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Neurovascular Complications of Type 2 Diabetes among Elderly Patients

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Abstract: Background: Multimorbidity increases the complexity of T2DM management of older adults and requires a more personalized approach to ensure adequate glycemic control alongside coexisting and competing treatment targets. The self-management of diabetes by older adults becomes more difficult with comorbidities. In addition, the development of comorbid conditions, such as heart failure and/or dementia, can render desirable treatment targets impossible or risky to achieve . Diabetes mellitus is not merely a disorder of carbohydrate metabolism, but a cause of vascular disease affecting nearly all blood vessel types and sizes. Indeed, vascular complications are responsible for most of the morbidity, hospitalizations, and death that occur in patients with diabetes mellitus

Keywords: *Neurovascular Complications, Type 2 Diabetes, Elderly Patients.*

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia and high glycated hemoglobin with or without glycosuria. Glucose metabolism disorder (GMD) results from a defect in insulin secretion by the pancreas, insulin action on the target tissues (or insulin resistance), or both **(1).**

Data regarding the epidemiology of DM in Egypt are sparse. Nevertheless, according to the IDF (International Diabetes Federation), Egypt ranks ninth in the prevalence of DM worldwide, and the number of adult diabetic patients was 8,850,400 in early 2020, with a prevalence of 15.2%. Egypt is a member of the Middle East and North Africa (MENA) region of the IDF **(2)**.

IDF estimates that the number of diabetic patients in the MENA region would double by 2045, reaching 108 million. In actuality, 40% to 50% of people with diabetes or prediabetes go undiagnosed, despite the fact that these numbers may appear to be quite high. The number of diabetic patients in Egypt is expected to be reached by 2035 **(3)**.

Epidemiology of T2DM in older adults

The prevalence of diabetes increases with age so, the highest estimated prevalence is in people older than 65. In 2019, International Diabetes Federation (IDF) estimated that the number of people with diabetes above 65 years is 135.6 million (19.3%). If this trend continues, the number will be 195.2 million in 2030 and 276.2 million in 2045, leading to a significant increase in the diabetes population of the aging societies in the next 25 years and the inevitable public health and economic challenges this will bring **(4).**

The strong link between age and diabetes is of great concern due to a progressive increase in life expectancy, which is likely to result in a substantial increase in the number of older people with diabetes, and a concomitant increase in the costs for the health system shortly. There is compelling evidence that diabetes in older people has differential characteristics compared with diabetes in middle-aged or earlier people **(5).**

Special consideration of Type 2 DM in elderly

The heterogeneity of T2DM among older adults reflects many factors. For example, clinical differences exist between late-onset T2DM and long-standing T2DM that a patient has had since middle age that affect the presentation and severity of the disease. Furthermore, older adults show considerable differences in functional status, in the ability to care for themselves and in the burden of comorbidities, all of which further add to the observed heterogeneity **(6).**

These factors can modify the disease process compared to that in younger adults and therefore affect the management of both T2DM and any comorbidities. Several common clinical aspects are considered here, namely the specific care needs relating to frailty and sarcopenia, multimorbidity, and the susceptibility to hypoglycemia **(6).**

Frailty

Frailty is a geriatric syndrome characterized by declining physiological reserves and impaired responses to stressors. Several definitions of frailty are available; however, two are most commonly used. First, are the criteria proposed by Fried et al. that include a loss of body mass and grip strength, reduced walking speed, physical inactivity, and exhaustion; the presence of three or more of these factors fulfil the criteria for frailty. The second commonly used definition is the deficit accumulation model proposed by Rockwood and Mitnitski, which is known as the frailty index or clinical frailty scale and assesses the level of dependency of an individual on care providers **(7).**

The prevalence of frailty in community-dwelling older adults is mostly estimated at 10–14% but rates as high as 40% have been reported in some studies48. This prevalence increases linearly with age, from ~7% in community-dwelling adults aged 65–69 years to up to 25% in those aged >80 years. Of note, frailty is more common and occurs earlier amongst those with diabetes mellitus than in those without, affecting about one-quarter of all individuals with diabetes mellitus aged >65 years **(7).**

Diabetes mellitus in combination with frailty is associated with an increased risk of complications, hospitalization and a faster functional decline than in those without frailty. Indeed, frailty is a better prognostic marker of risk of death in older adults with T2DM than T2DM alone or T2DM with comorbidities. Clinical trials in older adults with diabetes mellitus and frailty are scarce. However, observational studies involving older adults with frailty suggest that the degree of glycaemia has little effect on functional outcomes, provided that hyperglycemia is not severe. Instead, the evidence now suggests that a multifactorial intervention, rather than those singularly targeting glucose control, could be effective in delaying the progression of frailty **(8).**

