



METABOLIC AND CLINICAL SIGNIFICANCE OF DIABETES MELLITUS TYPE 2; IMPLICATION FOR RISING PREVALENCE IN NIGERIA

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Abstract

Type 2 diabetes mellitus (DM2) is now a global epidemic which is also ravaging developing countries including Nigeria. Its impact in the country is significant with the disease found to impact on hospital admissions, mortality and life expectancy of patients. Previous investigations done in Nigeria showed that DM2 patients have poor glycaemic controls with resultant high levels of disease morbidity and mortality. This was demonstrated by consistently elevated mean HbA1c levels (> 8.0%) in Nigerian diabetics over a decade of assessment of care of the patients. Similarly the prevalence of diabetic retinopathy rose by more than 200% between 1989 and 2008. Diabetic morbidity which is underpinned by hyperglycaemia is associated with diabetic retinopathy, nephropathy, foot ulcers and other clinical conditions such as hyperlipidaemia, altered sympathetic system, bone disorders, infertility, defective body sodium handling and renal compromise. Some investigators believe that persons of African ancestry are more susceptible to some diseases associated with DM2. This includes documented increased renal glomerular hyperfiltration in patients of African ancestry. The disease complications are linked to metabolic derangements which if properly understood and managed, may help to reduce the impact of the rising prevalence of DM2 in Nigeria. Furthermore, if the Nigerian medical team is aware of the peculiar susceptibility of blacks to DM2 complications, they will be able to apply appropriate treatment for improved care, despite rising disease prevalence.

Keywords: Clinical significance, Metabolic, Nigeria, Prevalence, Type 2 DM.

Introduction

Diabetes mellitus type 2 (DM2) is the commonest form of diabetic disease and it accounts for about 90–95% of the cases in hospital and community. Unlike type 1 diabetes mellitus which is characterised by absolute lack of insulin, DM2 patients have hyperinsulinaemia with relative insulin deficiency. Most patients, especially in the initial period of the disease, have normal or elevated insulin levels. The high concentration of plasma glucose despite raised plasma insulin levels indicates insulin resistance, suggesting a need for increased secretion of insulin by affected individuals in order to suppress elevated endogenous production of glucose, for the establishment of euglycaemia.¹ The contribution of obesity to DM2 prevalence is significant and it is a

major cause of insulin resistance. Due to a delay in diagnosis of DM2 and accompanying gradual development of hyperglycaemia, the patients are at a high risk of vascular (microvascular and macrovascular) complications. The essence of this review is to evaluate and identify peculiar issues of DM2 that pertains to persons of African origin. These are in terms of the disease mechanisms, prevalence and significance of diabetic complications and metabolic findings. It is particularly expected that at the end of this work, readers would have learnt specific pathophysiologic mechanisms that links the black patient to certain commoner complications and how to ameliorate them.

Epidemiology of Diabetes Mellitus

Diabetes mellitus is the commonest endocrine disorder affecting almost 6% of the world's population.^{2,3} The disease is now a global emergency that requires innovative public health and clinical management strategies in order to mitigate the projected increase in disease prevalence, morbidity and mortality.^{2,3} The World Health Organisation estimates that hyperglycaemia is the third highest risk factor for premature mortality, after hypertension and tobacco use.⁴ Over the past few decades, there has been a significant increase in the prevalence of DM in some regions of the world, hitherto with low levels. This has contributed significantly to the negative impact of the disease on the quality of health services in countries such as Nigeria⁵ and Mexico.⁶

Global and Local Projections of Diabetes Mellitus Prevalence

In 2001, the International Diabetes Federation⁷ predicted that the number of diabetic patients would reach 300 million in 2025 with more than 97% of them having type II diabetes.⁸ Over the years, various predictions of DM prevalence and projections,^{9,10,11} have underestimated the global burden of this disease. Wild et al, 2004 predicted that the global burden of DM will increase from 171 million in year 2000 to 366 million by 2030, but this has been shown by IDF¹² to be surpassed at 382 million people affected in 2013. A report by IDF in 2013 projects that the number of those affected by DM will be up to 600 million by 2035.¹² The increasing prevalence of diabetes is now predicted to continue to rise for the next 4 decades by some authors¹³ and thus will have significant impact on life expectancy^{5,14} as a result of increase in disease mortality.¹⁴

