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DIABETES MELLITUS: A REVIEW ON PATHOPHYSIOLOGY AND COMPLICATIONS

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ABSTRACT

Diabetes mellitus (DM), belongs to the class of metabolic diseases which the main symptom associated with this disease is the high sugar levels in blood for a long period. It can be categorized to the world's major diseases considering that affects high population in earth and presents two main types 1 and 2. Diabetes complications include possible blindness, amputation of lower limb, renal failure, and cardiac arrest or stroke. This review summarizes the pathophysiology and complications of both type I and type II DM. Until now injectable medications are more frequently used in order to achieve the desirable treatment. Patients prefer oral antidiabetic medications since are easier to be administered and for this reason researchers focus their studies at this direction. This work also aimed to present and evaluate possible oral formulations against DM type II.

KEYWORDS: Diabetes Mellitus, pathophysiology, Diabetic complications.

INTRODUCTION

Diabetes, epidemiology and pathophysiology

The term "Diabetes" and "Mellitus" are derived from Greek language. " Diabetes" denotes "a passer through, a siphon" whereas the "Mellitus" means a "sweet". It is believed that Greeks entitled it such a way, due to exaggerated urine proportions produced by diabetic patients which attracted flies and bees.[1,2] Diabetes is a lifelong (chronic) disease and is a group of metabolic disorders characterized by high levels of sugar in blood (hyperglycemia).[3]

Recently, it was recorded that only in 2012 at least 1.5 million deaths induced from diabetes.[4] More than 230 million people worldwide are affected, and it is expected to reach 350 million by 2025. Globally the affected people are unaware of the disease and one half receive adequate treatment.[5] It is caused due to deficiency of insulin or resistance to insulin or both. Insulin is secreted by beta-cells of pancreas to control blood sugar levels.[3] Blurry visions, excess thirst, fatigue, frequent urination, hunger, weight loss are some of the symptoms commonly seen in diabetic patients.[6]

Classification and diagnosis of diabetes

1. **Type I diabetes** is as a result of β-cell destruction which customarily provoke complete insulin insufficiency. It was formerly known as insulin dependent, juvenile or childhood-onset diabetes and it is occasioned by an autoimmune reaction, in which the immune system invaded against the insulin-producing pancreatic beta cells. Type I diabetes is distinguished by deficient insulin production in the body. In such type of DM, the patients require daily administration of insulin so as to normalize the glucose level in the blood. Have not taken the insulin, their life is being threatened and can be fatal. The reason of type I DM is not identified yet being presently not preventable albeit, the reasons for type I diabetes are still unclear, changes in environmental risk factors and/or viral infections may have an impact on the appearance of DM. Extreme urination and thirst, continuous hunger, weight loss, vision changes and fatigue are the main symptoms of this type of DM. More often than not, the number of people who diagnosed with type I diabetes is escalated.

2. **Type II diabetes** which earlier termed non-insulin-dependent or adult- on- diabetes, assumed to be a result from a continuous insulin secretary defect on the background of insulin resistant on account of the bodies in efficient use of insulin. Type II diabetes is the most typical DM. in this type, the body is capable of producing insulin but becomes so resistant that the insulin is ineffective. By the time, insulin levels could subsequently turn out insufficient. The cause of high blood glucose levels are both the insulin resistance and deficiency. The symptoms are generally less noticeable or absent. For various years, type 2 DM was observed only in adults, nowadays it has started to be seen also in children. Until present the exact causes for the development of type 2 diabetes are still unknown. Some significant risk factors being pointed out which includes: excess body weight, physical inactivity and poor nutrition. Other factors which impacted are ethnicity, family history of DM, past history of gestational diabetes and advancing age.[4,7,8-10]

3. Gestational diabetes mellitus (GDM) occurs in approximately 7% of pregnancies and there is a greater risk of morbidity and mortality to mother, fetus and subsequent neonates. Intensive monitoring and treatment are necessary for GDM. Women with the history of GDM have a subsequently increased risk of T2DM and of cardiovascular disease during next years after delivery.[11,12]

Etiology[13]

- Decline in pancreatic beta cell function.
- Destruction of beta cells
- Decreased beta cell mass
- Obese
- Combination of genetic susceptibility
- Environmental factors
- Buildup of glucose in bloodstream
- Increased absorption of glucose
- Genetic factors
- Viral infections
- Precipitating factors

Clinical Manifestations

Symptoms caused due to increased blood glucose levels.

