

## Editorial

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Volume 2 : Issue 2

Article Ref. #: 1000DROJ2e005

### Article History

Received: September 12<sup>th</sup>, 2016

Accepted: September 12<sup>th</sup>, 2016

Published: September 12<sup>th</sup>, 2016

### Citation

Ojo O. An overview of diabetes and its complications. *Diabetes Res Open J*. 2016; 2(2): e4-e6. doi: [10.17140/DROJ-2-e005](https://doi.org/10.17140/DROJ-2-e005)

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# An Overview of Diabetes and its Complications

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Diabetes mellitus is a metabolic disorder in which the body's capacity to utilise glucose, fat and protein is disturbed due to impairment in insulin secretion and/or insulin resistance leading to chronic hyperglycaemia. Therefore, having an understanding of the underlying pathophysiology and the acute and/or long-term complications of diabetes will enable the development of strategies for ameliorating the condition. Individuals may be classified as having pre-diabetes or diabetes based on their fasting blood glucose and/or postprandial blood glucose. In this regard, individuals with impaired fasting glycaemia (IFG) have fasting plasma glucose >6.1 mmol/L to <6.9 mmol/L.<sup>1</sup> On the other hand, impaired glucose tolerance (IGT) is in the range of >7.8 mmol/L to <11.1 mmol/L following a 2 hour oral glucose tolerance test and both IFG and IGT define the extent of glucose dysregulation between the range of normoglycaemia and type 2 diabetes. The diagnostic criteria for patients with diabetes are fasting plasma glucose  $\geq 7.0$  mmol/L and oral glucose tolerance Test (OGTT)  $\geq 11.1$  mmol/L.<sup>1</sup> While normal fasting glucose depends on the ability to sustain the production of basal insulin and promotion of insulin sensitivity at the level of the liver, IFG results from abnormalities of these metabolic functions and are often characterised by raised hepatic glucose output and defect in early insulin secretion.<sup>2</sup> However, during OGTT, the normal body's response is usually in the form of increased insulin secretion, decreased hepatic glucose production and enhanced glucose uptake in the liver and the muscle. Therefore, IGT is often associated with peripheral insulin resistance, mostly in the skeletal muscle. In addition to IFG and IGT, other risk factors for type 2 diabetes include genetics/family history, environmental factors such as type of diet and physical activity, obesity, age and body fat distribution.

It is clear that the symptoms of diabetes such as polyuria, blurring of vision, thirst and weight loss are common in patients with diabetes. In terms of complications, diabetes could be classified in a number of ways. It may be in the form of acute complications or long-term complications of diabetes. Acute or diabetic emergencies may include hypoglycaemia, hyperglycaemia, Diabetic ketoacidosis and hyperosmolar hyperglycaemic state. On the other hand, long-term complications of diabetes may include neuropathy, nephropathy, retinopathy and cardiovascular diseases.

Diabetic complications may also be classified based on whether the manifestation is physical such as lipohypertrophy or the complications are metabolic-hypoglycaemia, hyperglycaemia. However, in broad terms, diabetic complications can be classified into microvascular complications which are of major concern in patients with type 1 and type 2 diabetes and macrovascular complications which are common in patients with type 2 diabetes. Examples of microvascular complications are neuropathy, nephropathy and retinopathy, while common macrovascular complications include cardiovascular diseases, cerebrovascular disease and peripheral vascular disease.<sup>3</sup>

In terms of acute complications of diabetes, hypoglycaemia occurs when blood glucose levels fall below 4 mmol/L, but many people experience hypoglycaemic symptoms at higher or lower levels, depending on their own usual blood glucose levels. Although the symptoms of hypoglycaemia vary between individuals, they are partly due to lack of glucose for the nervous system (neuroglycopenia) and partly due to sympathetic nervous system and

adrenaline response. On the other hand, diabetic ketoacidosis (DKA) is characterized by hyperglycaemia, ketosis and metabolic acidosis. It results from absolute or relative insulin deficiency leading to glucose dysregulation, the release of counter regulatory hormones including catecholamines, glucagon and cortisol.<sup>4</sup>

Although lipolysis is a normal biochemical process, it becomes unregulated in DKA and leads to the formation of serum free fatty acids, which are used for the production of large quantities of ketone bodies (acetoacetate,  $\beta$ -hydroxybutyrate ( $\beta$ -OHB), and acetone), and consequently, metabolic acidosis.<sup>4</sup>

