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SCREENING FOR COMPLICATIONS OF DIABETES MELLITUS

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Abstract:

Introduction: *Diabetes is considered one of the main causes of end-stage renal disease, blindness, and nontraumatic lower-limb amputation. It has also been an important cause of cardiovascular morbidity and mortality and the estimated to be the 7th leading cause of death in the US alone. The economic burden of diabetes in the US in 2012 was estimated to be more than two hundred billion. Much of the disability and cost linked with diabetes are linked to the care of chronic complications.*

Aim of work: *In this review, we will discuss the most recent evidence regarding screening for diabetes complications.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The terms used in the search were: diabetes, complications, screening, primary care settings.*

Conclusions: *Diabetes is considered the main cause of end-stage renal disease, blindness, and nontraumatic lower-limb amputation. The greatest decrease in cardiovascular complications have been seen when multiple risk factors like hypertension, dyslipidemia, and hyperglycemia are well targeted at the same time. The advantage of taking aspirin as secondary prevention in patients with previous stroke or myocardial infarction has been well studied. Dilated eye examinations are very efficient in diagnosing eye -threatening diabetic retinopathy and have been linked to prevent blindness. The combined use of appropriate tools and clinical examination/inspection has been proven to provide greater than eighty percent specificity in the diagnosing of diabetic peripheral neuropathy. Early management of risk factors, involving hypertension, hyperglycemia, and dyslipidemia can delay or prevent diabetic nephropathy*

Key words: *diabetes, complications, screening, primary care setting.*

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INTRODUCTION:

Diabetes is considered one of the main causes of end-stage renal disease, blindness, and nontraumatic lower-limb amputation. It has also been an important cause of cardiovascular morbidity and mortality and the estimated to be the 7th leading cause of death in the US alone. The economic burden of diabetes in the US in 2012 was estimated to be more than two hundred billion. [1] Much of the disability and cost linked with diabetes are linked to the care of chronic complications.

In this review, we will discuss the most recent evidence regarding screening for diabetes complications.

METHODOLOGY:

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: diabetes, complications, screening, primary care settings

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

Overview:

New enhancements in research, therapies, and technology have improved the capability
to care for patients for the best with diabetes. Although these improvements, patients with diabetes remain to experience less optimal glucose, blood pressure, and cholesterol levels, exposing them to a higher risk for the development of acute and chronic complications.

CARDIOVASCULAR DISEASE:

Cardiovascular disease (CVD) is one of the main causes of morbidity and mortality in diabetic patients and is the greatest factor to the direct and indirect cost burdens
of the disease. Diabetics have a higher risk of coronary artery disease
(CAD), a higher degree of coronary ischemia, and have higher risk of myocardial infarction (MI). [2] Additionally, Diabetic patients with type 2 diabetes have a great rate of asymptomatic coronary disease and silent ischemia. [3]

New results from studies propose a decrease in cardiovascular complications in patients with diabetes mellitus. The biggest decline in cardiovascular complications are seen when many risk factors, like hypertension, dyslipidemia and hyperglycemia, are targeted at the same time. [4] In many diabetic patients, risk factors for CVD should be tested yearly. Diabetics should have their blood pressure measured on all routine visit. Home blood pressure measurements could be helpful in solving differences between office-based measurements and out-of-office values in specific patients. Additionally, blood pressure screening, adult patients with diabetes should have a fasting lipid profile obtained on an annual basis. Routine screening for CAD is not recommended in patients with diabetes who are asymptomatic. But, diabetics with typical or atypical cardiac symptoms or abnormal resting electrocardiogram are candidates for more advanced or invasive cardiac testing.

