

A review on the prevention and management of diabetes mellitus complications and the role of the pharmacist

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Abstract

Diabetes mellitus is a growing global public health problem, which has been on the increase for the past decade. If left untreated or inadequately treated, it leads to an array of systemic complications, which lead to increased morbidity and premature mortality. This article focuses on the prevention and management of these complications through a multidisciplinary team approach, as well as patient and community involvement. Pharmacological and non-pharmacological strategies are discussed for the prevention of diabetic complications. The article further describes the role of the pharmacist in the management of diabetes mellitus and its complications. The role of the pharmacist has significantly changed from the traditional role that focused only on medicine supply and, to some extent, patient counselling to a more patient-centred pharmaceutical care approach that is delivered in a cost effective manner.

Keywords: prevention, management, diabetes mellitus complications

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S Afr Pharm J 2020;87(4):22-25

Introduction

Diabetes mellitus (DM) is a chronic metabolic condition resulting from defective insulin secretion, insulin action or both. The hallmark characteristic of DM is chronic hyperglycaemia with abnormalities in the metabolism of carbohydrates, fats and proteins. DM is a non-communicable chronic disease with significant morbidity and premature mortality. Its prevalence globally is on an increase.¹ There are more than 425 million people with DM worldwide and 16 million in Africa. This number is expected to increase to 41 million by 2045. South Africa has a DM prevalence of 7.5% in adults.² As the disease progresses, it results in tissue and vascular damage leading to multiple organ dysfunction due to the direct or indirect effects of hyperglycaemia.³

The primary aim of DM pharmacotherapy is to preserve life and relieve symptoms while the secondary aim is prevention of long-term complications through the elimination of risk factors.⁴ Lifestyle management, which includes dietary modifications, physical exercises, self-management education and smoking cessation should form an integral part of DM management.⁵ If DM is not treated, it leads to the development of a variety of systemic complications which include diabetic retinopathy, nephropathy, neuropathy, cardiovascular diseases (CVD) and cerebrovascular accidents (CVA).

Diabetic retinopathy

Diabetic retinopathy (DR) is one of the most common microvascular complications in diabetes mellitus and the most common cause of progressive vision loss. It is assumed to affect 50–60% of patients with DM in varying stages.⁶ There is a 90% lifetime risk of developing DR in the DM population as compared to the non-DM population. The risk rises with cumulative duration of DM. As the

global DM prevalence is constantly on an increase, the incidence of DR is estimated to approximately triple in the subsequent four decades. DM causes microvascular damage in the retina, which then manifests as DR.⁷

Treatment

The main goals of DR treatment are to prevent and reverse vision loss where possible. The mainstay therapy for diabetic macular oedema and diabetic retinopathy is laser photocoagulation. It reduces the chances of progressing to moderate and severe visual loss.⁸ The Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) showed the benefits of laser photocoagulation in the treatment of DR.^{9,10} Data from recent clinical trials have shown that the use of anti-vascular endothelial growth factor (anti-VEGF) agents offers an effective treatment option for DR.⁸ Recent research has focused on the role of lipid lowering agents in slowing down or preventing vision loss. This was prompted by the possible effect of serum lipid levels on retinopathy in patients with diabetes mellitus.⁸

Diabetic nephropathy

Diabetic nephropathy (DN) can be described as a progressive increase in proteinuria and it occurs in 20–40% of DM patients.^{8,11} This gradual increase in proteinuria ultimately results in end stage renal disease (ESRD). The most common risk factors of DN include male gender, long duration of DM, obesity, cigarette smoking, hypertension and poor glycaemic control. DN usually develops after a DM duration of approximately a decade, but for type 1 diabetes mellitus (T1DM) it usually appears after five years. However, it is important to check for DN during type 2 diabetes mellitus (T2DM) diagnosis as it may be present at the time of diagnosis. The pathophysiology of DN follows three stages which

are: glomerular hypertrophy and hyperfiltration; glomeruli and tubulointerstitial regions inflammation; and cell number decrease due to apoptosis and extracellular matrix accumulation.^{8,11-13} DN is characterised by prolonged albuminuria, progressing from microalbuminuria to macroalbuminuria.

Treatment

The first step in the treatment of DN is the optimal control of glycaemia and blood pressure (BP). Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) can be used in normotensive and hypertensive patients as they have shown the benefits of reducing proteinuria, slowing down the progression of DN and also delaying dialysis in both groups.^{8,11} Protein intake should be reduced to 0.8g/kg body weight per day in people with DN as high protein intake has shown to increase proteinuria and renal function loss. This daily protein intake has shown some evidence of slowing glomerular filtrate rate (GFR) decline comparing with higher values. However, daily protein intake of levels less than 0.8g/kg body weight are not advisable as they do not change glycaemic levels and GFR decline.^{8,12}