For example, the MIDFRAIL study evaluated the effectiveness of a multimodal intervention (compared with usual care) comprising a 16-week individualized and progressive resistance exercise programme, structured diabetes and nutritional education, and optimized diabetes care in pre-frail adults (Fried score 1–2) with T2DM and in older adults with T2DM and frailty. At 12 months of follow-up, patients in the intervention group showed clinically relevant improvements in measures of physical and cognitive function and reduced episodes of hypoglycemia and hospital admissions compared with the group that received usual care. This improvement equated to an average annual health-care cost saving per patient of 428 euros **(8).**

Considerable uncertainty exists regarding the ideal targets for glycemic control in older adults with frailty and how these should be tailored to functional status. Nevertheless, there is a growing consensus for a less intensive approach in these individuals. This approach (for example, aiming for HbA1c levels of 7.5–8.5% (58–69mmol/mol)) in older adults with frailty is based on evidence that 8–9 years of intensive glycemic control (HbA1c levels of 6.5–7% (48–53mmol/mol)) are required to achieve measurable reductions in microvascular complications **(9).**

In patients with a short life expectancy, such intensive control increases the risk of hypoglycemia and lifestyle restrictions might compromise quality of life without providing tangible benefits. Clinical guidelines have now been published that advocate the assessment of frailty as an essential part of the management of older adults with diabetes mellitus, thereby recognizing the importance of frailty and the potentially limited long-term benefits of intensive glycemic control in older adults with frailty **(9).**

Of note, frailty assessment can inform functional status; therefore, it has been proposed as a useful measure to guide individualized treatment targets and therapeutic decisions. Thus, although an HbA1c target level of< 7.5% (58mmol/mol) might be appropriate for those who are fit and have fewer comorbidities, a less stringent HbA1c target level of 8.0–8.5% (64–69mmol/mol) has been considered reasonable in those who are frail or have a limited life expectancy **(9).**

Sarcopenia

Sarcopenia is defined as the progressive loss of muscle strength and mass associated with ageing60 and is an important component of the frailty phenotype. The decline in muscle strength and mass observed in sarcopenia can give rise to an increased risk of falls, hypoglycemia, disability, hospitalization and mortality **(10).**

Sarcopenia and T2DM share a relationship, with each condition exaggerating the effects of the other, leading to functional decline and disability. The gradual loss of muscle mass with ageing occurs at a rate of 1–2% per year from the age of 50 years, increasing to around 3% per year after the age of 60 years and considerably faster after the age of 75 years. The mechanisms by which age-related sarcopenia leads to insulin resistance and contributes to the development of T2DM were described earlier **(10).**

Of note, the rate of loss of skeletal muscle mass is typically 10–20% faster in men and 100% faster in women with T2DM than in healthy older adults. This rate of loss varies between muscle groups but invariably reduces muscle function. A number of longitudinal cohort studies have shown that the loss of both muscle strength and mass is accelerated in people with T2DM. For example, in the US Health, Aging and Body Composition Study, which observed 1,840 community-dwelling adults aged 70–79 years, the decline in maximal strength of leg muscles was one-third greater in those with T2DM over a 3-year period than in those without diabetes **(11).**

Furthermore, in the CHIANTI study, those with T2DM had statistically significantly lower muscle density, knee and ankle strength, less muscle power, and reduced muscle quality compared with those without T2DM. In Korean and Indian populations, strong associations have been noted between prediabetes, T2DM and sarcopenia, especially in those over 60 years of age **(11).**

The mechanisms by which T2DM accelerates the age-related loss of muscle mass and function involve nutritional, endocrine, inflammatory and neurological pathways. All these mechanisms can disrupt signaling downstream of the insulin receptor, which impairs the normal actions of insulin in muscle and thereby disrupts protein synthesis and increases protein catabolism. In addition, poor glycemic control and oxidative stress over time as well as the presence of complications (particularly neuropathy) impede muscle energetics and contribute to the further loss of muscle quantity and function leading to the increased risk of frailty **(12).**

Hypoglycemia

Although hypoglycemia is generally recognized as being more common in older than in younger people with T2DM, true frequencies of hypoglycemia in older adults with T2DM are not well established. Studies involving people with T2DM of all age groups have estimated that rates of symptomatic hypoglycemia are between 5 and

16 episodes per patient per year, with severe hypoglycemia rates between 0.10 and 0.44 episodes per patient per year **(13).**

