Metabolic Complications of Diabetes Mellitus: A Review

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Abstract

Diabetes mellitus is a metabolic disorder arising from deficiency of insulin by the pancreas or by the ineffectiveness of the insulin produced in the target cells. It is characterized by high levels of glucose in blood, which in turn damages many of the body systems particularly the blood vessels and nerves. This review explores the metabolic complications accompanying diabetes mellitus. It also provides a discussion of the pathogenesis of the complications of the disease.

Key words: Diabetes mellitus, Insulin, Complications, Pathogenesis

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Introduction

Diabetes mellitus is a chronic endocrinological disorder caused by inherited and/or acquired impairment in production of insulin by the pancreas or by the ineffectiveness of the produced insulin. The condition is characterized by high blood glucose levels, which in turn damages many of the body systems particularly the blood vessels and nerves. Such damage of the body systems is caused by disturbances in the regulatory systems responsible for the storage and utilization of the chemical energy from food. This includes the metabolism of carbohydrates, fats and proteins resulting from defects in insulin secretion, insulin action, or both.

There are two types of diabetes mellitus; type 1 or insulin dependent diabetes mellitus (IDDM) and type 2 or non-insulin dependent diabetes mellitus (NIDDM). Other forms of diabetes mellitus include secondary diabetes and gestational diabetes. However, it should be noted that assigning a type of diabetes to an individual often depends on the prevailing circumstances at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycaemic after delivery and may be destined to have type 2 diabetes mellitus. Similarly, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis.

According to WHO, more than 190 million people suffer from diabetes mellitus worldwide. The disease incidence is increasing rapidly and it is estimated that the figure will double by the year 2025. Most people with diabetes in developed countries will be aged 65 years or more by year 2025 yet, in developing countries the affected age bracket will be in the 45-65 year who are in their most productive years. It is expected that the prevalence of diabetes will continue to increase in Africa and Asia as a result of changes in lifestyles and urbanization. Forty nine million people suffer from the disease in South-East Asia; India alone accounts for almost a quarter of all patients in the region, with an estimate of 15 million people.

In the European continent an estimated 32.2 million patients suffer from diabetes; over a million of the cases being from United Kingdom alone. This figure accounts for over 2% of the UK population who suffer from the disease. Demographically, the Northern American continent has approximately 214 million. Latin America has an estimated 12.6 million diabetic patients. In the United States diabetes mellitus is the third leading cause of death after heart disease and cancer and it affects approximately 17 million adults. In Australia it is a disease of modern society and it is estimated that 700,000 people are diabetic. In 2000 there were 7.5 million cases of diabetes in Africa and the figure is expected to rise to around 18.2 million by the year 2030. All African countries are struggling to care for a large number of diabetic patients, yet more than 80% of the cases are undiagnosed.
The effects of diabetes mellitus include long-term damage and failure of various organs, progressive development of the specific complications such as retinopathy which leads to blindness, nephropathy which may lead to renal failure, and/or neuropathy which may cause foot ulcers, amputation, and autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular diseases. Several pathogenetic processes are involved in the development of diabetes. These include destruction of β-cells of the pancreas that lead to decreased sensitivity to insulin action\textsuperscript{16, 3}.

**Diabetic Complications**

Economic aspects of diabetes and diabetes care currently attract considerable attention as the world diabetes epidemic takes hold and the healthcare activities of countries come under pressure to accomplish more within constrained resources\textsuperscript{17}. Diabetes mellitus is a very expensive disease and has profound implications in terms of long-term microvascular and macrovascular complications and their associated cost. These complications reduce both life expectancy and quality of life\textsuperscript{18, 13}. The following is an in-depth discussion of the complications of diabetes mellitus.

**Diabetic Ketoacidosis**

Diabetic ketoacidosis (DKA) is one consequence of severe, out-of-control diabetes mellitus (high blood sugar, or hyperglycemia). In a diabetic, the spiral begins with a physiological stress that causes release of catecholamines, glucagon, and cortical. This stress may be emotional or physical, although the most common cause by far is infection (for instance, pneumonia or urinary tract infection)\textsuperscript{19}. Simply having uncontrolled hyperglycaemia may be sufficient to trigger an attack if significant dehydration occurs. This process is vastly more common in diabetes mellitus type I than in type II\textsuperscript{5}.