Available evidence shows that the global prevalence of DM has been rising since 1980 till 2014 when it was globally assessed in a study involving over 4 million people.³ During this study period, the number of global deaths secondary to diabetes increased by almost 400%. Consequent upon this huge impact of diabetes on mortality, morbidity and health systems cost, especially in developing countries, there is an urgent need for population-based interventions in the fight against the disease.³ Such a population-based approach in the evaluation and treatment options for DM will enhance early disease detection and possibly identify pharmacological interventions suitable for

prevention or delay disease progress in affected populations.³

The increase in DM prevalence is due to rising number of new cases of the disease which is driven by, amongst other factors, a high prevalence of obesity, an ageing population and lack of exercise.¹⁴ Obesity is a major factor responsible for the increasing prevalence of DM2 in different populations including those in developing countries.⁴ Recently, it has been shown via epigenome-wide association study that adiposity is linked to widespread changes in DNA methylation. Alteration in the DNA methylation is now thought to predict future development of DM2, thus making obesity a major contributor to the rising global prevalence of DM2.¹⁵ The public health burden of DM in developing countries is worrisome as about 80% of the global disease burden is borne by those living in such countries.¹⁶ According to the report by IDF,¹² the total number of persons affected by DM in Africa will increase by 109%; 19.8 million in 2013 to 41.4 million in 2035. This projected increase in Africa is the highest for all the regions compared, and is about 5 times the 22% increase anticipated for Europe over the same period.¹²

In 2000, the IDF report quoted a gross prevalence for adult DM in Nigeria to be 0.4%, but by 2014 the figure increased to 4.6%.¹⁷ At this rate Nigeria presently has a diabetic population of 3.8 million people and it is the highest on the Africa continent.¹⁷ These facts are of concern to health care workers in the country as there could be a proportionate burden of DM2 complications in the coming decades, unless the integrated approach suggested by Zimmet et al, 2014 is applied.¹⁶ The integrated approach involves understanding all factors related to the pathogenic mechanisms of DM2 in different populations. Otherwise, astronomic increases in diabetic populations will strain the capabilities of the already strained healthcare institutions in developing countries like Nigeria,⁵ thus worsening non-communicable disease death rates.¹³ The authors of this review are of the opinion that integrated approach, beyond understanding the pathogenic mechanisms, should involve appreciation of the metabolic processes underlying the disease complications. Some significant clinical metabolic conditions of DM2 include electrolyte disorders, lipid disorders, defective body sodium handling, hypertension, altered sympathetic nervous system, disorder of infertility, bone disorders, diabetic neuropathy and dementia.

These disorders are discussed in later sections of this review.

Status of glycaemic control in Nigerian type 2 Diabetes Mellitus patients and its implications

An earlier study that evaluated glycaemic control over a decade using HbA1c in Nigeria found no significant improvement in glycaemia among Nigerian diabetics of different regions.¹⁸ This study noted that HbA1c concentration in Ilorin, Nigeria in 2003 was $8.1\% \pm 1.4$, and similar studies in 2012 found similar HbA1c concentration of $8.2\% \pm 2.2$ in Edo State Nigeria^{18,20} and $8.3\% \pm 2.2$ in a multi-centre study involving 7 teaching hospitals in the country.^{18,19} These results suggest a widespread poor glycaemia among diabetic patients in the country. The HbA1c studies mentioned above also showed that over 60% of the diabetics had mean HbA1c $\geq 7.0\%$ indicating poor glycaemic control.^{19,20}

