, glomerular hyperfiltration leading to the expansion of the mesangial extracellular matrix (located in the middle portion of the renal glomerulus), resulting in a further elevation in urinary albumin excretion. This process continues to glomerular and tubular sclerosis, eventually leading to renal failure. Similar to diabetic retinopathy (DR) and peripheral neuropathy (PN), risk factors for DN encompass hyperglycemia, diabetes duration, age at diabetes onset, tobacco use, dyslipidemia, hypertension, and obesity (Cade, 2008).

4. Conclusion

Diabetes mellitus represents a persistent metabolic disorder, frequently underestimated owing to its prolonged course. Despite its extended duration, diabetes mellitus typically accompanies various macrovascular and microvascular complications that significantly impact an individual's quality of life. Theimplementation of suitable treatment measures can effectively mitigate the risk of additional complications arising from diabetes mellitus.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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