A key component of DKA is that there is essentially no circulating insulin. Without insulin, glucose cannot be transported out of the bloodstream to the cells. This occurs because the hormone glucagon inhibits cells from using glucose from outside, but instead secrete non-carbohydrate sources that can be used to make glucose, on which red blood cells are absolutely dependent and the brain mostly dependent in order to have energy\textsuperscript{20}. Glucagon is released into the bloodstream when circulating glucose is low. The main physiological role of glucagon is to stimulate hepatic glucose output, thereby leading to increases in glycemia. This provides the major counter-regulatory mechanism for insulin in maintaining glucose homeostasis in vivo\textsuperscript{21}.

By stimulation of glucagon, some amino acids can be converted to glucose (by gluconeogenesis). This is the only source in muscle tissue; the liver can also use the 'glycerol backbone' made available in its fat processing. Since neither protein nor amino acids are stored, amino acids used in glucose production must come from protein currently in use for other purposes. This explains the thin, wasted appearance of
those who have been starved: even in the face of adequate fat stores, muscle will be broken down to make glucose.\(^{20}\)

In starvation situations, the liver must produce another form of fuel. The brain is protected by the blood-brain barrier, which makes it unable to use fats for fuel. If it is to avoid using glucose, it must have a new energy source. The liver provides this by making ketone bodies from fats, then secreting them into the bloodstream. Normally, ketone bodies are produced in minuscule quantities, feeding only part of the energy needs of the heart and brain. In DKA, they rapidly become a major component of the brain's fuel.\(^{4}\)

As a result, the bloodstream is filled with glucose that it cannot use and that is spiraling higher and higher (as the liver continues gluconeogenesis and exporting the glucose so made). This significantly increases its osmolality. At the same time, massive amounts of ketone bodies are being synthesized, which in addition to increasing the osmolar load of the blood, are acidic. As a result, the pH of the blood is altered. Glucose begins to spill into the urine as the proteins responsible for reclaiming it from urine reach maximum capacity. As it does so, it takes a great deal of body water with it, resulting in dehydration. Dehydration worsens the increased osmolality of the blood, and forces water out of cells and into the bloodstream in order to keep vital organs perfused. The vicious cycle is now set, and if untreated will lead to coma and death.\(^{19}\)

**Diabetic Cataracts**

Cataracts occur commonly in patients with long-standing diabetes mellitus. It may be related to hyperglycemia. Glucose metabolism by the lens does not require presence of insulin. The epithelial cells of the lens contain the enzyme aldose reductase, which converts glucose into sorbitol. Sorbitol may be converted into fructose by sorbitol dehydrogenase. Sorbitol is retained inside the cells because of its difficulty to traverse plasma membranes. The rise in intracellular osmolality leads to increased water uptake and swelling of the lens.\(^{22}\)

**Retinopathy**

Diabetic retinopathy occurs when diabetes mellitus damages the tiny blood vessels in the retina. At this point, most people do not notice any changes in their vision. Some people develop a condition called macular edema. It occurs when the damaged blood vessels leak fluid and lipids onto the macula, the part of the retina that lets us see detail. The fluid makes the macula swell, blurring vision. As the disease progresses, it enters its advanced, or proliferative stage.\(^{23}\)

Fragile, new, blood vessels grow along the retina and in the clear, gel-like vitreous humour that fills the inside of the eye. Without timely treatment, these new blood vessels can bleed, cloud vision, and destroy the retina.\(^{24}\)
Neuropathy

Diabetic neuropathy results from decreased motor and sensory nerve conduction velocities caused by axonal degeneration and demyelination\textsuperscript{25}. Of the many types of diabetic neuropathy, both peripheral and autonomic, distal symmetric sensorimotor polyneuropathy is the most frequent. Besides causing pain in its early stages, this type of neuropathy eventually results in the loss of peripheral sensation. The combination of decreased sensation and peripheral arterial insufficiency often leads to foot ulceration and eventual amputation\textsuperscript{26}.