Persistent long term poor glycaemic control in Nigeria diabetics is responsible for increasing burden of diabetic complications such as diabetic retinopathy in the patients.^{21,22,23} Evaluation of the studies showed an increase of 200 to 300% in the prevalence of diabetic retinopathy in Nigerian diabetes mellitus patients, in less than 25 years i.e. 1989-2008 (See Table 1). Some investigators believe this increase could be because Africans are more susceptible to developing diabetic retinopathy compared to other races, even with comparable disease duration.²⁴ If this is true, Nigeria clinicians should pay more attention to better understanding of the biology of the disease so as to improve its overall management, especially managing disease complications. This suggestion is emphasised by DM burden on the health care systems in Nigeria. A Nigerian study found that 15% of admissions in a Nigeria tertiary hospital were due to diabetes mellitus²⁵ and 15% of admitted diabetics in another study had foot ulcers that will result in amputation in about 30% of them.²⁶

The rising prevalence of diabetes mellitus^{2, 3, 7} and associated complications^{18, 19, 20, 21} indicated above in Nigeria, may impact negatively on the quality of life and longevity of patients. Furthermore, it will put a lot of strain on health care funds, personnel and other resources thereby negatively affecting health services quality in Nigeria.

Table 1: Studies showing changes in prevalence of retinopathy as an index of diabetic complications in Nigeria.¹⁸

Studies	% Retinopathy
Erasmus RT et al. East Afr Med J. 1989; 66: 248–254. ²¹	15.1
Rotimi C et al. Ethn Dis. 2003; 13(Suppl.2): S110-S117. ²²	24.0
Ashaye A et al. ClinOphthalmol. Mar 2008; 2(1): 103–108. ²³	42.1
Chinenye S et al. Indian J EndocrinolMetab. 2012; 16(4): 558–564. ¹⁹	35.5

% = percentage. Note the increase in prevalence of retinopathy in populations of Nigerian diabetics from 15.1% in 1989 to a peak of 42.1% in 2008. This represents an increase of 180% in prevalence of retinopathy over 20 years.

Implications of ineffective management of Diabetes risk factors

Clearly, both microvascular and macrovascular complications of DM are related to level of dysglycaemia. The high mean level of HbA1c in our diabetic population^{19,27,20} and associated complications such as diabetic retinopathy,^{19,21,22,23} nephropathy¹⁹ and diabetic foot ulcers²⁶ are established facts. These complications are usually associated with long standing hyperglycaemia and poor quality of care of DM patients.

Beyond hyperglycaemia,²⁸ hypertension²⁶ hyperlipidaemia^{29,30} and obesity,³¹ are common in DM2 patients, and these conditions increase the risk of diabetic retinopathy. A Nigeria multicentre study of diabetics¹⁹ found that only 11% of the hypertensive diabetics had good blood pressure control. This may explain why high blood pressure has been found to be a major contributor to stroke mortality in diabetic patients in Nigeria.³² Hypertriglyceridaemia in particular has been emphasised to be addressed in Nigerian diabetics.³³ Apart from contributing to retinopathy and other complications of DM, hypertension and hypelipidaemia contributes significantly to observed increase in mortality among diabetics in Nigeria hospital.³² Efforts should be made to increase treatment compliance by patients and adherence to treatment guidelines by doctors in the management of these patients.³⁴ These measures can help ameliorate risk factors that are known to worsen glycaemia and its complications in DM patients.

The high prevalence of overweight and obesity in Nigeria diabetics, especially among female patients^{27,35} is another factor needing attention, as they contributes to worsening HbA1C over time in our

patients.^{20,27} In a previous study, we discussed management strategy of obese diabetes patients and identified strategies that can help to improve glycaemia and outcome of the patients.³⁵

Some metabolic & clinical significance of DM2

Type 2 DM is commonly associated with clinical manifestation of hyperglycaemia and disordered metabolism of fats and proteins.³⁶ The clinic-metabolic parameters that underpins the pathognomonic features of DM2 includes, β -cell dysfunction, hyperinsulinaemia, reduced peripheral utilisation of glucose, increased hepatic and renal glucose production, and elevated plasma levels of non-esterified fatty acids. Added to the above, a primary derangement (insulin resistance) found in the early stages of DM2 is the presence of defective or ineffective translocation of GLUT-4 proteins from cytoplasmic to plasma membrane location.³⁷ This is in addition to concomitant elevation of counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). These hormonal alterations are responsible for the increase in hepatic and renal glucose production, and impaired glucose utilization in peripheral tissues.³⁸