Diabetic neuropathy

Diabetic neuropathy usually develops within a decade of the onset of DM in 40–50% of the patients. Clinical diabetic neuropathy is generally absent in T1DM patients within five years of diagnosis while it may be present in T2DM patients at time of diagnosis. The extent and duration of hyperglycaemia corresponds with the intensity and degree of the anatomical and functional defects of diabetic neuropathy.^{8,14} The risk factors for diabetic neuropathy are poor glycaemic control, obesity, hyperlipidaemia, hypertension and smoking. Not all patients suffering from diabetic neuropathy are symptomatic, but those with the symptomatic disease suffer from neuropathic pain which limits work productivity, mobility as well as quality of life.^{14,15} Diabetic neuropathy is underdiagnosed due to the asymptomatic characteristic in most cases. This therefore prevents the benefits of early detection, management and prevention of disabilities. The major consequences of diabetic neuropathy are foot abnormality, ulceration and Charcot arthropathy. Diabetic foot amputations are usually as a result of a combination of diabetic neuropathy, infection and angiopathy.³ Table 1 shows a comparison between ischaemic and neuropathic diabetic foot ulcers.

Treatment

The treatment of diabetic neuropathy is primarily supportive. Strict glycaemic control when instituted early can delay the progression of neuropathy, however, if the neuropathy has already been established, strict glycaemic control will not add valuable benefit.^{3,14} Treatment usually involves symptomatic treatment of pain and other symptoms exhibited, using certain antidepressants, anticonvulsants, opioids and transcutaneous electrical nerve stimulation. The use of opioids should be limited to short term use due to their potential for causing tolerance, dependency, and diversion.¹⁴ Antidepressants used in the management of neuropathic pain include tricyclic antidepressants, such as amitriptyline, and serotonin-noradrenaline reuptake inhibitors, for example venlafaxine and duloxetine. The anticonvulsants used are γ -aminobutyric acid (GABA) analogs, e.g. pregabalin and gabapentin.¹⁶

Peripheral arterial disease

The risk of peripheral arterial disease (PAD) is increased threefold in DM patients as compared to the general population and is the major cause of lower limb amputation in the DM population.¹⁷ It simultaneously increases with age, duration of DM and the existence of peripheral neuropathy. The main feature of PAD is critical limb ischaemia (CLI) which leads to ulceration, infection and occasionally lower limb amputation.¹⁸ Apart from diabetic neuropathy, diabetic foot can be caused by PAD or can result from neuroischaemic aetiology.¹⁷

Treatment

A comprehensive treatment strategy which includes lifestyle modifications and medical therapy is required in the management of PAD. The main aims for PAD treatment include adverse cardiovascular risk reduction, functional capacity improvement and conservation of limb viability. Management should be comprehensive and must include lifestyle modification, lipid lowering therapy, antihypertensive therapy, glycaemic control and antithrombotic therapy. Statins are the preferred lipid lowering therapy while ARBs or ACE inhibitors and aspirin, clopidogrel or pentoxifylline are preferred antihypertensive and antithrombotic therapies respectively.¹⁹

Table 1: Differences between ischaemic and neuropathic diabetic foot ulcer^{3,14,20}

	Ischaemic	Neuropathic
Pain	• Painful	• Usually painless
Areas affected	• Toes and feet margins	• Plantar surfaces
Callus	• Absent	• Present
Palpation	• No pulse • Cold • No sensation	• Pulse present • Warm • Sensation present
Venous filling	• Venous guttering	• Good venous filling

Cardiovascular diseases

A mortality rate of 65–80% of DM patients results from heart disease as compared to the general population. The risk of cardiovascular disease (CVD) increases by two to threefold in men and three to fivefold in women with T2DM than in the general population.¹⁸ The risks of CVDs tend to increase with an increase in the plasma glucose levels.¹⁹ The most common comorbidities of DM are hypertension and dyslipidaemia which are potential risk factors for atherosclerotic cardiovascular disease (ASCVD). ASCVD is characterised by acute coronary syndromes (ACSs), myocardial infarction (MI), angina pectoris, arterial revascularisation, stroke, transient ischaemic attack, or peripheral arterial disease assumed to be of atherosclerotic origin.²¹

Treatment

Treatment must always include lifestyle modifications as well as pharmacological agents. Hypertension must be treated using either ACE inhibitors, ARBs, calcium channel blockers or thiazide-like diuretics.¹⁹ The management of ASCVD is achieved through

the use of statin therapy in combination with antiplatelet therapy. An acute thrombus that blocks the coronary arteries may be due to overactive and malfunctioning platelets, endothelial dysfunction, raised coagulation factors and/or diminished fibrinolysis. Angioplasty can be performed to allow reperfusion.²² Table II describes the general preventive measures that can be used in the slowing down or prevention of DM complications.

Cerebrovascular diseases

DM is a known risk factor for ischaemic stroke, with the risk increasing two to fourfold in DM patients compared to the general population. The disturbance in the normal metabolic state in diabetes may result in arterial endothelial dysfunction, requiring treatment to mitigate atherogenesis.²³ Previous studies have indicated that cerebrovascular disease increases drastically with advancing age.²⁴

Treatment

The main goal in the initial management of cerebrovascular disease is patient stabilisation and carrying out of initial evaluation and assessment. Treatment include thrombolytic therapy coupled with glycaemic control and blood pressure control.²⁵ Table II describes some of the strategies that are used in the prevention and/or slowing down of the development of DM complications.

