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TYPE TWO DIABETES MELLITUS: AN OVERVIEW OF PREVALENCE, PATHOGENESIS, COMPLICATIONS AND TREATMENT OPTIONS

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ABSTRACT

Type two diabetes mellitus (DM) is metabolic disorder characterised by hyperglycaemia and poses a major public health challenge due to its deleterious effects on the human vascular tree through subsequent associated morbidity and mortality. Insulin resistance and impaired insulin secretion disturb the balance by which insulin target tissues communicate with β-cells and vice versa through β-cell dysfunction, leading to increased hepatic glucose production. β-cell dysfunction and consequent destruction may be caused by any one or combination of lipotoxicity, glucose toxicity or β-cell exhaustion. Sustained hyperglycaemia will eventually result in DM, which when left untreated, will lead to the development of macro- and microvascular complications. Effective control and management of diabetes is necessary to delay the development of microvascular and macrovascular disease, and requires a concerted, multidisciplinary approach involving all healthcare workers as well as the patient to ensure compliance to a tailored treatment regime.

KEYWORDS

Type two diabetes mellitus (DM), Insulin resistance, hyperglycaemia

INTRODUCTION

Type two diabetes mellitus (DM) is metabolic disorder characterised by the interplay between β-cell dysfunction and insulin resistance,[1] posing a major public health challenge due to its deleterious effects on the human vascular tree[2] through subsequent associated morbidity and mortality.[3] There has been an increase in the prevalence of DM particularly in developing countries,[4] which is bordering on epidemic proportions, with a concomitant strain on healthcare resources.[5]

Worldwide statistics indicate that approximately 415 million people are currently diagnosed with DM, with the annual mortality due to DM complications reported in 3.8 million patients annually.[6] The prevalence of DM is projected to double by the year 2040,[7] with the numbers in Sub-Saharan Africa also on the rise. Although these numbers are staggering, they do not include the approximately 62% of cases in Africa which are undiagnosed.[7] With increasing influence of Western lifestyle and dietary habits, African societies have switched to energy-dense diets, increasing their consumption of sugar, fat and salt, giving rise to an increase in nutritional deficiencies, while causing overweight and obesity and subsequently, diabetes mellitus.[8]

In South Africa the prevalence of DM is estimated to afflict approximately 2.65 million of 32 million adults.[7] In fact, the mortality statistics in South Africa showed that DM had the second highest increase in cause of death after HIV from 2004-2005.[9] The prevalence varies in different ethnic groups, from13.1% to 26.3%.[10,11,12]

Although genetics has undoubtedly a role in the development of DM, the mode of inheritance remains unclear, and genetics only account for a small proportion of diabetes.[13] The upward trend in DM prevalence is thought to be fueled by the emergence of other factors, for example, environmental, the increased life expectancy as a result of improved pharmacotherapy[14] and by the increase in the population size. Another cause is attributed to urbanisation, particularly the adoption of a more sedentary lifestyle and the development of obesity, which acts to worsen insulin resistance and β-cell function.[15] When these factors are superimposed onto a glucose homeostasis system compromised by genetic propensity, they serve as triggers for the expression of those genes conferring risk for DM.[16] What is increasingly apparent is the strong influence of environmental factors, particularly obesity, in the pathogenesis of diabetes mellitus. This is of concern as current data shows that 13.5% of South African children aged 6-14 years are overweight,[17] comparable with developed countries, and one of the highest in Africa.[18] Patients with DM are considered to have a coronary artery disease risk equivalent to that of a patient without DM, but with a myocardial infarct history.[19] Therefore strategies aimed at staunching the development of this condition should be prioritised, and to do this, an understanding of the pathogenesis and pathophysiology of DM is useful.

PATHOGENESIS

Normally, plasma glucose concentrations are maintained within a narrow range through strict regulation between tissue sensitivity to insulin and insulin secretion.[20] The underlying pathophysiology of DM ensues as a result of the defects in insulin secretion, insulin action or a combination of both, leading to a deficiency in the metabolism of proteins, fats and carbohydrates.[21] The underlying physiological cause of diabetes is a failure of the pancreatic β-cells to provide sufficient amounts of insulin to meet the body's needs and this results in a progressive increase of plasma glucose levels. The current understanding is that the β-cell defect occurs at the time of transition from normal glucose tolerance to impaired glucose tolerance (IGT) and is the key pathogenic event that causes that progression to DM.[14] The exact mechanism for β-cell dysfunction at the cellular level is unknown, but current research supports a few hypotheses.

One such mechanism relates to that of lipotoxicity,[22] where, in a hyperglycaemic state, metabolites from excess fatty acids and precursors for oxidative stress lead to β-cell dysfunction and death.[23] Another mechanism for β-cell dysfunction is when they undergo glucose toxicity, where, in the presence of abnormally high glucose levels, fundamental β-cell physiology in the form of major metabolic pathways, key enzymes and gene expression is altered.[24] In the early stages, a compensatory increase in insulin secretion from the pancreas occurs in order to overcome impaired insulin action in the peripheral tissues, resulting in a compensatory increase in β-cell mass to maintain normoglycaemia[25] and is characterised by increased levels of plasma insulin which is the hallmark of impaired glucose tolerance and insulin resistance. As impaired glucose tolerance progresses to diabetes, insulin levels decline, due to decreased secretion from progressive deterioration of β-cell function in the form of ß cell exhaustion.[24] This continuing deterioration is the reason that patients with diabetes become non-responsive to oral pharmacological agents, and require insulin for glycaemic control.[26] The resulting hyperglycaemia contributes to the development of metabolic complications, which, over time, will lead to the development of micro-vascular complications.