Figure 1.0 shows the various actions of insulin which include lipogenesis (antilipolysis) and increased glucose utilisation. These insulin functions are impaired in DM2. The combination of insulin insufficiency/deficiency and increased counter-regulatory hormones in diabetes, leads to increased lipolysis and release of free fatty acids from adipose tissue to the plasma circulation. The increased plasma NEFAs is associated with pancreatic lipotoxicity and the characteristic β -cell defect found in some cases of IGT and early stages of DM2.³⁹

Metabolic events associated with IGT and DM2 have varied clinical manifestations; electrolyte disorders, lipid and vascular diseases, hypertension, muscle disorders, bone disorders and infertility, dementia amongst others. The elevated level of insulin in the early stages of DM2 subjects may not be effective in driving peripheral glucose metabolism, but is able to enhance other insulin mediated pathways. This has been observed in the sequential activation of Shc, Ras, Raf, and extracellular signal-regulated kinase mitogen-activated protein kinase (MAPK) by hyperinsulinaemia, in mitogenic pathway.⁴⁰ Enhanced mitogenesis under the influence of elevated insulin levels leads to growth of the cells, of vascular smooth

muscle, endothelial, and skeletal muscle.⁴⁰ These actions of insulin on vascular smooth muscle cells and endothelium impacts on the progression of cardiovascular diseases in affected patients.⁴¹



Figure 1.0 Actions of insulin on carbohydrates, fats and proteins in normal and pathophysiological states.

This diagram shows the various actions of insulin in the healthy state; reduction of plasma glucose, fatty acids, increased liver storage of carbohydrate (glycogen) and adipose tissue fat storage. Insulin also decrease breakdown of proteins. These various actions are affected in insulin disorders and they underlie the various clinical and biochemical findings of defective insulin actions.

Below are some of the metabolic processes and clinical conditions associated with DM2 that should be considered in Nigerian DM2 subjects.

Electrolyte disorders

Hyponatraemia is a common disorder in Diabetes mellitus. The disorder is independent of drugs or hyperglycaemia associated with the disease,⁴² but has been linked to increased frequency of impaired renal function, malabsorption syndrome, acid-base disorders and multidrug use, in affected patients.⁴³ Hyperglycaemia is known to increase serum osmolality which leads to diffusion of water from the intracellular space to the plasma thus resulting in haemodilution and hyponatraemia. In addition, improperly managed DM induces hypovolemic-hyponatremia due to osmotic diuresis. Particularly in diabetic ketoacidosis, ketone bodies (β -hydroxybutyrate and acetoacetate) cause urinary electrolyte losses thus aggravating renal sodium wasting.⁴⁴ Defective insulin metabolism is also associated with loss of body potassium. The mechanisms linked to hypokalaemia in diabetics include: (1) redistribution of potassium (K^+) from the

extracellular to the intracellular fluid compartment, especially due to exogenous insulin, (2) gastrointestinal loss of K^+ due to malabsorption syndromes in diabetes-induced motility disorders, and (3) renal loss of K^+ (due to osmotic diuresis and/or coexistent hypomagnesaemia). Hypomagnesaemia induced hypokalaemia occurs as a result of intracellular hypomagnesaemia (Mg^{2+}) induced activation of the renal outer medullary K^+ channel loss of K^+ .⁴⁵ On the other hand, the occurrence of chronic hyperkalemia, in some diabetics, is due to hyporeninemic hypoaldosteronism syndrome. The condition is associated with reduced renal loss of potassium.⁴³

Lipid disorders

In 1927 Joslin stated: "*I believe the chief cause of premature development of atherosclerosis in diabetes, save for advancing age, is an excess of fat, an excess of fat in the body, an excess of fat in the diet, and an excess of fat in the blood*".⁴⁶ About three decades later, Albrink reported that: "*Hypertriglyceridaemia is the hyperlipidaemia par excellence of the diabetic*".⁴⁷

