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SCREENING FOR COMPLICATIONS OF DIABETES MELLITUS

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Abstract:
Background: Diabetes, a chronic condition characterized by high levels of blood sugar, is widely recognized as a predominant factor contributing to end-stage renal disease, visual impairment, and nontraumatic lower-limb amputations. it has been identified as a significant contributor to cardiovascular morbidity and mortality, with statistics indicating that it ranks as the 7th leading cause of death exclusively in the United States. The financial impact of diabetes in the US was staggering in 2012, surpassing a staggering two hundred billion dollars. A considerable portion of the disability and financial burden associated with diabetes can be directly attributed to the management of its chronic complications, which often require extensive and costly medical interventions. The multifaceted nature of diabetes underscores the urgent need for comprehensive strategies aimed at prevention, early detection, and effective management of this complex condition to alleviate its far-reaching health and economic consequences.

Keywords: diabetes, complications, screening, primary care setting.

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

Diabetes complications:

Recent advancements in research, therapies, and technology have significantly enhanced the ability to provide top-notch care for patients suffering from diabetes. Thanks to these advancements, individuals with diabetes now have access to better treatment options and management strategies. Despite these positive changes, many patients with diabetes still struggle to maintain optimal glucose, blood pressure, and cholesterol levels, which in turn increases their susceptibility to various acute and chronic complications.

CARDIOVASCULAR DISEASE:

Cardiovascular disease (CVD) remains a significant contributor to the morbidity and mortality rates among individuals diagnosed with diabetes, standing out as the primary factor driving both the direct and indirect financial burdens associated with the condition. Diabetic patients exhibit an elevated susceptibility to coronary artery disease (CAD), demonstrating a heightened level of coronary ischemia, and facing an increased likelihood of experiencing myocardial infarction (MI)[2]. Moreover, individuals with type 2 diabetes are particularly prone to harboring asymptomatic coronary disease and silent ischemia, further underscoring the intricate relationship between diabetes and cardiovascular health[3].

Recent findings stemming from various research endeavors suggest a potential reduction in cardiovascular complications among those suffering from diabetes mellitus. The most pronounced decrease in such complications materializes when a multifaceted approach is adopted, simultaneously addressing key risk factors such as hypertension, dyslipidemia, and hyperglycemia[4]. It is advisable for a considerable number of diabetic patients to undergo annual assessments aimed at evaluating their susceptibility to CVD. Regular monitoring of blood pressure should be an integral component of routine medical visits for diabetics, with the potential incorporation of home-based blood pressure measurements to mitigate discrepancies between readings obtained in clinical settings and those captured outside the healthcare environment, especially in certain patient cohorts. Furthermore, as part of the comprehensive care protocol, adult individuals with diabetes ought to undergo fasting lipid profile testing on a yearly basis to proactively manage their cardiovascular health. While routine screening for CAD is not universally recommended for asymptomatic diabetic patients, those presenting with typical or atypical cardiac symptoms or displaying abnormalities in their resting electrocardiogram should be considered for more advanced or invasive cardiac diagnostic procedures, ensuring timely identification and intervention in cases warranting such measures.[4]

The importance of maintaining glycemic control, defined as keeping hemoglobin A1c levels below 7%, in order to prevent cardiovascular disease (CVD) has been extensively researched, particularly in individuals with type 1 diabetes. Numerous studies have demonstrated that patients who were previously assigned to receive intensive treatment in the Diabetes Control and Complications Trial (DCCT) experienced a significant reduction of about forty percent in the incidence of CVD, as well as a fifty percent decrease in the risk of nonfatal myocardial infarction (MI), stroke, or cardiovascular-related mortality when compared to those individuals in the standard treatment group. These findings underscore the critical role that glycemic control plays in mitigating the risk of developing CVD and its associated complications, highlighting the importance of proactive management of blood sugar levels in diabetic patients to improve cardiovascular outcomes and overall health.[5]

A trial conducted in the United Kingdom revealed a reduction of sixteen percent in cardiovascular complications within the group that implemented intensive glycemic control, however, this decrease was not deemed statistically significant. Even though there was a diminishing disparity in glycemic levels between the groups subjected to different treatments, the extended observation period following the UK Prospective Diabetes Study (UKPDS) displayed a continuous decrease in the risk of microvascular issues and a growing trend of risk reduction for myocardial infarction (MI) over the course of the 10-year post-trial monitoring.[6]

Hypertension is widely recognized as a crucial risk element in the progression of cardiovascular diseases among individuals diagnosed with either type of diabetes. Numerous research endeavors have demonstrated a strong correlation between elevated blood pressure levels exceeding 115/75 mm Hg and an increased incidence of cardiovascular diseases in patients with diabetes. The evidence clearly indicates that maintaining blood pressure below this threshold is paramount in reducing the risk of cardiovascular complications in diabetic individuals.[7] Numerous studies have demonstrated a reduction in cardiovascular issues, such as strokes, when systolic blood pressure is lowered to below 140/80 mm Hg.[8] Despite this, there is still a lack of extensive proof supporting the advantages of aiming for even lower systolic blood pressure levels.

