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EC MICROBIOLOGY
Review Article

Minimizing the Risks, Prevention, and Management of Type 2 Diabetes Mellitus Long Time Sequelae

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Received: January 11, 2021; **Published:** January 20, 2021

Abstract

Introduction: The impact of diabetes on quality of life and health care costs is affected by numerous factors in addition to diabetes-associated complications. Microvascular, macrovascular and distal symmetric polyneuropathy (DSPN) are the most common neurologic complication and a major cause of morbidity in diabetic patients.

Aim of the Work: Minimizing the risk, prevention, and management of long-term complications of diabetes mellitus will be addressed in this review.

Methods: This article is a non-systematic, non-analytic literature review of medical literature.

Conclusion: Ongoing evaluation should include history taking and physical examination 2 - 4 times per year. Hypertension, hypercholesterolemia, smoking and 75 - 162 daily aspirin are recommended in patients with, or at high risk for ASCVD.

Bariatric surgery can reduce neuropathy incidence and lifestyle interventions are essential to prevent onset and slow progression of neuropathy. Duloxetine, venlafaxine, amitriptyline, pregabalin and gabapentin are the first-line agents for pain management.

Keywords: *Diabetes Mellitus; Chronic Complications; Risks; Management*

Introduction

In the United State, the estimated prevalence of diabetes among adults ranges from 6.8 to 15.3 percent and is affected by race and ethnicity [1]. Diabetes consumes health care resources more than any other condition [2]. The impact of diabetes on quality of life and health care costs is affected by numerous factors in addition to diabetes-associated complications. Depression has a high prevalence among diabetic patients [3]. It also affects absenteeism, employment, and work productivity [4].

The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrate the importance of intensive glycemic control to protect against microvascular and cardiovascular disease (CVD) in type 1 diabetes [5,6]. However, the role of intensive glycemic control in reducing (CVD) risk has not been similarly established in type 2 diabetes. Although its benefit on microvascular disease was published in the United Kingdom Prospective Diabetes Study (UKPDS).

Distal symmetric polyneuropathy (DSPN) is the most common neurologic complication and a major cause of morbidity in diabetic patients. It's considered synonymous with the term "diabetic neuropathy". DSPN symptoms begin distally and symmetrically in the toes and feet due to gradual loss of integrity of the longest nerve fibers. Neurologic disability linked to sensory loss and risk of foot ulcers and amputations are common. Additionally, about 15 - 20 percent of patients have painful symptoms that further limit their functions and worsen quality of life. Patients with diabetic neuropathy require a systematic, stepwise management approach that consists of glycemic control, metabolic syndrome control, patient's education about foot care and safety measures, and treatment of pain symptomatically, if present.

Minimizing the risk, prevention, and management of long-term complications of diabetes mellitus will be addressed in this review. Micro- and macrovascular, and diabetic neuropathy are the main addressed complications.

Methods

This article is a non-systematic, non-analytic literature review of medical literature. PubMed, Crossref and Google scholar are mainly used in the search process. The search output was screened and all relevant articles are included. We have endeavored to cover different aspects of the topic as much as possible. However, word limits did not allow scrupulous details of all aspects. The term used in search include diabetes mellitus, complication, risk lowering, and prolonged management.

Periodic evaluation and glycemic control

Ongoing evaluation for diabetes-related complications should be done to all diabetic patients. This include taking history and conducting physical examination 2 - 4 times per year. The goal is to acquire information on physical activity, nutrition, control of diabetes and cardiovascular risk factors, and diabetes complications.

At every visit, we check blood pressure, inspect the feet, perform a thorough foot examination and refer patients for an annual dilated eye examination. The frequency of eye examinations may differ according to the presence of eye findings, their severity, and other factors. Glycated hemoglobin (A1C) should be checked every three months as if its level is not in the targeted range, therapy will require adjustment. While in patients with stable glycemic control who are meeting HbA1C goals, we measure it every six months only. Fasting lipids and urine albumin-to-creatinine ratio are measured yearly.