Acute-onset mononeuropathies in diabetes include acute cranial mononeuropathies, mononeuropathy multiplex, focal lesions of the brachial or lumbosacral plexus, and radiculopathies. Of the cranial neuropathies, the third nerve (oculomotor) is the most commonly affected, followed by the sixth (abducens) and finally the fourth (trochlear). All can present with diplopia and eye pain. In diabetic third nerve palsy, the pupil usually is spared, whereas in third nerve palsy caused by intracranial aneurysm or tumour, the pupil is affected in 80-90% of cases\textsuperscript{5}. However, consideration of nondiabetic causes for cranial nerve palsies is important, because 42% have been found to be due to causes other than diabetes\textsuperscript{26}.

Autonomic dysfunction can involve any part of the sympathetic or parasympathetic chains and produce myriad manifestations such as diabetic gastroparesis, vomiting, severe diarrhea, or bladder dysfunction and urinary retention\textsuperscript{27}.

Angiopathy

Angiopathy is a disease of the blood vessels (arteries, veins, and capillaries) that occurs when someone has diabetes for a long time. There are two types of angiopathies: macroangiopathy and microangiopathy. In macroangiopathy, fat and blood clots build up in the large blood vessels, stick to the vessel walls, and block the flow of blood. In microangiopathy, the walls of the smaller blood vessels become so thick and weak that they bleed, leak protein, and slow the flow of blood through the body. Then the cells, for example, the ones in the center of the eye, do not get enough blood and are damaged. Angiopathy increases the risk of coronary heart disease and stroke and leads to retinopathy and nephropathy\textsuperscript{28}.

Nephropathy

This is the damage to the glomeruli and its associated capillaries. It causes proteinuria and 25% to 30% of individuals treated for end-stage renal failure are diabetics\textsuperscript{29}. Patients with type 2 diabetes constitute the majority of diabetic patients with End Stage Renal Disease (ESRD). All patients with diabetes have the potential for renal impairment unless proven otherwise. Since chronic blood pressure elevation contributes to the decline in renal function, referral of patients with diabetes who are hypertensive for long-term blood pressure management is extremely important\textsuperscript{3}.
Atherosclerosis

Atherosclerosis is a condition caused by cholesterol build up and inflammation in arteries. This leads to lesions in arteries called plaques. These plaques are made up of excess cholesterol, other fats, and inflammatory cells in the artery wall. These plaques can lead to narrowing of arteries and cause symptoms from decreased blood flow such as chest pain (angina) or pain in legs (claudication). In addition these plaques can sometimes suddenly become unstable and rupture, leading to heart attacks and strokes. Atherosclerosis can be a progressive disease.

Epidemiologic data, autopsy findings, and prospective as well as retrospective analyses of clinical events in patients with diabetes mellitus indicate that atherosclerosis is the major cause of death. It has been estimated that men with diabetes have about a two-fold increased risk of death from cardiovascular disease and women greater than a four-fold risk when compared with age- and sex-matched populations. Major contributors to these statistics are deaths related to coronary artery atherosclerosis and peripheral vascular disease in the diabetic population. Atherosclerosis appears to proceed at a more rapid rate and is more extensive in diabetic than in non-diabetic patients. Yet, the process does not differ from atherosclerosis in the non-diabetic patient, either in its morphological appearance or in its distribution among vessels.

Atherosclerotic occlusive vascular disease is the most common complication of diabetes especially in type 2 diabetic patients. The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can have many characteristics of an inflammatory disease. These lesions occur principally in large and medium sized arteries and can lead to ischemia of the heart, brain, or extremities, resulting in infarction, stroke or peripheral extremity ischemia.

The diabetic individual has a 2-3 fold higher risk of dying prematurely of atherosclerosis than a non-diabetic individual. Therefore, the physician and diabetic patient must be aggressive in reducing the risk factors linked to heart attacks and strokes. The approach to prevent hyperlipidemia and atherosclerosis is therefore to reduce triglycerides while increasing HDL-cholesterol levels. A high cholesterol level is reduced by following a healthy diet and lifestyle.