SCREENING AND DIAGNOSTIC TESTING

The normal levels of plasma glucose are between 3.3mmol/L – 5.9mmol/L.[27] Blood glucose measurements for the diagnosis of DM should not be based on a single blood glucose measurement, particularly in the individual who does not display the classical symptoms (unexplained weight loss, polydipsia and polyuria).[27] The guidelines set out by the Society for Endocrinology Metabolism and Diabetes of South Africa (SEMDSA),[27] in consultation with the WHO recommend that the diagnosis of DM be based on the criteria outlined in Table 1.

Current data shows that this control is not being achieved in either state or public hospitals in South Africa,[28] and that the long-term complications which invariably result is creating an exceedingly higher burden on the healthcare system which is already contending with that of HIV and other infectious diseases.

COMPLICATIONS

Uncontrolled DM can lead to the development of complications, and may be grouped into either microvascular or macrovascular disease[2] -co-morbid conditions like hypertension or dyslipidaemia often accelerates the risk of these complications. The common mechanisms for the development of microvascular disease are related to aldose reductase, which is the initial enzyme in the polyol pathway.[2] In chronic hyperglycaemia, the excess glucose is shunted into the polyol pathway, and is converted into sorbitol.[29] Sorbitol accumulates within the cells, resulting in osmotic stress. Cell injury from irreversible cross-linked protein derivatives called advanced glycosylated end products (AGEs) is yet another mechanism that has been postulated, with these resulting in microaneurysm formation, basement membrane thickening and pericyte loss.[29]

Microvascular complications such as diabetic retinopathy is regarded as the most common microvascular complication of DM[2] and the main cause of visual impairment and blindness in people with DM.[30] Hyperglycaemia impairs retinal blood flow, increases inflammatory cell adhesion to retinal blood vessels, resulting in capillary blockage and consequent hypoxia to the retina.[31]

Diabetic nephropathy has similar underlying mechanisms as DR, and is defined by proteinuria > 500mg in 24 hours in the setting of diabetes.[32] This condition is accompanied by such changes as increased glomerular basement membrane thickness, glomerular hyperfiltration, mesangial extracellular matrix expansion, which increases urinary albumin excretion. These events eventually progress to glomerular sclerosis and ultimately, renal failure.[33]

Diabetic neuropathy is also very common complication in people with diabetes, and manifests as peripheral nerve dysfunction after a few years of poor glucose control.[34] Hyperglycaemia, through the accumulation of sorbitol and fructose, impairs neuronal structural microvasculature, causes abnormal action potential propagation, and eventually leads to demyelination. This may manifest as loss in sensation in the lower extremities, as well as impaired peripheral vascular function. This in turn, can contribute to lower-extremity ulceration.[29]

Diabetes-related cardiomyopathy is related to changes in the structure and function of the myocardium not directly linked to coronary artery disease (CAD) or hypertension,[35] which may confound the aetiology. Recent data suggests that myocardial insulin resistance may specifically predispose cardiac mitochondria to ROS overproduction and mitochondrial uncoupling and damage.[36] Diabetic cardiomyopathy is characterised by abnormalities in diastolic filling and relaxation, and later, systolic dysfunction and heart failure.[36]

Macrovascular disease occurs through a multifactorial process, which involves the vascular endothelium.[37] Hyperglycaemia inhibits the action of the enzyme responsible for the production of nitric oxide (NO), an arterial vasodilator (endothelial nitric oxide synthase [eNOS]). Hyperglycaemia also increases the production of ROS, which, together with AGE, leads to

Table 1: SEDSMA criteria for the diagnosis of diabetes mellitus, impaired glucose tolerance and impaired fasting glucose.[27]

Category	Diagnostic test			
	Fasting plasma glucose	OGTT	Haemoglobin A1c	Random plasma glucose
IFG	6.1-6.9mmol/L	<7.8mmol/l		
IGT	<7.0mmol/L	7.8-11.0mmol/l		
Diabetes mellitus	>=7.0mmol/L or	>=11.1mmol/l or	>=6.5% or	>=11.1mmol/l in presence of classic symptoms or hyperglycaemic crisis

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; OGTT: oral glucose tolerance test

further inhibition of eNOS production, impairing the vasodilatory response.[29,38] This impairment may be further exacerbated by the overproduction of vasoconstrictor substances like endothelin- 1. Another mechanism is through insulin resistance, which stimulates the protein kinase (PKC) pathway, increasing ROS generation, which in turn, reduces eNOS activity.[38] These processes contribute to impaired platelet function and a hyper coagulative state leading to increased risk of vascular occlusion and other cardiovascular events. The increased inflammatory state forms the substrate for atherosclerosis, which is the central pathological mechanism for the development of macrovascular disease in DM,[39] and may manifest as cerebrovascular and peripheral artery disease (PAD).