These broad ranges can be attributed to differences in the applied definitions of hypoglycemia and in the cohorts studied. Of note, the frequency of reported hypoglycemia also varies depending on the type of glucose-lowering agent used, with rates being greater in patients who are treated with insulin compared with those treated with other glucose-lowering agents **(13).**

Physiological changes associated with ageing substantially alter both the awareness of and responses to hypoglycemia in older adults. For example, studies of individuals without diabetes mellitus have shown that older adults recognize the symptoms of hypoglycemia at lower blood levels of glucose than younger adults, with a statistically significant attenuation of autonomic responses and longer recovery times in older adults. As these studies involved adults without diabetes, differences are probably due to ageing rather than the level of glycaemia **(14).**

In older adults with T2DM, factors associated with ageing, such as a decline in renal function, altered drug pharmacokinetics and the presence of other comorbidities (for example, cognitive decline), can further exaggerate the risk of hypoglycemia. Of note, the presentation of older adults with hypoglycemia is often atypical, presenting as falls, transient ischemia, nausea or unsteadiness, thus obscuring and delaying the diagnosis **(14).**

Hypoglycemia in older adults can have severe clinical consequences and an increased risk of death. For example, in older adults with T2DM, a strong association between hypoglycemia and fatal cardiovascular disease events has been noted in cardiovascular outcome studies **(15).**

Cognitive impairment

T2DM is now recognized as a notable risk factor for the development of cognitive impairment and dementia (including Alzheimer disease) in older adults, particularly in association with insulin resistance and vascular disease93. Indeed, diabetes mellitus in midlife is associated with a 19% greater cognitive decline over 20 years compared with individuals without diabetes as well as a 1.5–2.5-fold increased risk of dementia and Alzheimer disease in older adults **(16).**

Preliminary evidence shows an association between poor glycemic control and increased risk of dementia in type 1 diabetes mellitus; however, a definitive link has yet to be established and T2DM seems to account for most of the overall association between diabetes mellitus and dementia **(16).**

In addition to the overall risk of developing dementia, T2DM is associated with deficits across multiple domains of cognitive function in older adults. A bell-shaped association between HbA1c levels and cognitive function was reported in study amongst those aged >70 years; in this study, worse test scores for cognitive ability coincided with the lowest and highest HbA1c levels and women were more vulnerable than men to poor cognitive ability with increased HbA1c levels **(17).**

This study and others suggest a non-linear link between poor glycemic control and an increased risk of cognitive decline in older adults with diabetes mellitus. Furthermore, underlying chronic insulin resistance and absolute insulin deficiency are also recognized as underlying factors that are strongly detrimental to cognitive functions. In addition, excess body mass, impaired renal function, hypotension and comorbid depression are all reported as factors associated with an increased risk of dementia in older adults with T2DM **(17).**

The onset of dementia in older adults with T2DM is typically accompanied by a loss of executive function and delayed recall, which are cognitive domains that influence glycemic control; these changes are associated with an increased risk of falls. Moreover, cognitive impairment can adversely affect adherence to treatment regimens, making the management of older adults with cognitive decline even more challenging **(18).**

However, interventions exist that can potentially mitigate cognitive decline in older adults with diabetes mellitus. For example, even very modest exercise can moderate some of the cognitive decline observed in older adults with diabetes mellitus116 and reduce the risk of developing dementia **(18).**

Multimorbidity

Multimorbidity is defined as the coexistence of two or more chronic diseases. Importantly, multimorbidity is well recognized to increase the risk of death and constitutes a growing issue for older adults. Indeed, multimorbidity has been estimated to affect 55–98% of older adults, depending on the definitions applied and the age groups included. Increased disability, a reduced quality of life and an increased uptake of health-care services are closely associated with multimorbidity, further highlighting the impact of this problem **(19).**

Evidence suggests that frailty can contribute to the risk of older adults with diabetes mellitus developing multimorbidity. Adults of all ages with multimorbidity have an increased risk of death but the mortality risk of frailty itself can often outweigh that of multimorbidity when frailty and multimorbidity coexist. Frailty and multimorbidity evidently share a complex association, which requires further investigation **(19).**

An increased prevalence of multimorbidity in older adults with diabetes mellitus is attributed in part to advances in T2DM treatments and cardiovascular disease management, which have prolonged life expectancy but allowed other chronic conditions to manifest. Up to 40% of older adults with diabetes mellitus have four or more comorbid diseases **(20).**

The most common co-morbidity clusters include diabetes mellitus–hypertension, diabetes mellitus–arthritis–hypertension and diabetes mellitus–arthritis–hypertension– heart disease. Conditions associated with old age, including frailty, incontinence, chronic pain and falls, are also highly prevalent in older adults with diabetes mellitus and decrease the quality of life **(20).**