Diabetes morbidity is a result of both microvascular disease (nephropathy, retinopathy and neuropathy) and macrovascular disease (atherosclerosis). Due to insidious onset of type 2 diabetes, the diagnosis is delayed. Consequently, diabetes complications could be present at the time of diagnosis [7]. Their frequency also rises over time. This could be delayed with management hypertension, dyslipidemia, and glycemic control. Likewise, the progress of these complications can be reduced with the same management strategies. Along with the management of hypertension, starting an angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) and a sodium-glucose co-transporter 2 (SGLT2) inhibitor, may reduce nephropathy progression specifically. While advanced retinopathy and vision loss could be improved with laser therapy or intraocular injection of vascular endothelial growth factor (VEGF)-inhibiting agents.

This approach seems to diminish the incidence of several diabetes complications, including myocardial infarction, stroke, end-stage kidney disease, and lower-extremity amputations. In USA, the ultimate absolute declines were reported for acute myocardial infarction

and strokes [8]. Similar reductions in the rate of cardiovascular complications and lower-extremity amputation were reported in other countries [9].

Diabetic patients are at increased risk for vision loss. This is attributed to cataracts, refractive errors (correctable), glaucoma (which are more prevalent in patients with diabetes and retinopathy. Twenty percent of Americans with diabetes aged 40 years and older without retinopathy (or with only mild and moderate non-proliferative diabetic retinopathy) developed visual-related functional impairment. This was found by a study that used data from the National Health and Nutrition Examination Survey (NHANES) in the United States [10]. For those with severe NPDR or proliferative diabetic retinopathy, the prevalence was 48 percent. These data indicate the need for visual acuity assessment in addition to dilated eye examinations for retinopathy to identify individuals with reduced acuity, address treatable causes and improve quality of life. Recommendations for the type and frequency of routine eye examinations differ according to the type of DM, the level of risk factors such as HbA1C levels and the existence of specific eye findings [11]. Serial examinations are required due to the rise in incidence of retinopathy over time in diabetic patients and the ability to reduce risk for vision loss if timely interventions were done.

A complete foot examination should be done yearly to all diabetic patients. This help in identifying risk factors of ulcers and amputation. The feet should also be visually inspected at all routine visit to detect problems with nail care, fungal infections, poorly fitting shoes causing barotrauma and callus formation that can cause more severe foot problems [11]. This can be done in the primary care setting and must include inspection, checking pedal pulses and testing for loss of sensation. The morbidity from foot problems may be substantially reduced by systematic screening for neuropathic and vascular involvement of the lower limbs and careful inspection of feet.

The earliest clinical finding of diabetic nephropathy is increased urinary protein excretion. Therefore, measurement of the albumin-to-creatinine ratio in an untimed urine sample is preferred as a screening test in all patients with diabetes to detect elevation. It must be done yearly. It is uncommon to find an elevation before five years of the onset of disease in patients with type 1 diabetes so the screening could be deferred till that time. In patients with type 2 diabetes, the screening should start at diagnosis because many patients had diabetes for several years before diagnosis [11].

Large number of false positive results can occur. Therefore, all abnormal results should be repeated 2 - 3 times for confirmation over a 3 - 6 month [12]. Factors that can cause transient rise in urinary albumin-to-creatinine ratio include fever, heart failure, exercise, and acute poor glycemic control [12].

The urine albumin-to-creatinine ratio test (mg/g) provides a quantitative result that correlates with the 24-hour urine results (mg/day) of protein excretion. The rate of albumin excretion should be less than 30 mg/day (20 mcg/min) normally. When urine albumin-to-creatinine ratio result between 30 and 300 mg/gram persistently, it suggest that albumin excretion is between 30 and 300 mg/day. This is considered moderate albuminuria (historically called microalbuminuria). Moderate albuminuria is usually suggestive of diabetic nephropathy (unless there is another renal disease). Urine albumin-to-creatinine ratio result above 300 mg/gram creatinine persistently, (or 300 mg/day if a 24-hour urine is collected) are considered severe albuminuria. Clinical renal disease, overt proteinuria, or dipstick positive proteinuria are other commonly used names. Effective therapy for diabetic nephropathy with ACE inhibitors, ARBs and SGLT2 inhibitors is available thats the rationale for the annual screening of all diabetic patients for increased albumin excretion with either type 1 or type 2 diabetes. The value of yearly monitoring of the urine albumin-to-creatinine ratio is uncertain if the patient is commenced on a medication for increased urinary albumin excretion [13].

