Review Article

Complications of diabetes mellitus: A review

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia and complications that include microvascular disease of the eye and kidney and a variety of clinical neuropathies. DM, also known as simply diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. These high blood sugar levels produce the symptoms of repeated urination, increased hunger, and increased thirst. Untreated diabetes can cause many complications. Acute complications include diabetic ketoacidosis (DKA) and non-ketotic hyperosmolar coma. Serious long-term complications include heart disease, stroke, kidney failure, foot ulcers, and damage to the eyes. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the important role of insulin as an anabolic hormone. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for these metabolic abnormalities. The severity of symptoms is due to the type and duration of diabetes. Some of the diabetes patients are asymptomatic, especially those with type 2 diabetes during the early years of the disease. Others with marked hyperglycemia, especially in children with absolute insulin deficiency, may suffer from polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Uncontrolled diabetes may lead to stupor, coma, and if not treated death, due to ketoacidosis or rarely from non-ketotic hyperosmolar syndrome. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the beta-cells of the pancreas with consequent insulin deficiency to the abnormalities that end in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of the hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality is the primary cause of hyperglycemia.

KEY WORDS: Complications, Dentistry, Diabetes mellitus, Hyperglycemia, Hypoglycemia, Insulin

INTRODUCTION

A metabolic disorder of various etiology characterized the by chronic hyperglycemia with interference of carbohydrate, fat, and protein metabolism arising from defects in insulin secretion, insulin action, or both is known as diabetic mellitus (DM). Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. Prevention and treatment involves healthy diet, physical exercise, no tobacco use, and having a normal body weight. Blood pressure control and proper foot care are also important for people with the disease. Type 1 diabetes must be managed with insulin injections. Type 2 diabetes may be treated with medications with or without insulin. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is an effective measure in those with type 2 DM. Gestational diabetes usually resolves after the birth of the baby. The effects of diabetes mellitus (DM) include long-term damage, dysfunction, and failure of various organs.[1,2]

The two main types of diabetes are Type 1 diabetes and Type 2 diabetes. Other categories of diabetes include gestational diabetes (a state of hyperglycemia which develops during pregnancy), and DM due to rarer causes (genetic syndromes, acquired processes such as pancreatitis, and diseases such as the cystic fibrosis, exposure to certain drugs, viruses, and

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unknown causes). Furthermore, there are intermediate states of hyperglycemia (impaired fasting glucose or impaired glucose tolerance), which are significant in that they can progress to diabetes, but with weight loss and lifestyle changes, this progression can be prevented or delayed.[3]

In the short term, hyperglycemia causes symptoms of increased thirst, increased urination, increased hunger, and weight loss. However, in the long term, it causes blindness, renal failure, impotence, foot disorders, and possibly amputation. As well, it also increases the risk of heart disease, stroke, and insufficiency in blood flow to legs. Studies have shown that good metabolic control prevents or delays these complications. Thus, the primary aim of treatment is to bring the elevated blood sugars down to a normal range, both to improve symptoms of diabetes and to prevent or delay diabetic complications. Achieving this goal requires a comprehensive, coordinated, patient-centered approach on the part of the health-care system.[4,5]

SIGNS AND SYMPTOMS

Polyuria, polydipsia, and polyphagia are the most common symptoms of untreated diabetes. Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes. Others include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Glucose absorption in the lens of the eye brings about changes in its shape and results in vision changes that can be caused by prolonged high blood pressure in diabetic patients. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes. Retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of the foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction are some of the long-term complications of diabetes. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and also cerebrovascular disease. People with diabetes often show hypertension and abnormalities of lipoprotein metabolism in their body.[6-8]

DIABETIC EMERGENCIES

People (usually with type 1 diabetes) may also experience episodes of DKA, a type of metabolic problems characterized by nausea, vomiting, and abdominal pain, the smell of acetone on the breath, deep breathing known as Kussmaul breathing, and, in severe cases, a decreased level of consciousness. A rare but equally severe possibility is hyperosmolar non-ketotic state (HNS), which is more common in type 2 diabetes and is mainly the result of dehydration.[9]

PATHOPHYSIOLOGY

The uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue is regulated by the principal hormone, insulin. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of DM. Gluconeogenesis is the generation of glucose from non-carbohydrate substrates in the body. The intestinal absorption of food, breakdown of glycogen, and the storage form of glucose found in the liver are the main three ways the body gets glucose. Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen.[10] Insulin is released into the blood by β-cells, found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. The glucose is used as fuel, for conversion to other needed molecules, or for storage when two-thirds of the body's cells absorb it from the blood with the help of insulin. Lower glucose levels result in decreased insulin release from the β-cells and in the breakdown of glycogen to glucose. The hormone glucagon mainly controls the process of breakdown of glycogen to glucose, which acts in the opposite manner to insulin.[11]