Multimorbidity increases the complexity of T2DM management of older adults and requires a more personalized approach to ensure adequate glycemic control alongside coexisting and competing treatment targets. The self-management of diabetes by older adults becomes more difficult with comorbidities. In addition, the development of comorbid conditions, such as heart failure and/or dementia, can render desirable treatment targets impossible or risky to achieve **(21).**

Indeed, the analysis of a health database in the USA involving 23,430 adults with diabetes mellitus suggested that 16 of 17 investigated comorbid conditions hamper the management of hyperglycaemia. The perceived treatment priorities might differ between clinicians faced with managing diabetes mellitus in older adults with multimorbidity. For example, fewer than 40% of patient–clinician partnerships agree that taking medication is one of the most important treatments strategies **(21).**

Diabetes mellitus is not merely a disorder of carbohydrate metabolism, but a cause of vascular disease affecting nearly all blood vessel types and sizes. Indeed, vascular complications are responsible for most of the morbidity, hospitalizations, and death that occur in patients with diabetes mellitus **(21).**

Microvascular Disease

Retinopathy

Microvascular disease is strongly associated with hyperglycemia. Over the range of chronic hyperglycemia commonly seen in practice, there is an 11-fold increase in retinopathy compared with a 2-fold increase in coronary artery disease. Despite the importance of hyperglycemia, some patients may develop early evidence of retinopathy as long as 7 years before the development of frank type 2 diabetes mellitus, indicating a contribution of insulin resistance **(22).**

In addition to severity of hyperglycemia and duration of diabetes mellitus, other factors associated with retinopathy include hypertension, smoking, and dyslipidemia. These and other pathophysiologic mechanisms, including insulin resistance and inflammation, may contribute to the microvascular disease process **(22).**

The earliest histopathologic sign of diabetes mellitus–related retinopathy is a loss of pericytes. Pericytes wrap around the arteriolar and capillary endothelial cells and participate in maintenance of capillary tone, growth, and resistance to damage from oxidative stress. The disease is then marked by basement membrane thickening, endothelial cell permeability, and the formation of microaneurysms. Broadly, there are 2 types of retinopathies, non-proliferative (background) and proliferative **(23).**

In non-proliferative retinopathy, patients may develop dot hemorrhages, which are small hemorrhages in the middle of the retina surrounded by hard lipid exudates. Retinal edema also may be seen. Proliferative

retinopathy is the development of neovascularization on the retina, which can be complicated by vitreous hemorrhage. These latter changes, without treatment, can lead to vision impairment **(23).**

In an analysis of the National Health and Nutrition Survey, the prevalence of retinopathy in the diabetic population was 28.5%, and 4.4% of the total had threatened loss of vision. Male sex, higher glycosylated hemoglobin levels, longer duration of diabetes mellitus, higher blood pressure, and use of insulin all were associated with developing retinopathy. The presence of microvascular disease is also a marker of diffuse vascular disease. Diabetic patients with retinopathy have a higher rate of atherosclerosis than diabetic patients without retinopathy **(24).**

Diabetic retinopathy is a leading cause of blindness in the United States. It was responsible for 8% of cases of legal blindness and 12% of all new cases of blindness in the United States each year in the last decade of the twentieth century. However, new treatments have improved outcomes with a significantly reduced rate of severe visual impairment **(25).**

Despite the increase in diabetes mellitus over the last few decades and a commensurate increase in the number of patients with diabetic retinopathy to ≈4 to 5 million people in the United States, the number of patients with diabetes mellitus with visual impairment has decreased from 26% in 1997 to ≈19% in 2011,21 whereas the overall rate of visual impairment in the civilian population has remained stable at 9.3% **(25).**

Nephropathy

The pathophysiology of nephropathy in diabetes mellitus bears many similarities to retinopathy, including the development of basement membrane thickening and microaneurysm formation. In addition, glomerular hyperfiltration is associated with expansion of the extracellular matrix and the progression of tubular and glomerular sclerosis. These changes cause albuminuria. Nephropathy is defined as the loss of >500 mg/d of protein. It is preceded by microalbuminuria, defined as a loss of 30 to 299 mg/d **(26).**

Diabetic nephropathy is found in as many as 7% of type 2 diabetic patients at the time of their diabetes mellitus diagnosis. It occurs in ≤12% patients with type 1 diabetes mellitus by 7 years, and as many as 25% of patients with type 2 diabetes mellitus have evidence of nephropathy by 10 years after the diagnosis is made. The prevalence is significantly worse in Asia **(27).**