Diabetic dyslipidaemia is a cluster of plasma lipid and lipoprotein abnormalities that are metabolically interrelated. Hyperinsulinaemia in subjects with DM2, especially in those that have visceral obesity and fatty liver, has been linked to excessive flux of substrates for VLDL assembly and upregulation of the metabolic machinery for VLDL particles synthesis in the liver.⁴⁸ In clinical practice, DM2 patients commonly present with reduced plasma high-density lipoprotein cholesterol (HDL-C), elevated small dense low density lipoprotein (sLDL-C) and raised triglyceride;⁴⁹ a triad associated with significant atherogenic lipid profile.⁵⁰ Increased atherosclerosis risks in DM patient is enhanced by the presence of small dense LDL particles in such patients. These particles are able to transverse the endothelium of blood vessels into the sub-endothelial space where they are retained by proteoglycans and oxidised, thus setting the stage for the development of diabetic cardiovascular complications.⁴⁹

Hypertension

The pathogenesis of hypertension in DM involves genetic predisposition and a range of environmental and biological factors. These include unhealthy high salt diets, sedentary living, increased body sodium retention, visceral obesity, autonomic derangements, premature arterial stiffening, and endothelial dysfunction.⁵¹ DM2 patients are more prone to hypertension and have increased propensity for age-adjusted cardiovascular death for any given systolic blood pressure. Some investigators suggest this maybe due to the absence of nocturnal BP dips in diabetics. Despite similar daytime office and home BP recordings, a "non-dipper" has a higher 24-hour and nocturnal BP values, with the latter in particular being a strong predictor of cardiovascular death.⁵² Data drawn from death certificates implicates hypertension in 44% of deaths among patients with diabetes mellitus. Therefore, hypertension is a key factor in the clinical evaluation of DM2 subjects and vice-versa.

As mentioned above, hyperinsulinaemia in DM2 worsen hypertension by stimulating subintimal smooth muscle and fibroblast proliferation.⁴¹ Furthermore, atherosclerosis in DM patients is accentuated by the negative impact of increased plasma insulin signaling on endothelial responses.⁵³ The combination of increased mitogenesis, elevated exchangeable sodium and sympathetic activity, endothelial dysfunction and dyslipidaemia, due to hyperinsulinaemia increases CVD risks including hypertension in DM2 subjects.

Ethnic susceptibility to increased kidney dysfunction

It is known that there is increased risk of renal disease in DM and metabolic syndrome patients. The pathogenic mechanisms implicated in this include increased glomerular hyperfiltration and enhanced proximal sodium reabsorption.⁵⁴ Increased proximal tubular reabsorption of sodium seen in affected patients triggers glomerular hyperfiltration.⁵⁵ Renal hyperfiltration in DM is associated with accelerated loss of kidney function and hypertension.⁵⁴ Another contributor to renal dysfunction in DM2 is stimulation of the renin-angiotensin-aldosterone system (RAAS).⁵⁶ Some investigators⁵⁷ believe that activation of the RAAS is a primary event in the development of hypertension in affected patients. Attenuation of activated RAAS has been shown to slow down the

progression of microvascular and macrovascular complications in patients with DM2. Thus, this system has become a target of interest in clinical management of diabetic patients, and this should be an area of concern in the management of Nigerian DM2 patients. Importantly, the high prevalence of glomerular hyperfiltration and enhanced proximal tubular reabsorption of sodium has been particularly reported in persons of African descent who have impaired fasting glycaemia or DM2.⁵⁵ Another significant finding in those with African ancestry is higher prevalence of impaired renal autoregulation.⁵⁸ These defects add up to cause increased chance of developing progressive glomerulosclerosis in blacks, even with modest blood pressure elevation. Therefore, it is important that there should be strict clinical monitoring and management of blood pressure in diabetics, especially in African diabetics.⁵⁸ as they are more prone to hypertension and kidney dysfunction.

