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Complication of Diabetes Mellitus: Microvascular and Macrovascular Complications

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ABSTRACT

Diabetes complications are categorized as microvascular (nephropathy, neuropathy, and retinopathy) or macrovascular (cardiovascular and cerebrovascular disease). The most common chronic complications were erectile dysfunction (64%), visual disturbance (33.8%), and cardiovascular disorders (30.1%), though hypertension alone was (68%), neuropathy (29.5%), and nephropathy (15.7%). Diabetic foot ulcers and infections are responsible for >30% of the hospitalizations related to diabetes mellitus. Diabetic foot ulceration is also an expensive complication of diabetes mellitus, owing to both medical care and on account of time lost from work and loss of income and financial independence. Diabetic gastroenteropathy as a complication of diabetes mellitus includes all form of diabetic complication on the gastrointestinal tract, which causes various symptoms involving heartburn, abdominal pain, nausea, vomiting, even constipation, diarrhea, and fecal incontinence. Heart failure a major cardiovascular complication of diabetes mellitus has finally emerged as a significant and increasing clinical and public health problem. Several changes in society have coalesced to cause this merger of heart failure with diabetes mellitus. Diabetic myonecrosis or diabetic muscle infarction is an uncommon manifestation of long-standing and poorly controlled diabetes mellitus.

Keywords: Complications, Diabetes mellitus, Macrovascular, Microvascular

INTRODUCTION

Complications of diabetes mellitus are progressive and almost resulting by chronic exposure to high blood levels of glucose caused by impairments in insulin metabolism and biological macromolecules such as carbohydrates, lipids, proteins and nucleic acids. Diabetes mellitus and its complications are rapidly becoming the world's most significant cause of morbidity and mortality [1-3]. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia in which glucose is underutilized due to defects in insulin secretion, insulin action, or both. It has various long-term complications which negatively impact the individuals' quality of life and potentially their life spans, causing deleterious effects for both individuals and societies. Diabetes complications are categorized as microvascular (nephropathy, neuropathy, and retinopathy) or macrovascular (cardiovascular and cerebrovascular disease). The most common chronic complications were erectile dysfunction (64%), visual disturbance (33.8%), and cardiovascular disorders (30.1%), though hypertension alone was (68%), neuropathy (29.5%), and nephropathy (15.7%). Likewise acute complications had similar trend which ranges 30.5% among which diabetic ketoacidosis was 71%, followed by hypoglycemia (19.4%) but hyperosmolar hyperglycemic state was insignificant. Diabetes related complications are the major cause of premature deaths and disability in the world, which is 2-4 times more prevalent in patients with diabetes mellitus than in the general population [4]. Insulin resistance involves complex and variable disturbances in the insulin signaling pathway, eventually culminating in impaired glucose utilization by muscle and adipose tissues, contributing to the impairment of glycemic. Furthermore, insulin resistance aggravates hyperglycemia by favoring the output of glucose from the liver by increasing gluconeogenesis. Compensatory hyperglycemia, in turn, is not able to neutralize hepatic glucose production, whereas, in a non-resistant pathway, induces an increase in lipogenesis mediated by the over activation of sterol regulatory element-binding protein 1, which aggravates peripheral insulin resistance and favors a pro-atherogenic

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state. Then, plasma glucose levels are dictated by interplay of mechanisms triggered by insulin resistance and hyperinsulinemia in one or more different organs [5]. The long-term sequelae of type 1 and type 2 diabetes take years to develop. More than 90% of diabetic deaths result from long-term complications. Most long-term complications occur secondary to disruption of blood flow, owing to either macrovascular or microvascular damage [2].

MICROVASCULAR COMPLICATION OF DIABETES MELLITUS

Damage to small blood vessels and capillaries is common. The basement membrane of capillaries thickens, causing blood flow in the microvasculature to fall. Destruction of small blood vessels contributes to kidney damage, blindness, and various neuropathies. Microvascular injury is directly related to the degree and duration of hyperglycemia [1].