Neuropathy

The development of diabetic neuropathy is associated with vascular and nonvascular abnormalities. In addition to basement membrane thickening and pericyte loss, there is evidence of decreased capillary blood flow to C fibers, resulting in attenuated perfusion of the nerves and attendant endoneuria hypoxia. The neuropathy is characterized by axonal thickening and eventual loss of neurons **(28).**

The clinical manifestation of diabetic neuropathy can vary widely, although there are 2 major types. The most common is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy, which is associated with severity and duration of hyperglycemia. The pathophysiology of this subtype is similar to the other microvascular manifestations of diabetes mellitus. Less common are polyneuropathies that develop at more unpredictable times during the course of diabetes mellitus that may not be symmetrical. The polyneuropathies commonly present with pain or autonomic symptoms and the course may be fluctuating **(28).**

Cardiovascular Disease

Coronary Artery Disease

The linkage between diabetes mellitus and macrovascular disease was made >40 years ago, with the heighted risk of myocardial infarction (MI) and cardiovascular death shown in several different populations. The appreciation of the impact of diabetes mellitus on cardiovascular disease was increased substantially when it was reported in a Finnish population study that diabetes mellitus alone carried the same risk of future MI and cardiovascular death as patients without diabetes mellitus but a previous MI. Although diabetes mellitus alone is not the risk equivalent of prior myocardial infarction for future myocardial infarction, diabetes increases the risk of future MI more than any other risk factor, save cigarette smoking **(29).**

Despite the persistently higher rate of coronary heart disease events in diabetic compared with nondiabetic patients, cardiovascular events have dropped precipitously over the last 2 decades. These improvements are

likely related to more frequent use of effective medical and revascularization strategies. Indeed, differences in the use of well-proved therapies have been associated with better outcomes after acute MI **(30).**

Stroke

Associating diabetes mellitus with the risk of stroke is complex because of the variety of stroke types. In the Nurses Health Study of 116316 women aged 30 to 55 years followed for 26 years, type 1 diabetes mellitus was associated with increased risk of both ischemic and hemorrhagic strokes, whereas type 2 diabetes mellitus increased the risk of ischemic stroke but not hemorrhagic stroke. Similarly, in a survey of 40000 Asian patients, type 2 diabetes mellitus associated with increased risk of ischemic but not hemorrhagic stroke **(29).**

Interestingly, metabolic disturbances may play an important role. Recent studies have suggested that the risk of stroke is increased in diabetic patients with hyperglycemia, but not in those without hyperglycemia. The relationship of the metabolic syndrome is more complex. The risk of first stroke doubles with the presence of the metabolic syndrome, but recurrent stroke is not affected **(30).**

Diabetes mellitus worsens the outcomes from stroke, as it does in coronary artery disease. A study of nearly 12 000 community-dwelling men in western Australia found that diabetes mellitus significantly increased the risk of death in patients with stroke. Moreover, the duration of diabetes mellitus was a significant cofactor, suggesting a dose–response relationship of diabetes mellitus exposure to stroke severity **(29).**

These observations are similar to those reported in a German nationwide health insurance study and a Veterans Affairs investigation. Diabetic patients also have a higher rate of neurological deterioration compared with nondiabetic patients after an acute ischemic stroke and do worse than nondiabetic patients even for strokes of the same size and severity **(31).**

Peripheral Artery Disease

Like the other manifestations of atherosclerosis, peripheral artery disease (PAD) is linked strongly to diabetes mellitus. Several large epidemiological surveys have demonstrated a 2- to 4-fold increase in the risk of developing PAD, as determined by an ankle–brachial index ≤0.90.90,91 In the German Epidemiological Trial on Ankle Brachial Index study, 26.3% of the patients with diabetes mellitus developed PAD compared with 15.3% of the nondiabetic patients, and diabetes mellitus increased the risk of PAD to a greater extent than it did for CAD or stroke. Diabetes mellitus also increases the rate of disease development in younger patient groups. In the Chicago Healthy Aging Study, diabetes mellitus increased the rate of PAD by >7-fold during the 39-year follow-up period **(32).**

In patients with diabetes mellitus, detecting PAD may present challenges. Diabetes mellitus is associated with medial calcinosis, which may artifactually raise the ankle–brachial index because of noncomparability of leg arteries, despite significant artery occlusive disease and reductions in the actual ankle perfusion pressure. For patients for whom there is a high suspicion of PAD, a toe–brachial index may be obtained, which is less likely to be affected by vascular calcification. Here, a toe–brachial index **(33).**

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