Hyperosmotic Diabetic Coma

This is also known as nonketotic hyperosmolar syndrome (HNKS). It has some symptoms in common with DKA, but a different cause, and requires different treatment. In anyone with very high blood glucose levels, water is osmotically driven out of cells into the blood. The kidneys also "dump" glucose into the urine, resulting in concomitant loss of water, causing an increase in blood osmolality. The osmotic effect of high glucose levels combined with the loss of water results in such a high serum osmolality that the body's cells become directly affected as water is drawn out from them. Electrolyte imbalances are also common. This combination of changes, if prolonged, results in symptoms similar to
ketoacidosis, including loss of consciousness. This is the diabetic coma to which type 2 diabetics are prone and, for still obscure reasons, less common in Type 1 diabetics.\(^{39}\)

**Diabetic Foot Ulcers**

Diabetic foot ulcers contribute significantly to the morbidity and mortality of patients with diabetes mellitus. The risk factors for developing diabetic foot ulcers are manageable. The diabetic foot ulcer risk factors include poor glycaemic control, diastolic hypertension, dyslipidaemia, and infection and poor self-care. Therefore, specific attention should be paid to the management of these risk factors in patients with or without diabetes foot ulcers in the clinic.\(^{40}\)

Diabetic foot leads to peripheral neuropathy, peripheral vascular disease, superimposed infection, or a combination of these complications. Between 50% and 70% of all nontraumatic lower-extremity amputations occur in diabetic patients. The insensate, poorly perfused foot is at risk for ulcers from pressure necrosis or inflammation from repeated skin stress and unnoticed minor trauma. Diabetic foot ulcer can both evolve into cellulitis, osteomyelitis, or nonclostridial gangrene and end in amputation.\(^{41}\)

Diabetic patients presenting with wounds, infections, or ulcers of the foot should be treated intensively. Many patients need a vascular evaluation in conjunction with local treatment of the foot ulcer, since in some cases a revascularization procedure is required to provide adequate blood flow for wound healing.\(^{41}\)

**Infections**

Infections, such as malignant otitis externa, rhinocerebral mucormycosis, and emphysematous pyelonephritis, occur in patients with diabetes. Certain infections, such as Staphylococcal sepsis, occur more frequently and result in greater mortality rates in patients with diabetes. Others, such as Pneumococcal pneumoniae, affect diabetic patients at a similar frequency to that of the general population. Patients with long-standing diabetes also tend to develop micro- and macro-vascular diseases with resulting poor tissue perfusion and increased risk of infection. The ability of skin to act as a barrier to infection is compromised when the diminished sensation of diabetic neuropathy results in unnoticed injury.\(^{26}\)

Malignant or necrotizing otitis externa occurs in diabetic patients older than 35 years and is caused by Pseudomonas aeruginosa. The infection starts in the external auditory canal and spreads to the adjacent soft tissue, cartilage, and bone.\(^{62}\) Patients with diabetes have an increased risk of cystitis of upper urinary tract infection. Intrarenal bacterial infection is considered in the differential diagnosis of any patient with diabetes who presents with flank or abdominal pain. Sensory neuropathy, atherosclerotic vascular disease, and hyperglycemia all predispose diabetic patients to skin and soft-tissue infections. Diabetic patients have a greater incidence of Staphylococcal and P. pneumoniae infections.
than persons without diabetes. Diabetes is also a risk factor for reactivation of tuberculosis\textsuperscript{43}. Cryptococcal infections and coccidioidomycoses are more virulent in diabetic patients. Mucormycosis is also common in diabetics. Mucormycosis is the name given collectively to the infections caused by various ubiquitous molds. Invasive disease occurs in patients with poorly controlled diabetes, especially in conjunction with DKA\textsuperscript{44}.

**Hyperlipoproteinemia**

Abnormalities in circulating lipids are seen in diabetics. The most characteristic pattern is that of increased Very Low Density Lipoprotein (VLDL), which is manifested by elevation of plasma triacylglycerols and cholesterol but the former predominates. Insulin deficiency leads to hyperglycemia and enhanced lipolysis. Glucose and free fatty acids flow to the liver, where they are utilized for VLDL synthesis\textsuperscript{23}.

This complication predisposes to atherosclerosis and myocardial infarction. Increased levels of Very Low-Density Lipoproteins (VLDL) are associated with type 2 diabetics\textsuperscript{36}. High-Density Lipoproteins (HDL) are lower in diabetics\textsuperscript{35}. This is expected in light of the cholesterol content of the different types of lipoproteins.