Diabetic retinopathy

Diabetic retinopathy, a microangiopathy affecting all of the small retinal vessels, such as arterioles, capillaries and venules, is characterized by increased vascular permeability, ocular hemorrhages, lipid exudate, by vascular closure mediated by the development of new vessels on the retina and the posterior vitreous surface. Diabetic retinopathy, the most common microvascular complication of diabetes mellitus, is predicted to be the principal reason of new blindness among working population. Micro-angiopathy due to hyperglycemia in patients with diabetes mellitus results in vascular leakage, which causes diabetic macular edema on one hand, and capillary occlusion on the other hand. Capillary occlusion then again causes retinal ischemia and increased levels of vascular endothelial growth factor which are responsible for the development of neovascularization and the proliferative stage of diabetic retinopathy [1,6]. The type 2 diabetes mellitus is responsible for a higher percentage of patients with visual loss. The incidence of diabetic retinopathy is related primarily to duration and control of diabetes and is related to hyperglycemia, hypertension, hyperlipidemia, pregnancy, nephropathy, and anemia [7,8]. Retinopathy is accelerated by hyperglycemia, hypertension, and smoking. Chronic hyperglycemia increases quantity of diacylglycerol, which is leading to activate protein kinase C. This activation leads to increase vascular permeability and upregulation of vascular endothelial growth factor in the retinal structure. However, this abnormal pathway may lead to increase the activation of leukocytosis and significant changes in extracellular matrix protein synthesis. Eventually, diacylglycerol and protein kinase C pathway adversely affect inflammation, neovascularization, and retinal hemodynamics, which redound to progression of diabetic retinopathy [9,10].

Nephropathy

Nephropathy is a chronic complication characterized by increased urinary albumin excretion (Proteinuria) or reduced kidney glomerular filtration rate in both forms of diabetic mellitus, type 1 diabetes mellitus and type 1 diabetes mellitus. Proteinuria was seen in about 30% of type 1 diabetes mellitus patients and 40% of type 2 diabetes mellitus patients. It's also the major source of end-stage renal disease development in the world, accounting for about 40% of new renal replacement therapies. This includes the creation of basement membrane thickening and the growth of microaneurysms. In addition, the development of the extracellular matrix and the progression of tubular and glomerular sclerosis are consistent with glomerular hyperfiltration. The risk of nephropathy among patients with type 1 diabetes is 12 times higher than among patients with type 2 diabetes [11-13].

Neuropathy

Pathological neuronal changes: oxidative stress, polyol pathway activation, early end product glycation development, and protein kinase C activation are only several of the molecular pathways linked to functional nerve dysfunction. Hyperglycemia and risk factors for artery disease create barrier pathways in the long run, resulting in disruption to the micro vessel endothelium, nerve back cells, and nerve axons. Recent advancements propose that through the generation of reactive oxygen species and mitochondrial dysfunction, the combined impact of these injurious events might result in neuronal death. Symptoms of diabetic neuropathy which are usually bilateral and symmetric include tingling sensations in the fingers and toes (paresthesia's), pain, and loss of sensation [14,15].

Diabetic foot ulcers

Diabetic foot ulcers are lacerations that usually occur on the soles of the feet in patients with diabetes mellitus due to peripheral neuropathy or peripheral arterial disease on all skin layers, necrosis or inflammation, around 15% to 25% of diabetic patients will grow foot ulcers during their lives, the leading cause of non-traumatic subtraction worldwide [16]. Diabetic foot ulcers and infections are responsible for >30% of the hospitalizations related to diabetes mellitus. The rationales why serious infection can occur in diabetes mellitus patients are hyperglycemia provides a glucose-rich environment for bacteria to grow; diabetes can suppress immune function, and thereby compromise host defenses against infection; and diabetic neuropathy can prevent the patient from feeling discomfort and other sensations that would signal that a serious infection is developing. Diabetic foot ulceration is also an expensive complication of diabetes mellitus, owing to both medical care and on account of time lost from work and loss of income and financial independence. Endothelial cell inflammation and smooth cell imperfections are caused by hyperglycemia in peripheral arteries. Endothelial dysfunction is the most serious condition causing microcirculation, due to developments in endothelial cell differentiation, thickening of the vault membrane, reduced nitric oxide secretion, elevated blood

viscosity, improvements in microvascular tone and decreased blood volume [17,18].