The glucose will not be absorbed properly by the body cells when the amount of insulin available is insufficient or if cells respond poorly to the effects of insulin, and the glucose will also 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. The kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine which is known as glycosuria when the glucose concentration in the blood remains high over time. This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Replacement of lost blood volume will occur osmotically from water held in body cells. Body parts will help in replacement of lost blood volume by osmotic process, which will bring about to dehydration and increased thirst (polydipsia).[12]

COMPLICATIONS OF DM

People who have well-controlled blood sugar levels show far less common and severe complications of DM. Wider health problems accelerate the deleterious

effects of diabetes. Smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise increase the adverse effects of diabetes.[13]

ACUTE COMPLICATIONS

DKA

A medical emergency and prompt medical attention are always required for DKA, which is an acute and dangerous complication. The liver changes fatty acid to ketone for fuel during low insulin levels, where the ketone bodies that are produced act as intermediate substrates in that metabolic sequence. It can become a serious problem if sustained levels are present periodically. When blood's pH is decreased due to elevated levels of ketone bodies, it leads to DKA. Typical dehydration with rapid and deep breathing is seen in the patient with DKA. Abdominal pain is common and may be severe. Even though lethargy may develop to coma, the level of consciousness is typically normal until late in the process. Ketoacidosis can easily become severe enough to cause hypotension, shock, and death. Levels of ketone bodies which have exceeded their renal threshold blood levels appear in the urine, often before other overt symptoms. Although death can result from inadequate or delayed treatment, or from complications such as brain edema, proper treatment usually results in full recovery. Ketoacidosis is much more common in type 1 diabetes than type 2.[14]

Hyperglycemia Hyperosmolar State

Although HNS has many of the symptoms common with DKA, it is an acute complication with an entirely different origin and different treatment. Water will be osmotically drawn out of cells into the blood and the kidneys eventually begin to dump glucose into the urine in a person with very high blood glucose levels, which is usually considered to be >300 mg/dl (16 mmol/L). Loss of water and an increase in blood osmolarity are the final results. The osmotic effect of high glucose levels, combined with the loss of water, will not eventually lead to dehydration if the fluid is nor replaced by either mouth or intravenously. The body's cells become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common and are always dangerous. Urgent medical treatment that commonly begins with fluid volume replacement is necessary as with DKA patients. Lethargy may ultimately progress to a coma, though this is more common in type 2 diabetes than type 1 diabetes.[15,16]

Hypoglycemia

Several diabetes treatments which could bring an acute complication are known as hypoglycemia or abnormally low blood glucose level. It is rare otherwise, either in diabetic or non-diabetic patients. The patient may become agitated, sweaty, and weak and have many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings akin to dread and immobilized panic. In extreme cases, consciousness of the patients can be altered or even lost which may lead to coma, seizures, or even brain damage and death. In patients with diabetes, this may be caused by several factors such as too much or incorrectly timed insulin, too much or incorrectly timed exercise (exercise decreases insulin requirements), or not enough food (specifically glucose containing carbohydrates). The identification of cause of hypoglycemia is difficult in many instances since there are various interactions.[17,18]

It is more accurate to note that iatrogenic hypoglycemia is typically the result of the interplay of absolute (or relative) insulin excess and compromised glucose counterregulation in type 1 and advanced type 2 diabetes. The primary glucose counterregulatory factors that normally prevent or correct hypoglycemia more/less rapidly are decrements in insulin, increments in glucagon, and increments in epinephrine. In insulin-deficient diabetes, (exogenous) insulin levels do not decrease as glucose levels fall, and the combination of deficient glucagon and epinephrine responses causes defective glucose counterregulation.[19]

Furthermore, reduced sympathoadrenal responses can cause hypoglycemia unawareness. The recent incidents of hypoglycemia that causes both defective glucose counterregulation and hypoglycemia unawareness are assumption of the concept of hypoglycemia-associated autonomic failure in diabetes. By shifting glycemic thresholds for the sympathoadrenal (including epinephrine) and the resulting neurogenic responses to lower plasma glucose concentrations, antecedent hypoglycemia leads to a vicious cycle of recurrent hypoglycemia and further impairment of glucose counterregulation. Hypoglycemia unawareness in affected patients is reversed by short-term avoidance in many cases, although this is easier in theory than in clinical experience.[20]