An annual assessment of risk factors (blood pressure, fasting lipid profile, smoking history) should be done to detect patients who may benefit from intensive cardiovascular risk factor treatment. Exercise stress testing is not routinely done in asymptomatic diabetic patients, including those with type 2 diabetes who are at increased risk for atherosclerotic cardiovascular disease (ASCVD) than healthy people [14]. For sedentary patients (age > 50 years) with diabetes who are starting an exercise program, we obtain a resting electrocar-

diogram and counsel beginning a gentle exercise program with slow progression as tolerated. The higher risk of asymptomatic coronary artery disease in diabetic patients who have other risk factors suggests that the decision to implement stress testing prior to starting an exercise program should be individualized, taking into consideration those at very high risk, as diabetic patients who also have carotid or peripheral artery disease. Despite the relative increased frequency of silent ischemia in diabetic patients, detecting asymptomatic disease or starting early intervention beyond guideline-recommended ASCVD risk factor treatment didn't improve outcomes in those patients [14].

Glycemic control

All patients with DM who use insulin and some patients who take other glucose-lowering drugs that can cause hypoglycemia should self-monitor their glucose level to maintain a safe, target-driven glucose control. Generally, self-monitoring is needless in patients who are managed with diet alone or who take injectable or oral drugs that do not cause hypoglycemia.

HbA1C goal in diabetic patients should be tailored to each one. This is done by balancing the demonstrated benefits of prevention and delay of the microvascular complications (by intensive glycemic control) with the risk of developing hypoglycemia. A reasonable target of therapy might be an HbA1C value of ≤ 7.0 percent [15]. In order to achieve this HbA1C target, a fasting glucose of 80 - 130 mg/dL (4.4 to 7.2 mmol/L) and a postprandial glucose (90 - 120 minutes after a meal) less than 180 mg/dL (10 mmol/L) are generally required, however, higher levels may be sufficient [16].

In older patients, patients with comorbidities, patients with a history of severe hypoglycemia or other major adverse medication events or polypharmacy, or patients with a limited life expectancy and little likelihood of benefit from intensive therapy the HbA1C target should be set higher.

HbA1C should be obtained twice yearly at least in patients who are meeting treatment targets and who have constant glycemic control and quarterly in patients whose therapy needs adjustment, or who are not meeting glycemic targets.

Macro- and microvascular sequelae

Avoidance of cardiovascular complications is a priority for patients with diabetes, especially type 2. Diabetic patients are at higher risk for developing and dying from atherosclerotic cardiovascular disease (ASCVD); compared with healthy people, they also have reduced life expectancy [17]. At the time of diagnosis of type 2 diabetes, several patients already have one or more risk factors for macrovascular complications and many have confirmation of overt atherosclerosis.

Controlling the ASCVD risk factors, including HTN, hypercholesterolemia and smoking, will decrease cardiovascular mortality. Smoking cessation is important for patients who smoke, in addition, use of aspirin (75 to 162 mg/day), and use of some glucose-lowering drugs in patients with or at high risk for ASCVD can decrease recurrent ASCVD events and mortality.

A survey in the USA (2001 to 2010) demonstrated that the adjusted prevalence of cigarette smoking was lesser and quit attempts greater among adults with versus without diabetes [18]. A meta-analysis of several of the cardiovascular risk reduction trials revealed that cessation of smoking had a much higher benefit on survival than most other interventions [19]. These findings suggest that smoking cessation is one of the most main aspects of treatment in diabetic patients who smoke.

For the secondary prevention of ASCVD in diabetic patients, 75 - 162 mg of aspirin is recommended. Some experts recommend similar dose of aspirin for the primary prevention of ASCVD in diabetic patients who are at high cardiovascular risk (10-year risk > 10 percent) However, the evidence supporting this strategy is weak and should be balanced with the higher risk of gastrointestinal bleeding. We do not routinely provide aspirin for the prevention of ASCVD in diabetic patients at low risk (10-year ASCVD risk < 10 percent). The decision

to provide aspirin for the prevention of cardiovascular events in diabetic patients must be made using shared decision-making on an individual basis, taking into consideration potential advantages and risks. Large trials studying the role of aspirin for the primary prevention of cardiovascular events in diabetic patients have been done or are underway [20].