MACROVASCULAR COMPLICATION OF DIABETES MELLITUS

Diabetic mellitus is a complicated and persistent condition that includes lifelong medical treatment, consisting of coronary artery disease, cerebrovascular disease and peripheral artery disease, with a high risk of disease on patients with multiple macrovascular complications associated with it. The frequency of acute myocardial infarction is 2.13 times greater in males and 2.95 times higher in females than in non-diabetic groups [19,20].

Cardiovascular disease

Cardiovascular disease is the leading cause of death among diabetic patients. Diabetes carries an increased risk of heart disease, hypertension, and stroke. Much of this pathology is due to atherosclerosis, which develops earlier in diabetics than in nondiabetics and progresses at a faster rate. Macrovascular complications result from a combination of hyperglycemia and altered lipid metabolism [21].

Heart failure

Heart failure a major cardiovascular complication of diabetes mellitus has finally emerged as a significant and increasing clinical and public health problem. Several changes in society have coalesced to cause this merger of heart failure with diabetes mellitus. Heart failure incidence increases with age and is present in 6 to 10 % of individuals 65 years or older [22-25]. The incidence of heart failure in patients with clinically diagnosed diabetes mellitus is approximately 2.5 times that in patients without diabetes mellitus [22,26]. Heart failure may occur in the presence of reduced left ventricular ejection fraction or preserved left ventricular ejection fraction. The definition of normal left ventricular ejection fraction has varied over the years. In a 2015 joint guideline from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, normal left ventricular ejection fraction was defined as being between 53 and 73 %. Popular norms set echocardiographic normative value as left ventricular ejection fraction ≥ 55 %; however, in many clinical trials and population-based studies, values as low as ≥40 or 45 % have been considered normal. In addition to left ventricular ejection fraction, the patient demography, comorbid conditions, pathogenesis, outcomes, and responses to therapies are somewhat different between the two types of heart failure [22,27-29].

Coronary Artery Disease

Coronary heart disease is the main cause of morbidity and mortality around the world. Diabetes is associated with an increased risk of coronary heart disease. In patients with no previous history of myocardial infarction, the seven-year risk of myocardial infraction is 20.2 percent and 3.5 percent, respectively, for diabetics and non-diabetics. Likewise, the 7-year myocardial infraction risk for diabetics and non-diabetics is 45.0 percent and 18.8 percent, respectively, for patients with a history of myocardial infraction. Diabetics are more likely to experience greater, more frequent, and more severe coronary artery injury, which is linked to a worse prognosis. In diabetic patients with no coronary artery disease results, necropsy tests revealed that in the late stages, 50 percent and 75 percent of patients under and over the age of 65, respectively, had coronary artery disease [30,31].

ANOTHER TYPE OF DIABETIC MELLITUS COMPLICATION

Periodontal diseases

Periodontitis is a chronic inflammatory disorder affecting the gingivae and the periodontal tissue initiated by bacteria. The micro-flora in the dental plaque that forms daily adjacent to the teeth are causes this inflammatory process [32,33]. Periodontal disease has been reported with increased prevalence and severity in patients with type 1 and type 2 diabetes. The mechanism by which hyperglycemia can induce periodontal destruction is not yet fully understood. However, there are many theories which propose factors such as advanced glycation end products, changes in collagen statue, and altered immune function that causes impaired polymorphonuclear leukocyte function which may facilitate bacterial persistence in the tissue and the accumulation of advanced glycation end products, which results from prolonged and chronic hyperglycemia and increased secretion of pro-inflammatory cytokines such as tumor necrosis factor-α and prostaglandin E-2. The increase in collagenase activity together with the reduction in collagen synthesis will adversely influence collagen metabolism [32,34,35].

Tuberculosis

Diabetes mellitus and tuberculosis have a bidirectional relationship. Approximately 25% of patients with tuberculosis are estimated to have diabetes mellitus, and tuberculosis occurs in up to 8% of patients with diabetes mellitus. Tuberculosis in patients with diabetes mellitus might present with atypical features, such as predominant lower lobe involvement, and thereby delay the diagnosis. Also, cure rates of tuberculosis are lower in patients with diabetes mellitus than those with tuberculosis alone (treatment failure rates 4.2% versus 0.7%). Prompt diagnosis and initiation of antituberculosis chemotherapy, along with achievement of tight glycemic control, are essential to ensure cure and prevention of reactivation of tuberculosis [36-38].