The significance of glycemic control (hemoglobin A1c <7%) to prevent CVD has been well studied in diabetics especially with type 1. Many trials showed that Patients previously randomized to the intensive arm of the DCCT had a about forty percent decrease in CVD and a fifty percent decrease in the risk of nonfatal MI, stroke, or cardiovascular death compared with those subjects in the standard arm. [5]

A trial in UK showed that there was a sixteen percent decline in cardiovascular complications in the intensive glycemic control arm, but the change was not significant. In spite of a loss of glycemic differences between the treatment and control groups, the long-term follow-up to the UKPDS showed a continued decline in microvascular risk and emergent risk reductions for MI during the 10-year posttrial follow-up. [6]

Hypertension is considered a critical risk factor for the development of CVD in patients with both type of diabetes. Many studies have proven that blood pressures higher than 115/75 mm Hg are linked with higher CVD in patients with diabetes.[7]Many trials have proven to decrease in cardiovascular complications, involving stroke, with the decreasing of systolic blood pressure to less than 140/80 mm Hg. [8] There continues to be limited evidence regarding the benefits for lower systolic blood pressure targets.

Diabetics patients and hypertensives must be managed with an aim of blood pressure of less than 140/80 mm Hg. Lifestyle changes involving weight loss, the dietary approaches to stop hypertension (DASH) diet, decrease in sodium intake (1500 mg/d),

and higher physical activity should accompany the pharmaceutical approach.

Several trials have concluded that the beneficial effects of statin therapy for primary and secondary prevention of CVD. Trials in patients with diabetes have proven a similar trend. [9]

Retinopathy

Diabetic retinopathy is one of the most prevalent causes of blindness among adults patients twenty to seventy five years of age. The pathophysiology, natural history, and clinical presentation of diabetic retinopathy are well established with recognizable stages of the disease. Early signs of retinopathy consist of small outpouchings from the retinal capillaries known as microaneurysms and dot intraretinal hemorrhages. As the disease progresses, macular edema, ischemic changes, collateralization, and proliferative changes can result in visual impairment or vision loss. Risk factors for developing diabetic retinopathy consist of duration of diabetes, severity of hyperglycemia, hypertension, and dyslipidemia. 20 years following the diagnosis of diabetes, most patients with type 1 diabetes and about eighty percent of patients with type 2 diabetes have some degree of diabetic retinopathy. [10]

During the last thirty years there has been a decrease in both the incidence and risk of progression of diabetic retinopathy. [11] The Wisconsin Epidemiologic Study of Diabetic Retinopathy showed that more than seventy percent decrease in the annual incidence of proliferative retinopathy in patients with type 1 diabetes mellitus (T1DM) 40 There are accurate, safe, and well accepted screening tests (ophthalmoscopy and retinal photography) for diabetic retinopathy. Regular dilated eye examinations are extremely effective in diagnosing sight-threatening diabetic retinopathy and have been proven to prevent blindness. [12] Patients with macular edema and diabetic retinopathy may be asymptomatic at the time of diagnosis, so all patients with diabetes should undergo comprehensive screening.

Screening for diabetic retinopathy in patients with type 1 diabetes must start within five years after the diagnosis. This screening recommendation is reinforced by evidence that retinopathy is estimated to take five years to develop after the onset of hyperglycemia. Patients with newly diagnosed type 2 diabetes could had asymptomatic hyperglycemia for several years before the diagnosis and so have a higher risk of diabetic retinopathy at the time of diagnosis. So, patients with type 2 diabetes should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Ophthalmoscopy continues to be the most common methods for monitoring diabetic retinopathy. But the use of nondilated ophthalmoscopy by non–eye care providers has been proven to have poor sensitivity compared with retinal photography. Screening for diabetic retinopathy using a nonmydriatic camera has become more common. Many studies have investigated the efficacy of digital retinal photographs as a screening tool for retinopathy. A new meta analysis of twenty studies using nonmydriatic digital retinal photographs concluded more than eighty percent sensitivity and eighty eight specificity for the diagnosis of diabetic retinopathy. [13]

Variations in glycemic control or other hormonal factors during pregnancy can hasten diabetic retinopathy. But, the ACCORD study failed to show that decreasing blood pressure to less than 120 mm Hg offered further benefit. Retinal photocoagulation for the treatment of diabetic retinopathy was introduced in the 1960s.