In most cases, hypoglycemia is treated with sugary drinks or food. An injection of glucagon or an intravenous infusion of dextrose is used in most of the severe cases of hypoglycemia, and it is used only if the person is in an unconscious state. In any given incident, glucagon will only work once as it uses stored liver glycogen as a glucose source; in the absence of such stores, glucagon is largely ineffective. Intravenous dextrose is most commonly used in hospitals.[21]

Diabetic Coma

Medical emergency that occurs in a person with DM who is unconscious is known as diabetic coma. It happens due to one of the following acute complications of diabetes:

- Severe diabetic hypoglycemia.
- DKA advanced enough to result in unconsciousness from a combination of severe hyperglycemia, dehydration, shock, and exhaustion.
- Condition in which extreme hyperglycemia and dehydration alone are sufficient to cause unconsciousness is known as hyperosmolar non-ketotic coma.

When a physician is confronted with an unconscious patient about whom nothing is known except that he has DM, it is termed as diabetic coma and is referred to as the diagnostical dilemma. An unconscious patient who has been brought to hospital wearing a medical identification tag saying *diabetic* might be such an example for a physician working in an emergency department. The unconscious persons will be rescued by paramedics when they are identified as diabetic by their friends. Brief descriptions of the three major conditions, followed by a discussion of the diagnostic process used to distinguish among them, as well as a few other conditions must be considered.[22,23]

Respiratory Infections

The individuals with DM show impaired immune response. Hyperglycemia reduces both the functions of immune cells and increases inflammation as have been shown in cellular studies. The increased susceptibility to respiratory infections such as pneumonia and influenza can change the lung function due to vascular effects of diabetes among individuals with diabetes. Several studies also show that diabetics are associated with a worse disease course and show slower recovery from respiratory infections.[24]

Periodontal Diseases

Diabetes is associated with periodontal disease (gum disease) and may make diabetes more difficult to treat. Gum disease is frequently related to bacterial infection by organisms such as *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*. A number of trials have found improved blood sugar levels in type 2 diabetics who have undergone periodontal treatment.[25]

CHRONIC COMPLICATIONS

Pathogenesis

The damage of blood vessels in people with diabetes is caused by chronic elevation of blood glucose levels. The endothelial cells lining the blood vessels take in more glucose than normal, since they do not depend on insulin. Then, the basement membrane starts to grow thicker and weaker since these endothelial cells form more surface glycoprotein than normal. In diabetes, the resulting problems are grouped under "microvascular disease" (due to damage to small blood vessels) and "macrovascular disease" (due to damage to the arteries). The hypothesis of hyperglycemia as the cause of diabetic complication has been taken up as challenge in many researches. The fact that 40% of diabetics, who carefully control their blood sugar, nevertheless develop neuropathy, and that some of those with good blood sugar control still develop nephropathy, requires explanation. Even though the blood sugar content is normal in body, it has been found out that the serum of diabetics with neuropathy is toxic to nerves in the body.[26]

Recent research suggests that in type 1 diabetics, the continuing autoimmune disease which initially destroyed the β-cells of the pancreas may also cause retinopathy, neuropathy, and nephropathy. Rather than controlling the blood sugar level, it has been suggested by one researcher that retinopathy may be better treated by drugs to suppress the abnormal immune system of diabetics. The familial clustering of the degree and type of diabetic complications indicates that genetics may also play a role in causing complications such as diabetic retinopathy and nephropathy. It has been found that there is an increased arterial stiffness and neuropathy in non-diabetic successors of type 2 diabetic despite normal blood glucose levels, and non-diabetic first-degree relatives of diabetics showed an elevated enzyme level associated with diabetic renal disease. Even rapid control of blood glucose levels has been shown to worsen rather than improve diabetic complications, though it has usually been thought that complications would improve over time with maintenance of normal blood sugar levels.[26] One study continued for 41 months found that the initial worsening of complications from improved glucose control was not followed by the expected improvement. In terms of pathophysiology, studies show that the two main types of DM (DM1 and DM2) cause a change in balancing of metabolites such as carbohydrates, lipids, and blood coagulation factors, and subsequently bring about complications such as microvascular and cardiovascular complications.[27]

Types of Chronic Complications

The one or more of the following are caused by the damage of small blood vessels that bring about to a microangiopathy: [28]

- Diabetic cardiomyopathy
- Diabetic nephropathy
- Diabetic neuropathy
- Diabetic retinopathy
- Diabetic encephalopathy.