The advantages of daily aspirin treatment in patients with existing ASCVD are widely accepted. A meta-analysis from the Antithrombotic Trialists' Collaboration of randomized trials of antiplatelet treatment for the secondary prevention of ASCVD in high-risk patients revealed that aspirin produced both statistically and clinically significant reductions in the risk of subsequent myocardial infarction, stroke, and vascular death among a wide range of high-risk patients [21]. In the subset of diabetic patients, there was a nonsignificant, 7 percent reduction in serious cardiovascular events [21].

The advantages of daily aspirin for the primary prevention of ASCVD in diabetic patients with risk factors is unclear. In a meta-analysis of 10 trials assessing aspirin for the primary prevention of ASCVD in patients with diabetes, aspirin achieved modest but significant decrease in the risk of major cardiovascular events compared with placebo or no treatment [22]. However, aspirin did not significantly decrease the risk of any of the endpoints (coronary heart disease, stroke, myocardial infarction, ASCVD, or all-cause mortality), in addition, there were variances in effect according to underlying ASCVD risk, gender, and compliance.

In a subsequent trial, 15,480 diabetic patients without evidence of ASCVD were randomly allocated to aspirin (100 mg daily) or placebo [20]. Participants were also randomly allocated to receive 1 gram n-3 fatty acid or placebo one per day. Most patients were commenced on statins and antihypertensive medication. After a mean follow-up of 7.4 years, serious vascular complications (except intracranial hemorrhage), TIA, or death from any vascular cause happened in a smaller part of patients in the aspirin arm. Aspirin didn't significantly decrease the risk of any of the individual endpoints. The benefits of aspirin in reducing serious vascular events were offset by an estimated 1 percent absolute rise in the risk of bleeding, mainly gastrointestinal and extracranial.

In exploratory analyses, the effects of aspirin on severe vascular complications and on safety events did not evidently vary according to baseline patient characteristics, including group allocated to n-3 fatty acids and baseline ASCVD risk.

Aspirin main adverse effect is bleeding. In the trial described above, major bleeding events (the first incidence of a composite of intracranial hemorrhage, vision-threatening bleeding in the eye, GI bleeding, or bleeding that resulted in hospitalization, transfusion, or fatality) happened in a higher proportion of patients in the aspirin group [21]. However, aspirin did not significantly escalates the risk of any of the individual endpoints. While in a Japanese trial there was a surge in nonfatal intracranial hemorrhage and subarachnoid hemorrhage in patients taking aspirin [23]. Moreover, extracranial hemorrhage necessitating transfusion or hospitalization was also more common in the aspirin group.

Aspirin does not appear to raise retinal hemorrhagic events in patients with diabetic retinopathy, even if advanced. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that patients with mild to severe non-proliferative or early proliferative diabetic retinopathy treated with scatter retinal photocoagulation in one eye. The 3711 participants were also randomly allocated to take either aspirin, 650 mg daily, or placebo. During this trial, periodic fundus photography of the eyes not getting photocoagulation noticed vitreous or pre-retinal hemorrhages in 32 versus 30 percent of patients treated with aspirin or placebo, respectively [24]. About 40 percent of these hemorrhages lead to loss of visual acuity to less than 20/40, however, the severity and rate of resolve of these hemorrhages were not changed between the aspirin- and placebo-treated groups. Likewise, in the large trial described above (15,480 diabetic patients), the risk of visual-threatening bleeding did not change between the aspirin and placebo groups [20]. These studies, as well as a meta-analysis of other randomized clinical trials, established that there were no ocular contraindications to the use of aspirin (650 mg/day) in diabetic patients who need this medicine for treatment of ASCVD or for other medical reasons [24].