Altered sympathetic nervous system

In addition to the factors discussed above, increased activity of the sympathetic nervous system (SNS) is a mediator of hypertension in DM2. This occurs via increased stimulation of renal sodium reabsorption, increase in blood volume and cardiac output.^{59,60} In the Normative Ageing Study, elevated insulin level in obesity was associated with increased SNS,⁶¹ and these factors have also been reported in the development of hypertension.⁶² Therefore, early interventions targeted at disordered renal autoregulation, activation of RAAS in obese African patients with impaired glucose tolerance/DM2^{57,58} and increased SNS activity⁶² could be beneficial in the clinical management of black DM2 patients. Such pathophysiological targeted approaches will help to mitigate macrovascular complications (coronary artery disease, stroke, and peripheral arterial disease) and microvascular complications (diabetic neuropathy, nephropathy, and retinopathy) in DM2 subjects.

Disorders of infertility

Some investigators have associated observed decrease in fecundity in modern societies to DM2⁶³ and its associated metabolic dysfunctions.⁶⁴ The impact of DM on fertility affects both males and females but more so the women.⁶⁴ One study found that compared with non-diabetics, couples in which the men were

diabetic were three times more likely to seek treatment for infertility. Another study noted that despite similar fertilization rates and embryo quality among diabetic and non-diabetic unions, pregnancy rates were lower in couples with a diabetic male.⁶⁵ Other factors associated with diabetic male infertility are erectile dysfunction, retrograde ejaculation, decreased libido and impotence.⁶⁶ Other biochemical changes in male DM patients include higher concentrations of spermatozoa with disrupted transmembrane mitochondrial potential, activated caspase 3, reactive oxygen species as well as fragmented nuclear and mitochondrial sperm DNA.⁶⁷ Further molecular perturbations by DM on spermatogenesis include subtle but vital changes including increased sperm DNA damage which has been implicated in poor embryo quality and implantation, in assisted reproductive therapy (ART). The above defect is associated with increase in the number of miscarriages.⁶⁵ Hence, it is advisable to rule out glucose intolerance and DM2 in infertile couples, especially among male partners. It is important that the above factors are considered in patients undergoing ART.

Bone disorders

The relationship between diabetes and bone disease is non-linear, as the effect of DM1 and DM2 on bones are different. While the bone mineral density (BMD) is consistently low in DM1, it is similar in non-diabetic and DM2 subjects. Nevertheless, both forms of diabetes are associated with an increased risk of bone fracture.⁶⁸ Studies have shown that the risk of hip fracture in DM2 patients is increased by 1.7-fold, compared with non-diabetic controls, despite non-diminished bone mineral density (BMD) in the patients. In addition, vertebral fracture risk of DM2 patients is increased compared to healthy non-diabetics. Some researchers have interpreted this to mean that bone fragility in DM patients depends on bone quality deterioration rather than bone mass reduction.^{69,70,71} The mechanisms responsible for the impact of DM2 on bone integrity include increased urinary excretion coupled with lower intestinal absorption of calcium, inappropriate homeostatic response to parathyroid hormone secretion, alteration of vitamin D regulation, increased insulin and IGF-1 concentrations, accumulation of end products of glycation on bone tissue.^{68,71}

Diabetic neuropathy

Diabetic neuropathy (DN) is the commonest complication of diabetes mellitus and a source of significant morbidity and mortality in affected patients. It is a microvascular complication defined by the presence of symptoms and/or clinical signs of altered nerve conduction after exclusion of other causes of neuropathy. The global prevalence of DN is up to 65%,⁷² but in Nigeria it was reported 59.2%¹⁹ and 69% in Mexico.⁷³ The microvascular complications underlying DN make diabetic patients 15 times more prone to lower limbs amputation compared to the general population.⁷⁴ Clinical significance of DN was captured in a study that reported it being implicated in 50-75% of non-traumatic amputations.⁷⁵

Peripheral DN is associated with peripheral nerves myelin damage and decrease in nerve conduction velocity.⁷⁴ The myelin sheath is a multilayered membrane produced in the peripheral nervous system by differentiation of the plasma membrane of Schwann cells. The function of the myelin membrane is to allow efficient transmission of nerve impulses along the axons. A major biochemical difference between myelin and other biological membranes is its high lipid-to-protein ratio. An isolated myelin sheath is made up of 70-80% lipids and 20-30% proteins.⁷⁶ The syndromes affecting peripheral nerves can be separated into quickly reversible manifestations and chronic progressive syndromes. The chronic progressive syndromes of DN manifest as symmetric polyneuropathies and focal or multifocal neuropathies.⁷⁴