Cerebrovascular disease occurs when intracranial or extracranial atherosclerosis diminishes cerebrovascular circulation, with a 2- to 4-fold greater risk of development in patients with diabetes.[40] PAD is characterised by the occlusion of the lower-extremity arteries, and patients would experience claudication and pain on physical exertion.[32] Severe PAD may progress to foot ulceration and eventual lower-extremity amputation.

Early detection and management of DM is critical to reduce the development of complications related to hyperglycaemia.

STRATEGIES FOR CONTROL AND TREATMENT OF HYPERGLYCAEMIA

Achievement of glycaemic control is the main goal of effective DM management, and this can be done by adopting any of a variety of strategies. Frequent reassessment of glycaemic control is necessary for monitoring outcomes as well as detecting complications before they advance. In addition, recent data advocates for a multidisciplinary approach to DM management,[41,42] and some of the strategies are described below.

• *Education and self-monitoring of blood glucose*

It is already established that education of patients with DM improves patient adherence with therapeutic goals and treatment strategies in order to delay complications associated with DM.[41] However, this approach needs full patient participation and motivation in core areas like the disease pathophysiology, treatment options including nutrition and lifestyle changes, how to monitor their blood glucose as well as how to recognise and delay complications.[42]

• *Pharmacological*

Biguanides such as metformin are anti-hyperglycaemic, but not hypoglycaemic. They act in various ways such as increasing peripheral uptake of glucose,and reducing hepatic glucose output by approximately 20-30% as well as impairing the absorption of glucose from the gut.[43]

Insulin secretagogues like sulfonylureas cause hypoglycaemia in a functional pancreas by stimulating the release of insulin from the pancreatic β-cells. Sulfonylureas bind to sulfonylurea receptors on the β-cell plasma membrane, causing closure of adenosine triphosphate- sensitive potassium channels, leading to depolarisation of the cell membrane. This in turn opens voltage gated channels, allowing influx of calcium ions and subsequent secretion of preformed insulin granules.[44]

• *Insulin*

Insulin therapy is regarded as the most effective treatment for lowering extremely high glucose, and inhibit glucotoxicity, which in turn, may preserve functional β-cell mass.[45] But in order for insulin to achieve its desired effects, it needs to be administered correctly and timeously, and in dosages which are appropriately titrated.

Thiazolidinediones are a class of oral anti-diabetic drugs which enhance target tissue insulin sensitivity. Although the exact mechanism of action is not currently understood, the major action is to improve insulin sensitivity in the muscle and adipiose tissue.[44]

• *Lifestyle changes*

There is a plethora of evidence to show that onset of diabetes in persons with IGT may be delayed with adoption of low glycaemic index or low-fat diets, together with weight loss through an exercise programme.[46] However, this traditional approach has been challenged by Professor Tim Noake's high fat, low carbohydrate diet,[47] which has attracted much criticism and controversy regarding its actual benefits,[48] with the SEMDSA[27] cautioning against 'restrictive diets and fad diets ("carb-free", "high-protein", "fat-free", very low calorie diets etc.)'.

• *Bariatric surgery*

Recent reports show that bariatric surgery has been effective in DM remission and restoration of euglycaemia in the majority of patients.[49,50] Although the exact mechanism remains unclear, the 'hindgut hypothesis'[51] suggests when nutrients arrive at the distal intestine, insulin otropic hormones like glucagon like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY) are produced. In spite of the benefits bariatric surgery is also subject to the risks of any surgical procedure, with the added negative effects as a result of malnutrition: patients may develop iron-, vitamin B12 deficiency, as well as reduced calcium and vitamin D absorption being very common.[52] In addition, long-term evaluation to weigh the risks against the benefits has yet to be established.

CONCLUSION

There is currently no cure for type two diabetes mellitus, but the risk of complications due to long-term diabetes can be reduced by adopting healthy lifestyle choices, including control of blood sugar levels through physical activity, healthy diet and medication. In keeping with international trends, the prevalence is poised to increase, and South Africa will not be spared. Our lifestyle habits are fueling the onset of the prevalence of DM in younger individuals, with increases in childhood obesity and augurs poorly for the future burden of this condition.[14] This review supports the call to direct resources to further research that unlocks understanding of the social and physical environments and factors which influence as well as promote unhealthy behaviour and practices amongst South Africans, so that these may be remedied.[53] Although healthy lifestyle intervention programmess have been shown to be effective in reducing the incidence of diabetes,[28] the challenge remains to develop multidisciplinary strategies to reduce the incidence of DM.

One such strategy should be early identification of pre-diabetes and preventing its progression to DM,[27] particularly in high-risk individuals using screening tools. However, to achieve maximum benefit from these interventions, support from government and public health authorities needs to be garnered. In addition,

until newer advances in pharmacotherapy is made available to the community, further research must be undertaken to elucidate screening methods which would be cost-effective and display high sensitivity, yet be accessible and simple enough to use in the South African context, which is at the resource-limited primary health care clinic level.

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