General symptoms Increased thirst (polydipsia), increased hunger (polyphagia), weight loss, frequent urination (polyuria), blurred vision, fatigue, delayed wound healing, tiredness, lack of sleep, (Insomnia), increased cholesterol, presence of ketones in urine, burning, pain and numbness of feet, skin and vaginal infections, gum infections, dry mouth, tingling sensation in hands, irritability.[14]

Common symptoms in Men

Erectile dysfunction, poor muscle strength and muscle growth, low testosterone.[15]

Common symptoms in women

Urinary tract infections, dry skin, itchy skin, frequent urination.[16]

Complications

Diabetes is root cause for several complications such as cardiovascular diseases, cerebrovascular diseases, renal disorders, inflammation and immunity, and obesity.[17] Epidemiological studies of DM have shown that gender, age, and ethnic background are important factors when considering the development of DM and its complications.[18] Diabetic complications include hypertension, retinopathy, end-stage renal disease, neuropathy, peripheral vascular disease, electrolyte imbalance, immune suppression, erectile dysfunction, and complications of pregnancy.[18] Diabetes leads to increased levels of endothelial micro particles.[19]

Diabetic Retinopathy

Diabetic retinopathy (DR) is damage to the eye's retina that occurs with long-term diabetes. Diabetic retinopathy is the most common cause of blindness in most of the countries. It is commonly seen in both type 1(40%) and type 2 DM (20%). They are two types of diabetic retinopathy. They are non-proliferative which develops first, Proliferative is the more advanced and severe form of the disease. In patients with T2DM, involvement of fovea by edema and hard exudates or ischemia is the most common cause of visual impairment.[20] Symptoms of diabetic retinopathy appears only after the damage occurs to eyes which include- blurred vision and slow vision loss over time, floaters, shadows or missing areas of vision, trouble seeing at night. The vascular commitment is the most serious and common condition in DM. The factors for vascular damage of DM include poor glycemic control, lipoprotein abnormalities, hypertension, oxidative stress (OS), inflammation and advanced glycation end-products (AGE'S). Retinopathy is characterized by increased vascular permeability, by vascular closure mediated by the formation of new blood vessels-neovascularization, on the retina and posterior surface of the vitreous.[21,22] Diagnosis of retinopathy is based on finding the diagnostic signs of retinopathy on eye exams by fundoscopy.[23]

Diabetic Maculopathy

Diabetic maculopathy is the most commonly seen in T2DM whereas macular ischemia is more frequently seen in T1DM. Diabetic maculopathy consist of macular edema and ischemia.

Macular Ischemia

Macular ischemia is a devastating condition that causes irreversible visual loss. It is seen mostly in T1DM. Basement membrane thickening, viscosity of blood and endothelial cell damage occurs in the pathogenesis of macular ischemia.[24]

Nephropathy

Nephropathy is the leading cause of chronical renal failure, the initial marker being microalbuminuria, which can be screened by measurement of albumin to creatinine ratio in a random spot collection.[25] Initial microalbuminuria associated with diabetic nephropathy was observed in the range of 30-299 mg/24 hours in a 24 hours urinary collection, 20-199 µg/min in a timed urine collection or 30-299 µg/mg creatinine in a spot urine collection on at least two occasions within a three-to-six-month period. A greater proportion of patient with type 2 DM compared with type 1 DM develop microalbuminuria.[26] The abnormal value of microalbuminuria based on 24 hr urine collection method is 150-300 mg/day whereas for macroalbuminuria it is more than 300 mg/day.[27] Even though diabetic nephropathy can be categorized into stages: micro and macro albuminuria based on the values of urinary albumin excretion, yet it has been seen that the risk for developing diabetic nephropathy and cardiovascular disease starts even when urinary albumin excretion values are within the normal albumin uric range.[28]

Neuropathy

Diabetes mellitus is the most common cause of neuropathy worldwide. Neuropathies are classified into symmetrical or asymmetrical (focal or multifocal) forms, the symmetrical form is primarily sensory and autonomic whereas asymmetric form can be sensory, motor or both as well as affecting the individual cranial or peripheral nerves. Diabetic peripheral neuropathy is defined as stocking- glove neuropathy or somatic and/or autonomic neuropathy which affects the longest nerve first before progressing proximally.[29,30,31,32] Distal symmetrical form of diabetic peripheral neuropathy otherwise known as diabetic sensorimotor peripheral neuropathy is the primary risk factor for the development of diabetic foot ulcer, responsible for 85% of lower extremity amputation in diabetic patients.[33] Thus, it is necessary to monitor neuropathy if at all present and to find its significance level to take the proper treatment strategy. A standard neuropathy disability score (NDS) of over 6 indicates the presence of significant neuropathy.[34]

Diabetic macular edema

Diabetic macular edema (DME) is the leading cause of visual loss in patients with non-proliferative diabetic retinopathy. DME is the consequence of accumulation of fluid in the retina after dysfunction of the blood retinal barrier.[35] Breakdown in blood retinal barrier at the level of the perifoveal vessels results in edema.[36,37]

Cataract

Cataract develops at an earlier age in diabetic patients which is characterized by clouding of the eye lens. In cataract the lens becomes opaque, reducing the amount of light reaching the retina. Connexins (Cx) are a family of proteins that forms hemichannels that communicate the cytoplasm with the extracellular space. Under oxidative stress conditions such as diabetes, it is possible that Cx oxidation may contribute to cataract formation.[38,39] Neurotrophic corneal ulcers may develop in patients with DM.[40]

Glaucoma

Glaucoma is a condition in which increase in fluid pressure inside the eye which leads to optic nerve damage and loss of vision. A person with diabetes is more prone to get glaucoma compared to others.