Diabetic Peripheral Neuropathy

Diabetic neuropathy is considered one of the most common complications of both type 1 and type 2 diabetes. The term diabetic neuropathy incorporates a spectrum of clinical syndromes with different distributions, clinical courses, and underlying pathogenic mechanisms. Each syndrome is described by diffuse or focal damage to peripheral somatic or autonomic nerve fibers resulting from hyperglycemia. Diabetic neuropathy is classically categorized into diabetic peripheral neuropathy (DPN) and autonomic neuropathy. DPN has been known as the presence of symptoms and/or signs of peripheral nerve dysfunction after the exclusion of other causes. The prevalence of diabetic neuropathy in newly diagnosed patients with diabetes is calculated to be more than five percent and higher than fifty percent in patients with long-standing disease. [14] Diabetic neuropathy continues to be the main cause of nontraumatic limb amputations. Many studies have concluded that the duration and severity of diabetes are significant risk factors for the development of diabetic neuropathy in patients with type 1 and type 2 diabetes. [15]

Symptoms like burning, tingling, numbness, shooting (electric shock), and stabbing are present in thirty three percent of patients with DPN. Patients might first experience symptoms in their toes that gradually

travel proximally. These symptoms are most frequently worst at night and may affect sleep quality. The high prevalence of diabetic neuropathy leads to marked morbidity, involving a higher risk of recurrent lower-extremity infections, ulcerations, depression, foot and ankle fractures, and lower-limb amputations. [16]

The mechanism of DPN is multifactorial and consist of a combination of metabolic, vascular, and hormonal factors that shift the balance between nerve fiber damage and repair. The combination of direct nerve injury caused by hyperglycemia, endothelial injury, and microvascular dysfunction leads to nerve ischemia. Additionally, nerve
ischemia and hypoxia, increased cytokine levels can also be responsible in the formation of DPN. [17]

Many questionnaires have been established to help doctors assess the diagnosis of DPN.76 The douleur neuropathique 4 questions (DN4) questionnaire can be completed Very fast and is not difficult to easy to use with high sensitivity and specificity. There are many simple clinical tests that should be used to screen patients for DPN. Patients with type 1 and type 2 diabetes should be screened for DPN on an annual basis. Pinprick sensation and light touch perception should be assessed using a 10-g monofilament. In addition, vibratory threshold should be assessed using a 128-Hz tuning fork. The combined use of appropriate tools and clinical examination/inspection has been shown to provide greater than 87% specificity in the detection of DPN. Improved glycemic control has been proven to enhance nerve function in patients with diabetes. Intensive glycemic control has also been shown to reduce the risk of developing diabetic neuropathy in patients with type 1 diabetes and may reduce the risk in patients with type 2 diabetes. The results for glycemic control and the prevention of neuropathy in patients with type 2 diabetes is not as strong. The UKPDS investigators reported a 25% risk reduction in microvascular complications after 10 years of intensive treatment. but, most of the risk reduction was driven by the decrease in retinopathy. Studies have proven a slowing of the progression of diabetic neuropathy with improved glycemic control in patients with type 2 diabetes.
Intensive glycemic control, particularly early in the disease, seems to provide a long-term benefit for the prevention of diabetic neuropathy. The EDIC trial followed approximately 95% of the subjects enrolled in the DCCT cohort for several years.
During the EDIC trial, the glycemic separation between the intensively treated group and the standard treatment group disappeared.

Diabetic Nephropathy

Nephropathy is considered one of the most common complication of both type 1 and type 2 diabetes. It is estimated that the prevalence of diabetic nephropathy is 15% to 25% and 30% to 40% of patients, respectively. In the analysis of patients
enrolled in the UKPDS trial, 24.9% of patients with type 2 diabetes progressed to microalbuminuria, 5.3% developed microalbuminuria, and 0.8% revealed increased creatinine levels or required dialysis within the first 10 years after diagnosis. Diabetes is the leading cause of end-stage renal disease (ESRD) in both developed and emerging countries. The clinical presentations of diabetic nephropathy, including proteinuria, increased blood pressure, and decreased glomerular filtration rate (GFR), are the same in patients with type 1 and type 2 diabetes. but, by the time the laboratory or clinical abnormalities of diabetic nephropathy become evident, marked pathologic changes are already present within the kidney.