While DKA may become evident within hours of onset, the commencement of Hyperosmolar Hyperglycaemic State (HHS) may present in days and as a result there is increased risk of dehydration and extreme metabolic disturbance.<sup>5</sup> Therefore in patients with HHS, there is usually high osmolality (often  $\geq 320$  mOsmol/Kg); high blood glucose level (usually  $\geq 30$  mmol/L) and severe dehydration.<sup>5</sup>

The microvascular complications of diabetes often have long-term impact. There is increasing evidence that hyperglycaemia may be responsible for the range of pathological changes that result in diabetic complications following prolonged exposure to high glucose levels.<sup>3</sup> Firstly, glucose is the primary source of energy production through oxidative phosphorylations and hyperglycaemia has a major impact on metabolic pathways which are related to cellular energy production especially in the mitochondria. Most cells have the capacity to enhance glucose transport across the plasma membrane into the cytosol to maintain glucose homeostasis in the presence of hyperglycaemia. However, some cells such as capillary endothelial cells in the retina, mesangial cells in renal glomeruli and neuronal cells in the peripheral nerves are not able to adapt and promote glucose transport significantly to prevent intercellular changes in glucose concentration.<sup>3</sup> Therefore, chronic tissue damage may be present in patients with diabetes and this is generally related to the severity and duration of hyperglycaemia. According to Tagulchi and Brownlee,<sup>6</sup> most of the effect of chronic diabetes relates to the microcirculation. With the long standing disease, there is a progressive narrowing and subsequent blockage of vascular lumina, resulting in poor perfusion, ischaemia and dysfunction of the tissues that are affected.<sup>6</sup>

The four possible mechanisms of microvascular complications may be based on hyperglycaemia induced biochemical changes and includes; increased flux of glucose and other sugars through the polyol pathway; formation of advanced glycation end-products (AGEs); activation of protein kinase C (PKC) isoforms and increased flux through the hexosamine pathway.<sup>7</sup>

The polyol pathway is normally inactive, but may become active when intracellular glucose levels rise. The impact of increased glucose flux *via* the polyol pathway includes the production of powerful glyating sugars (methylglyoxal, acetol and triose phosphates), enhanced oxidative damage and Protein Kinase C (PKC) activation.<sup>6</sup> In this pathway, aldose reductase reduces glucose to its sugar alcohol, sorbitol. Aldose reductase is found in tissues such as nerves, the retina, the glomeruli and the blood vessel walls where glucose uptake is independent of GLUT 4 and insulin.<sup>7</sup> In addition, sorbitol is subsequently oxidised to fructose which eventually contributes to the mitochondrial respiratory chain. Sorbitol does not diffuse easily across the cell membranes and damage may occur because of sorbitol induced osmotic stress.

On the other hand, AGEs are formed by the reaction of glucose and other glyating compounds such as methylglyoxal with proteins. AGEs may cause damage to cells through changing of cellular protein function by cross-linking extracellular matrix molecules such as collagen and laminin, which in the blood vessels increases wall thickness and permeability, and decrease elasticity.<sup>3,7</sup> The binding of AGEs to its receptors leads to the generation of reactive oxygen species and increased vascular permeability.

Protein kinase C (PKC) is an enzyme that phosphorylates a large number of proteins and exists in several isoforms. It is activated by diacylglycerol which is stimulated by hyperglycaemia. Excessive activation of PKC is a further mechanism by which glucose may induce tissue damage in organs that are prone to complications.<sup>3</sup> The over production of PKC has been implicated in increased vascular permeability, blood flow changes and increased basement membrane synthesis.

With respect to the Hexosamine pathway, this occurs when intracellular glucose is high. Then the normal glucose-6-phosphate metabolic cascade is disrupted and a series of moieties are produced that bind to transcription factors and increase the synthesis of some proteins which have adverse effects on blood vessels. Hyperglycaemia shunts glucose into the hexosamine pathway and fructos-6-phosphate is diverted from glycolysis to form UDP-N-acetylglucosamine, used in the synthesis of glycoproteins.<sup>7</sup>

Despite the challenges of acute and/or long term complications of diabetes, these can be prevented and their progression can be delayed through tight control of blood glucose and reduction of other risk factors of diabetes.

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