The role of the pharmacist

The role of the pharmacist has slowly moved from merely supplying medication into more active patient management and follow-up. With the implementation of pharmaceutical care, in which pharmacists are actively involved with the patient, there is a significant opportunity for pharmacists to have a greater role in DM patient care. The contributions of pharmacists include detection of possible and actual medication-related problems and suggesting possible adjustments to the treatment plan to the physician and other health care professionals.³⁵ However, this requires professional commitment and collaboration with the patient and the physician.

The pharmacist is strategically positioned to play a pivotal role in DM management and improve therapeutic outcomes.³⁴ This is achieved by screening of patients at an increased risk of DM, assessment of the patient's health status, compliance to standards of care and patient education to achieve self-care. Pharmacists can also assist in the monitoring of therapeutic outcomes of the patient's current regimen as well as referring them to other healthcare professionals according to their individual needs. Patients visit the pharmacist on a monthly basis to collect their medication between consultations with the doctor to evaluate if the desired therapeutic outcomes were achieved during the past

Table II: General measures to prevent complications in DM^{18,22-34}

Strategy	Description
Strict glycaemic control	<ul style="list-style-type: none"> The occurrence of DM complications correlates with chronic hyperglycaemia, therefore, normoglycaemia slows down or prevents complications.
Low-density lipoprotein control e.g. statins (simvastatin, atorvastatin)	<ul style="list-style-type: none"> All DM patients over the age of 40 should be considered for moderate-dose statin therapy. Statin therapy provides CVD risk reduction.
Blood pressure control	<ul style="list-style-type: none"> Blood pressure < 140/80 mmHg has shown reductions in the occurrence of microvascular complications.
Antiplatelet therapy	<ul style="list-style-type: none"> Aspirin has shown positive results in the prevention of arterothrombotic events.
Smoking cessation	<ul style="list-style-type: none"> Smoking presents an independent risk factor for increased morbidity and mortality in DM patients. Smoking increases the risks of MI by three times and CVA by 30%. Smoking also speeds up the progression of diabetic nephropathy to ESRD and is associated with poorer glycaemic control in the diabetic population. Smoking cessation helps reduce cardiovascular and cerebrovascular risks, decreases the risk of ESRD and improves glycaemic control
Dietary modifications	<ul style="list-style-type: none"> The main aim is to promote and support healthy eating habits and ensuring consumption of a variety of nutrients in their appropriate quantities. If individualised, it helps achieve BP, lipid, and glycaemic and body weight goals, thereby delaying the onset and progression of complications leading to an improved overall patient health. It should be regularly revised to accommodate concurrent therapies and treatment goals.
Physical activity	<ul style="list-style-type: none"> Benefits of physical activity includes: <ul style="list-style-type: none"> improved glycaemic control, increased insulin sensitivity, improved cardiopulmonary fitness, body weight control, improved BP control, reduced morbidity and mortality, and physical activity and cardiopulmonary fitness are associated with 39–70% reductions in mortality in T2DM patients.
Diabetes self-management education and support (DSME/S)	<ul style="list-style-type: none"> DSME/S forms an integral part of DM management. It empowers the patients to appropriately adjust their lifestyle, diet, physical activity and to actively participate in the management of their condition. Several meta-analysis studies shows that DSME/S has some clinical benefits which include reduced HbA1c.

DM – diabetes mellitus, CVD – cardiovascular disease, MI – myocardial infarction, CVA – cerebrovascular accidents, ESRD – end stage renal disease, BP – blood pressure, T2DM – type 2 diabetes mellitus, HbA1c – glycated haemoglobin

six months. Pharmacists may use the general preventive measures described in Table II to help patients to implement appropriate lifestyle changes, monitor, evaluate and counsel DM patients appropriately, to try and slow down or prevent the development of complications. The pharmacist's regular interaction with the patient provides the opportunity for pharmacists to use their knowledge and skills to assess, monitor, refer, educate and counsel patients when necessary.³⁶

Conclusion

There are a variety of DM complications with complex aetiologies that originate from chronic hyperglycaemia. In order to prevent the occurrence of DM complications, a patient-centred approach involving a multidisciplinary team must be employed from the time of DM diagnosis. The active participation of the patient and each member of the multidisciplinary team helps reduce morbidity and premature mortality due to DM complications. Diabetes management must be revised with each visit in accordance with the current laboratory parameters and physical assessments and screenings of the patient. Significant evidence supporting the role of pharmacists in the provision of DM care, extending from screening to ongoing management is mounting. Nevertheless, the full implementation of these services by pharmacists depends on patient acceptance, professional dedication, inter-professional collaboration, funding and an appropriate legislative framework.

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