Glomerulosclerosis, thickening of the glomerular basement membrane, mesangial cell expansion, loss of podocytes, renal cell hypertrophy, and tubulointerstitial fibrosis are the main pathologic alterations that occur during the progression of diabetic nephropathy. 116–119 These changes lead to progressive albuminuria, decrease in GFR, increase in blood pressure, and fluid retention. Chronic kidney disease is linked with a significant increased risk for CVD that is independent of the traditional CVD risk
factors.[18] Screening for diabetic nephropathy should consist of the assessment for increased urinary albumin excretion using an albumin/creatinine ratio on a random spot urine collection. An albumin/creatinine ratio should be done on patients with type 1 diabetes for more than five years and in all patients with type 2 diabetes at the time of diagnosis. Clinicians should obtain a serum creatinine level with estimated GFR on a yearly basis in all patients with diabetes regardless of the degree of urine albumin excretion. Clinical studies have found decreased GFR in patients without evidence of increased urine albumin excretion. The role of continued annual assessment of urine albumin excretion after the diagnosis of albuminuria has been made remains unclear. The American Diabetes Association recommends continued monitoring of urine albumin excretion to assess both response to therapy and progression of disease. The development of complications from chronic kidney disease correlates with level of kidney function, particularly GFR. It is highly suggested that doctors start screening for complications of chronic kidney disease

in patients with estimated GFR less than 60 mL/min/1.73m2.

The best approach to therapy in patients with diabetic nephropathy involves targeting multiple factors, such as hypertension, hyperglycemia, and dyslipidemia. Early treatment of risk factors can delay or prevent diabetic nephropathy. In the UKPDS trial, intensive blood pressure control was associated with a thirty percent risk decrease for the development of microalbuminuria. The best lower limit for systolic blood pressure for the prevention of diabetic nephropathy has not yet been established. Adequate blood pressure control with drugs that change the renin-angiotensin system has been shown to reduce the incidence and progression of diabetic nephropathy. In patients with type 1 diabetes and diabetic nephropathy, remission or regression could happen with control of systemic blood pressure, particularly with ACE inhibitors. Several large, prospective, randomized trials in patients with type 1 diabetes have shown that reduction of systolic blood pressures (<140 mm Hg).

After four years of follow-up there was a marked decrease in blood pressure and in the rate of new-onset microalbuminuria. The effects of ACE inhibitors and ARBs are promising and seem to be independent of blood pressure reduction, proposing a direct kidney protection. manyclinical trials have concluded that ARBs decreased the progression of albuminuria as well as ESRD in patients with type 2 diabetes and diabetic nephropathy. Other classes of antihypertensive agents can be used in addition to ACE inhibitors and/or ARBs to further reduce blood pressure or in patients who cannot tolerate an ACE inhibitor or ARB.

Intensive glucose control has been proven to lower the risk of development and delay or prevent progression of diabetic nephropathy. The DCCT and its long-term follow-up, the EDIC trial, revealed that intensive glucose control prevented the progress of microalbuminuria in patients with type 1 diabetes. In patients with type 2 diabetes, the UKPDS showed that intensive glucose control decreased the risk of microalbuminuria or proteinuria by thirty three percent.

Doctors must consider referral to a nephrologist if there are questions about the cause of the patient's kidney disease. Consultation with the nephrologist in patients with stage IV chronic kidney disease has been found to decrease cost, improve quality of care, and delay the need for dialysis. Additional considerations for referral could include anemia, secondary hyperparathyroidism, or electrolyte disturbances.

CONCLUSIONS:

Diabetes is considered the main cause of end-stage renal disease, blindness, and nontraumatic lower-limb amputation. The greatest decrease in cardiovascular complications have been seen when multiple risk factors like hypertension, dyslipidemia, and hyperglycemia are well targeted at the same time. The advantage of taking aspirin as secondary prevention in patients with previous stroke or myocardial infarction has been well studied. Dilated eye examinations are very efficient in diagnosing eye -threatening diabetic retinopathy and have been linked to prevent blindness. The combined use of appropriate tools and clinical examination/inspection has been proven to provide greater than eighty percent specificity in the diagnosing of diabetic peripheral neuropathy. Early management of risk factors, involving hypertension, hyperglycemia, and dyslipidemia can delay or prevent diabetic nephropathy

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