Macrovascular complications

Coronary artery diseases (CAD)

A study conducted on DM population revealed that more than 3 out of 4 diabetic patients die of causes related to atherosclerosis and in most cases (75%) because of CAD. Type 2 DM increases with the risk of CAD by 2-4 times in the overall population.[41] CAD is caused by atherosclerosis which is characterized by the formation of plaques. With increase in the size of the plaques leads to the acute coronary syndrome (ACS), which is a medical emergency.[42] ACS may occasionally occur in the absence of electrocardiographic changes or elevations in biochemical markers, still the main diagnostic tool of ACS, unstable angina and acute myocardial infarction is the measurement of cardiac enzymes and markers. Measurement of cardiac markers like troponin T and troponin I gives an idea regarding ACS and myocardial infarction. As per the British Cardiac Society (BCS) working group a 12 hr serum troponin T concentration of less than 0.01µg/l indicates ACS with unstable angina, serum troponin T concentration≥0.01 µg/l and <1.0 µg/l indicates ACS with myocyte necrosis and troponin T concentration ≥1.0 µg/l indicates ACS with clinical myocardial infarction.[43] Thus, these

values play a crucial role to the identification of the very specific problems associated with ACS.

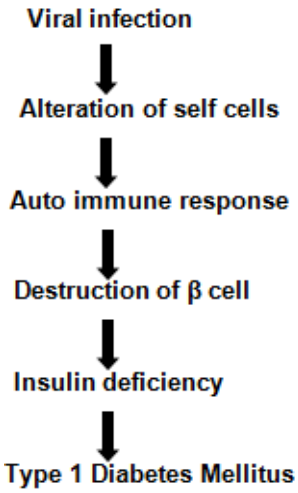
Pathophysiology of diabetes mellitus

- Insulin is the principle hormone that regulates the uptake of glucose from the blood into most of the cells in the body, especially liver, muscle and adipose tissue. Therefore, deficiency of insulin or the insensitivity of its receptor plays a central role in all forms of diabetes mellitus.
- The body acquires glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver, and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body.
- Insulin plays a crucial role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can of stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen.
- Insulin is released into the blood by beta-cells, found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, particularly after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin results from the beta-cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner too insulin.
- If the amount of insulin is available is insufficient, if cells respond poorly to the effects of insulin (insulin sensitivity or insulin resistance) or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

Type I DM

Type I DM (5%-10% of cases) usually develops in childhood or early adulthood and results from autoimmune-mediated destruction of pancreatic beta-cells, resulting in absolute deficiency of insulin. The autoimmune process is mediated by macrophages and T

lymphocytes with autoantibodies to beta-cell antigens (e.g.: islet cell antibody, insulin antibodies).



Type II DM

Type 2 DM (90% of cases) is characterized by a combination of some degree of insulin resistance and relative insulin deficiency. Insulin resistance is manifested by increased lipolysis and free fatty acid production, increased hepatic glucose production, and decreased skeletal muscle uptake of glucose.

- Uncommon causes of diabetes include endocrine disorders (e.g., acromegaly, Cushing syndrome), gestational diabetes mellitus (GDM), diseases of the exocrine pancreas (e.g., pancreatitis), and medications (e.g., glucocorticoids, pentamidine, niacin, α-interferon).
- Microvascular complications include retinopathy, neuropathy, and nephropathy.
- Macrovascular complications include coronary heart diseases, stroke, and peripheral vascular disease.

CONCLUSION

This comprehensive review delves into the pathophysiology and complications associated with Diabetes Mellitus (DM), encompassing both Type I and Type II. The global impact of DM on public health is significant, with increasing prevalence and a range of complications affecting various organ systems. The review highlights the etiological factors, clinical manifestations, and complications, emphasizing the profound impact on cardiovascular, renal, ocular, and neurological systems. Additionally, the article discusses the significance of oral antidiabetic formulations and the current emphasis on developing convenient treatment options. The thorough exploration of the pathophysiology, classification, and complications

provides valuable insights for researchers, healthcare professionals, and pharmaceutical practitioners working towards better management and prevention strategies for DM. This review contributes to the ongoing efforts in understanding the complexities of DM and exploring potential therapeutic avenues.

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