DN is an insidious disease which in clinical practice presents as apparition of pains in the lower limbs and plantar ulcers. The complication of DN is initiated by hyperglycaemia and associated metabolic abnormalities in long standing diabetic disease.⁷⁴ The Diabetes Control and Complications Trial studies confirmed this when it showed that intensive insulin treatment reduced the development and progression of diabetic neuropathy.⁷⁷ It is known that reduced or abnormal fatty acid synthesis plays an important role in altered myelin lipid and protein composition. This alteration in myelin affects membrane fluidity and function, ultimately contributing to the pathogenesis of DN.⁷⁸ In support of the above, gamma-linoleic acid (GLA) supplementations showed promise in reducing the symptoms of DN in a study reported over two decades ago.⁷⁹ The early observation by Keen and co-workers in 1993⁷⁹ is significant because despite

control of risk factors of macrovascular and microvascular diseases (blood pressure, lipids and blood glucose levels) DN complications still occur.⁸⁰ Therefore, it is important that targeted therapies to the underlying mechanisms of DN should be further investigated and instituted in the management of affected patients.

Dementia

Cardiovascular risk factors including DM, hypertension and hyperlipidaemia are associated with dementia.⁸¹ As the prevalence of DM increases, there is a concomitant rise in the level of dementia⁸² and this will have significant implication for developing economies like Nigeria where increase in DM2 prevalence is now a cause for concern.¹⁸ The World Alzheimer Report of 2015 states that over 46 million people live with dementia worldwide, and that this number is estimated to increase to 131.5 million by 2050 with most of the increase occurring in low income (264%), middle income (223%) and upper middle income (227%), countries.⁸³ Population based studies shows that DM2 patients have a twofold increased risk of developing either vascular dementia or Alzheimer's disease.⁸⁴ Another recent population based study concluded that the hyperglycaemia of DM and not its association with hypertension or hyperlipidaemia is the main driver of dementia.⁸² The association between DM2 and dementia has also been demonstrated in Nigeria.^{85,86}

Dementia is a common cause of morbidity in late stages of diabetes mellitus and it is one of the commonest and most disabling late life mental disorders.⁸⁷ The pathogenic mechanisms linked to dementia in DM2 subjects are hyperinsulinaemia, brain infarcts, white matter disease, advanced glycosylated end products, and lipoprotein related proteins.⁸⁸ Furthermore, poor glycemic control and chronic episodes of hypo- or hyperglycemia have been linked to microangiopathy, neuronal loss, and cognitive impairment in diabetic states.⁸⁹ This emphasizes the need for quality management of DM2 so as to reduce the risk of dementia.

The disease complication is associated with huge economic burden with current global cost estimate put at US \$818 billion. The projection in 2015 was that this cost could reach a trillion dollar by this year.⁸³ This huge cost occasioned by the management of dementia cannot be afforded by most developing countries, especially by those in sub-Saharan Africa.

Little wonder that about 94% of people living with dementia in low and middle income countries are cared for at home.⁸³ A more sustainable program for mitigating dementia and other complications of DM2 in developing countries like Nigeria will involve efficient public and clinical management of the disease.¹⁸

Conclusion

The high prevalence of diabetic complications in Nigerian patients is associated with poor glycaemic control. This can be improved by a more integrated care model earlier suggested by Zimmet and co-workers in 2014.¹⁶ This approach when combined with better understanding of the metabolic derangements of the DM2, especially in the recognition of increased susceptibility of Africans to some diseases, could help to improve quality of care offered to Nigerian diabetics.

Take home messages

1. The prevalence of DM 2 is rising in Nigeria and so are the complications of the disease.
2. Diabetic patients of Africa origin including Nigerians are more susceptible to certain disease complications, and these should be noted in clinical evaluations.
3. Improved understanding of DM2 biology and relevant metabolic consequences will help patients' management and outcomes.
3. The poor level of glycaemia may be improved by improved use of HbA1c.

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