Hypertension (HTN) is a common problem in type 1 and especially in type 2 diabetes, thus early and effective treatment of high blood pressure is important. It can prevent cardiovascular disease (CVD) and reduce the rate of progression of diabetic nephropathy and reti-

nopathy. Measuring blood pressure at every routine diabetes visit, with individualization of treatment goals is recommended by the ADA. For most patients with hypertension, the ADA suggests treating goals to systolic and diastolic blood pressures of < 140 and < 90 mmHg, respectively [14]. Lower treatment goals could be appropriate for individuals at high risk of CVD, if they can be reached without undue treatment burden. The 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines suggest a goal blood pressure in diabetic patients of < 130/80 mmHg [25].

Lipid disorders undoubtedly contribute to a higher risk of ASCVD. The ADA recommends screening for lipid abnormalities at the time of diagnosis and every five years after [14]. Lifestyle modifications such as weight loss and increased physical activity are recommended to improve lipid profile in diabetic patients [14]. In patients with **clinical ASCVD, statin therapy should be started regardless of baseline lipid levels.** The intensity of statin is adjusted according to ASCVD risk, side effects, tolerability, and LDL levels.

Metformin appears to reduce cardiovascular events in certain populations. Moreover, sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists lead to reduction in CVD outcomes.

Diabetic neuropathy

Symptomatic diabetic neuropathy is generally not reversible, therefore, treatment aims to slow the progression and prevent complications, like foot ulcers, arthropathy and falls. The importance of glycemic control for decelerating the progression of neuropathy and other microvascular complications of diabetes differ by type of diabetes.

In type 1 diabetes, high-quality evidence recommends aiming for stable glycemic control in the management of diabetic neuropathy [26]. In a meta-analysis of Diabetes Control and Complications Trial and one additional trial in a total of 1228 patients with type 1 diabetes, enhanced glycemic control decreased the annual risk of neuropathy [27]. In type 2 diabetes, glycemic control has a more modest effect on neuropathy. A meta-analysis of four trials in 6669 patients with type 2 diabetes demonstrated a nonsignificant reduction in the annual risk of neuropathy with enhanced glycemic control [27]. This could be attributed to the difference in the pathophysiology of neuropathy in type 2 diabetes [28].

Bariatric surgery, as a surgical treatment of type 2 diabetes, can reduce neuropathy incidence, along with other microvascular complications [29]. Rates of retinopathy and nephropathy were also decreased in those patients.

Lifestyle interventions are essential to prevent onset and progression of neuropathy, particularly in patients with prediabetes and type 2 diabetes [26]. Vascular risk factor treatment is also recommended to slow the progression of diabetic neuropathy, including control of blood pressure, lipids, smoking cessation and avoidance of excess alcohol consumption [26].

Burning or stabbing feet pain is reported by Approximately 15 - 20 percent of patients with diabetic neuropathy due small myelinated nerve involvement [30]. The pain may resolve spontaneously within one year in 50 percent of these patients [31]. However, persistent symptoms and disability related to pain may affect large proportion. Hence, the symptomatic interventions to relive neuropathic pain are essential.

Several types of antidepressants and gabapentin antiepileptic drugs are used as a first-line options for neuropathic-related pain [32]. The most common antidepressants are duloxetine, venlafaxine **and** amitriptyline. Examples of gabapentinoid antiepileptic drugs are and the gabapentinoid antiepileptic drugs pregabalin and gabapentin.

Conclusion

Ongoing evaluation for diabetes-related complications should be done to all diabetic patients. This include taking history and conducting physical examination 2 - 4 times per year. The frequency of eye examinations may differ according to the presence of eye findings, their

severity, and other factors. Glycated hemoglobin (A1C) should be checked every three months as if its level is not in the targeted range, therapy will require adjustment.

Controlling the risk factors for atherosclerotic cardiovascular disease (ASCVD) are the backbone of management of micro- and macrovascular complications. These include hypertension, hypercholesterolemia, and smoking. In addition, the use of 75 - 162 daily aspirin in patients with or at high risk for ASCVD can decrease recurrent ASCVD events and mortality.

Symptomatic diabetic neuropathy is generally not reversible, therefore, treatment aims to slow the progression and prevent complications, like foot ulcers, arthropathy and falls. Bariatric surgery can reduce neuropathy incidence and lifestyle interventions are essential to prevent onset and slow progression of neuropathy. Duloxetine, venlafaxine, amitriptyline, pregabalin and gabapentin are the first-line agents for pain management.

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