**Macrovascular Disease**

Macrovascular disease is the leading cause of death in patients with diabetes. Diabetes alone causes a higher risk of myocardial infarction (2-fold increase in men, 4-fold increase in women), and many diabetic patients have other risk factors for Myocardial Infarction (MI) as well. The risk of stroke is double that of non-diabetic patients and the risk of peripheral vascular disease is 4-fold higher in diabetic patients than in non-diabetic patients. Subtle differences in the pathophysiology of atherosclerosis in patients with diabetes result in both earlier development and a more malignant course. Patients with diabetes must therefore have their measurable lipid abnormalities treated aggressively to lessen their risk of developing serious atherosclerosis\textsuperscript{26}.

Patients with diabetes have an increased incidence of silent ischemia. Silent ischemia, however, is common in many patients with cardiovascular disease (CAD), and the apparent higher incidence in patients with diabetes is related to the fact that they are more likely to have CAD to begin with\textsuperscript{3}.

**Hypoglycemia**

Hypoglycemia causes numerous neurogenic problems, ranging from the mild to severe coma, seizures, and death. The level of blood glucose when symptoms become obvious varies but tends to be less than 500mg/L for adults and 400mg /L for newborns. This potentially life-threatening disorder is the result of treatment of hyperglycemia with insulin, due to mismanagement. However, aggressive use of insulin treatment to maintain normoglycemia increases the risk of hypoglycemia\textsuperscript{45}. 
Effects of Diabetes on the Foetus

The fetus of a pregnant diabetic is at risk for adverse complications directly resulting from hyperglycemia. These include spontaneous abortion, birth defects, and macrosomia. The risk for these complications is directly related to the degree of maternal hyperglycemia and is reduced if greater glycemic control is enforced, especially during the early weeks of pregnancy\textsuperscript{46,47}.

Pathogenesis of Diabetic Complications

Protein Glycosylation

Glycosylation of the basement membrane of blood vessels causes basement membrane thickening similar to that found in most if not all diabetics\textsuperscript{48}. Functional alterations of immunoglobulin G (IgG) by nonenzymatic glycosylation are associated with increased susceptibility to infection. Based on these and other findings, it is possible that “many of the complications of diabetes are caused by glycosylation of specific proteins, which impairs their functions and results in diseases such as diabetic nephropathy”\textsuperscript{49}.

Nonenzymatic protein glycosylation commonly occurs in erythrocytes, glomeruli and nerve cells as well as in other tissues. The extent of the glycosylation is proportional to extracellular glucose concentrations. Excessive glycosylation produces significant alterations in a protein’s physical and biochemical properties. For example, glycosylation of α-crystallin, a protein occurring in the lens of the eye, greatly reduces its solubility. Hyperglycaemia in rats increases α-crystallin glycosylation simultaneously with cataract formation\textsuperscript{50}.

Sorbitol Accumulation

The intracellular accumulation of sorbitol could also explain diabetic complications. Aldose reductase reduces glucose to sorbitol, which is in turn oxidised to fructose by sorbitol dehydrogenase. Sorbitol does not easily cross cell membranes. The removal of sorbitol from the cell depends on its conversion to fructose, which passes through the cell membrane. However, in hyperglycemic conditions, the quantities of sorbitol produced outstrip the cell’s ability to convert sorbitol to fructose, resulting in the intracellular accumulation of sorbitol. Intracellular accumulation of ketones, glucose and sorbitol causes osmotic swelling and injury to cell structures\textsuperscript{51}.

Only cells that do not depend on insulin for glucose transport across plasma membranes are affected. These cells include nerve, ocular lens and glomerulus cells. This osmotic effect is the cause of life-threatening cerebral edema that occurs during treatment of DKA and HNKS. The decreased blood osmolality after treatment increases the shift of extracellular water into brain cells. This possibility is supported by elevations in sorbitol and fructose levels in the nerve and ocular lens cells\textsuperscript{51}. The strongest support of this possibility is derived from studies utilizing aldose reductase inhibitors such as sorbinol and tolrestat, which improve nerve conduction in diabetic rats and humans\textsuperscript{52}.
Conclusion

Diabetes mellitus affects multiple organ systems. The management strategies should be as common as the eye, foot, and kidney evaluations that are routinely performed as part of preventive medical therapies. Medical professionals with a thorough understanding of current medical treatment regimens and the implications of diabetes should help their diabetic patients achieve and maintain the best possible state of health. Early diagnosis of diabetes mellitus greatly assists in management of blood glucose levels, a situation that subsequently alleviates the possibility of onset of the complications of diabetes mellitus.

References