The one or more of the following are caused by macrovascular disease: [29]

- Cardiovascular disease, to which accelerated atherosclerosis, is a contributor. Coronary artery disease leading to angina or myocardial infarction ("heart attack")

- Diabetic myonecrosis ("muscle wasting")
- Intermittent claudication which is exertion-related leg and foot pain and diabetic foot are contributed by peripheral vascular disease
- Stroke (mainly the ischemic type).

Diabetic foot, often occurs due to a combination of sensory neuropathy (numbness or insensitivity) and vascular damage, increases rates of skin ulcers (diabetic foot ulcers) and infection and, in serious cases, necrosis and gangrene. It is why diabetics are prone to leg and foot infections and why it takes longer for them to heal from leg and foot wounds. It is the most common cause of non-traumatic adult amputation, usually of toes and/or feet, in the developed world.

Diagnosis

Repetitive or constant hyperglycemia is the features of DM and is diagnosed if one of the following situations exists: [30]

- Fasting plasma glucose level ≥7.0 mmol/l (126 mg/dl).
- Plasma glucose ≥11.1 mmol/l (200 mg/dl) 2 h after a 75 g oral glucose load as in a glucose tolerance test.
- Symptoms of hyperglycemia and casual plasma glucose ≥11.1 mmol/l (200 mg/dl).
- Glycated hemoglobin (Hb A1C) ≥6.5%.

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above methods on a different day. Since the assessment and the significant time obligated for formal glucose tolerance testing take about 2 h to complete and offer no prognostic advantage over the fasting test, it is favorable to measure a fasting glucose level. Two fasting glucose measurements >126 mg/dl (7.0 mmol/l) are considered to be diagnostic for DM according to the current definition.

People with fasting glucose levels from 6.1 to 6.9 mmol/L (110–125 mg/dL) are considered to have impaired fasting glucose as per the World Health Organization. People with the plasma glucose at or >7.8 mmol/L (140 mg/dL), but not over 11.1 mmol/L (200 mg/dL), 2 h after a 75 g oral glucose load are considered to have impaired glucose tolerance. The major risk factor for progression of full-blown DM as well as cardiovascular disease is of these two prediabetic states. The American Diabetes Association since 2003 uses a slightly different value for impaired fasting glucose with range of 5.6–6.9 mmol/L (100–125 mg/dL). The determination of risks of the cardiovascular disease and death from any cause is best by glycated Hb than the fasting glucose. The rare disease diabetes insipidus has similar symptoms to DM, but without disturbances in the sugar metabolism (*insipidus* means "without taste" in Latin) and does not involve the same disease mechanisms.

Prevention

There is no known preventive measurement for type 1 diabetes. A person by maintaining normal body weight, physical exercise, and following a healthy diet can prevent type 2 diabetes. Dietary changes known to be effective in helping to prevent diabetes include a diet rich in whole grains and fiber, and choosing good fats such as polyunsaturated fats found in nuts, vegetable oils, and fish. Diabetes can also be prevented by eating less red meat and other sources of saturated fat along with limiting sugary beverages in their daily life. Active smoking is also associated with an increased risk of diabetes, so smoking cessation can be an important preventive measure as well.[31]

CONCLUSION

The word "metabolic curse" should be a trigger for those willing to pursue the understanding of biochemical and molecular basis of this metabolic disorder. Such an understanding will inform efforts to elucidate more effective management interventions against DM. Synthetic insulin with rapid actions, less adverse effects, ability to traverse all body compartments, as well as with longer durations of actions needs to be designed in the future. The oral hypoglycemic agents, which are apparently bedeviled by side effects, need to be optimized to mitigate these demerits. An optimized lifestyle management should be maintained to achieve the intended goal of lowering the glycemic index in diabetics.

Gene therapy will doubtlessly address the complications of DM. The pioneering gene therapy approach to DM was occasioned by the cloning of the insulin gene. The non-insulin producing cells that could be manipulated to produce insulin using a suitable promoter and insulin gene construct are the strategy for gene therapy. It was thought that these substitute cells could reclaim insulin production diabetics. Advances in molecular biology have enabled unraveling of the human genome. This development can be utilized to distinguish the insulin gene for its upcoming use in the management of diabetes. The immunological concerns underlying gene therapy can also be addressed by the current advances in molecular biology. However, regardless of all these analyses, it is essential to always perceive that the merits of the gene therapy of diabetes exceed the demerits and present advantages as compared with conventional treatment before this approach could gain widespread acceptance in general medical practice.

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