Diabetic myonecrosis

Diabetic myonecrosis is a rare complication of diabetes mellitus which usually present with sudden onset pain of the involved muscle. It affects both type 1 and type 2 diabetic

patients who have long duration of diabetes and frequently have other microvascular complications. Diabetic myonecrosis or diabetic muscle infarction is an uncommon manifestation of long-standing and poorly controlled diabetes mellitus. The exact pathogenesis is not known but may involve hypoxia-reperfusion injury, atherosclerotic occlusion, or vasculitis with thrombosis. Atheroembolism of small vessels has also been proposed as the possible mechanism. Another proposed theory is the participation of the coagulation cascade leading to hypercoagubility [39-41].

Diabetic cardiomyopathy

Diabetic cardiomyopathy is referred to as a pathological heart type and presentation in the absence of other cardiac risk factors, such as coronary artery disease, hypertension and severe valve dysfunction. Diabetic cardiomyopathy is categorized as weakened heart structure and presentation, such as coronary artery disease, hypertension and severe volvuli disease; in the absence of other cardiac risk factors diabetic cardiomyopathy's pathophysiologic processes have still not been fully elucidated. The incidence of diabetic cardiomyopathy is multifactorial and numerous causes are indicated, including insulin resistance, microvascular failure, subcellular component defects, metabolic disorders, autonomic cardiac dysfunction, renin-angiotensin system changes, and maladaptive immune response [42].

Dental caries

The occurrence of dental caries in patients with diabetes mellitus has been studied, but no specific association has been identified. The relationship between dental caries and diabetes mellitus is complex. Children with type 1 diabetes often are given diets that restrict their intake of carbohydrate-rich, cariogenic foods, whereas children and adults with type 2 diabetes which often is associated with obesity and intake of high-calorie and carbohydrate rich food can be expected to have a greater exposure to cariogenic foods. Furthermore, a reduction in salivary flow has been reported in people with diabetes who have neuropathy, and diminished salivary flow is a risk factor for dental caries. The literature presents no consistent pattern regarding the relationship of dental caries and diabetes [43,44].

Diabetic gastroenteropathy

Diabetic gastroenteropathy is one of the most common complications in prolonged diabetic patients, particularly in patients either with poor glycemic control or with other complications concurrently. Diabetic gastroenteropathy as a complication of diabetes mellitus includes all form of diabetic complication on the gastrointestinal tract, which causes various symptoms involving heartburn, abdominal pain, nausea, vomiting, even constipation, diarrhea, and fecal incontinence. These symptoms significantly impair patients' quality of life, as well as increasing patients' morbidity from dehydration, electrolyte imbalance, and poor glycemic control [45-48]. The underlying pathophysiology on every diabetic gastroenteropathy manifestations is different on each organ or symptom. However, from every existing factor, autonomic neuropathy is the one most important aspect of the symptoms. Gastrointestinal neuropathy can affect vagal nerve, sympathetic and parasympathetic nervous system, or innervations of anal sphincter. Neuropathy on the autonomic nervous system is commonly found simultaneously progressing in chronic diabetes due to prolonged hyperglycemia [45,49,50].

CONCLUSION

Complications of diabetes mellitus are progressive and almost resulting by chronic exposure to high blood levels of glucose caused by impairments in insulin metabolism and biological macromolecules such as carbohydrates, lipids, proteins and nucleic acids. The type 2 diabetes mellitus is responsible for a higher percentage of patients with visual loss. The incidence of diabetic retinopathy is related primarily to duration and control of diabetes and is related to hyperglycemia, hypertension, hyperlipidemia, pregnancy, nephropathy, and anemia. Diabetic foot ulcers are lacerations that usually occur on the soles of the feet in patients with diabetes mellitus due to peripheral neuropathy or peripheral arterial disease on all skin layers, necrosis or inflammation, around 15% to 25% of diabetic patients will grow foot ulcers during their lives, the leading cause of non-traumatic subtraction worldwide.

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