Diabetic patients and individuals with hypertension should be carefully managed with the goal of achieving a blood pressure lower than 140/80 mm Hg. It is essential to implement lifestyle modifications such as shedding excess weight, following the Dietary Approaches to Stop Hypertension (DASH) eating plan, reducing sodium intake to 1500 mg per day, and engaging in regular physical activity alongside the use of medications. Numerous research studies have shown that statin therapy offers significant benefits in both primary and secondary prevention of cardiovascular disease. Similarly, trials conducted on patients with diabetes have demonstrated comparable positive outcomes, indicating the efficacy of this approach in improving cardiovascular health in individuals with diabetes. These findings emphasize the importance of a comprehensive treatment strategy that combines pharmacological interventions with lifestyle adjustments to effectively manage blood pressure and reduce the risk of cardiovascular complications in diabetic and hypertensive patients. By addressing both the medical and lifestyle factors contributing to these conditions, healthcare providers can optimize the overall care and outcomes for individuals dealing with diabetes and hypertension.[9]

Retinopathy:

Diabetic retinopathy stands out as a highly prevalent cause of blindness in the adult population ranging from twenty to seventy-five years old. The pathophysiology, natural progression, and clinical manifestation of diabetic retinopathy have been extensively documented, outlining distinct stages of the condition. Initially, signs of retinopathy manifest as small bulges emerging from the retinal capillaries, identified as microaneurysms, along with punctate intraretinal hemorrhages. As the disorder advances, complications such as macular edema, ischemic alterations, collateralization, and proliferative changes may ensue, potentially leading to compromised vision or even complete loss of sight. Factors contributing to the development of diabetic retinopathy include the duration of diabetes, the severity of hyperglycemia, hypertension, and dyslipidemia. Notably, two decades post the diabetes diagnosis, a majority of individuals with type 1 diabetes and approximately eighty percent of those with type 2 diabetes exhibit varying degrees of diabetic retinopathy.[10]

Over the past three decades, there has been a noticeable reduction in both the frequency and likelihood of advancement of diabetic retinopathy, showcasing significant improvement in the management and prevention of this serious eye condition.[11] The Wisconsin Epidemiologic Study of Diabetic Retinopathy revealed a significant reduction of over seventy percent in the yearly occurrence of proliferative retinopathy among individuals diagnosed with type 1 diabetes mellitus (T1DM) at the age of 40. Screening tests such as ophthalmoscopy and retinal photography are not only precise but also secure, widely embraced methods for detecting diabetic retinopathy. It has been firmly established that routine dilated eye exams play a crucial role in the early identification of diabetic retinopathy that poses a risk to vision and have shown to be effective in preventing blindness.[12] Therefore, it is imperative for all diabetes patients to undergo thorough screening as individuals with diabetic retinopathy and macular edema may display no symptoms at the time of diagnosis.

Screening for diabetic retinopathy in individuals diagnosed with type 1 diabetes should ideally commence within five years after the initial diagnosis, as suggested by medical guidelines. This recommendation is supported by scientific evidence indicating that the development of retinopathy typically occurs around five years following the onset of elevated blood sugar levels. On the other hand, patients with newly detected type 2 diabetes might have experienced asymptomatic

hyperglycemia for an extended period before receiving a diagnosis, thus increasing their susceptibility to diabetic retinopathy at the time of diagnosis. Consequently, individuals with type 2 diabetes are advised to undergo a thorough dilated eye examination promptly upon diagnosis to assess their retinal health comprehensively.

Ophthalmoscopy remains a widely utilized technique for monitoring diabetic retinopathy progression. Nevertheless, research has demonstrated that the sensitivity of nondilated ophthalmoscopy conducted by healthcare providers outside the field of ophthalmology is relatively low compared to retinal photography. The utilization of a nonmydriatic camera for diabetic retinopathy screening has gained popularity in recent years due to its convenience and effectiveness. Numerous research studies have delved into the reliability of digital retinal images as a screening tool for detecting retinopathy in diabetic individuals. A recent meta-analysis incorporating data from twenty separate studies utilizing nonmydriatic digital retinal imaging reported a sensitivity exceeding eighty percent and a specificity of eighty-eight percent for accurately diagnosing diabetic retinopathy.[13]

Variations in glycemic control or other hormonal factors while pregnant might accelerate the progression of diabetic retinopathy. However, the findings of the ACCORD study did not demonstrate any additional advantages in reducing blood pressure to below 120 mm Hg. The technique of retinal photocoagulation as a treatment for diabetic retinopathy was first developed in the 1960s. It involves using a laser to seal or destroy abnormal blood vessels in the retina, thus helping to prevent further vision loss.

Diabetic Peripheral Neuropathy:

Diabetic neuropathy is widely recognized as a prevalent complication in individuals diagnosed with both type 1 and type 2 diabetes. This medical condition encompasses a wide range of clinical syndromes that exhibit varying distributions, clinical progressions, and underlying pathogenic mechanisms. Each distinct syndrome manifests itself through either diffuse or focal harm to peripheral somatic or autonomic nerve fibers, which stems from elevated levels of blood glucose. The classic classification of diabetic neuropathy consists of diabetic peripheral neuropathy (DPN) and autonomic neuropathy, each presenting its unique set of symptoms and characteristics associated with nerve dysfunction, following the exclusion of alternative causes. Research indicates that the incidence of diabetic neuropathy among newly diagnosed diabetes patients exceeds five percent, while it surpasses fifty percent in those with long-standing diabetes.[14] This complication remains a leading cause of nontraumatic amputations in affected individuals. Numerous research studies have emphasized that the duration and severity of diabetes play crucial roles as significant risk factors in the development of diabetic neuropathy among patients diagnosed with either type 1 or type 2 diabetes.[15]

Thirty-three percent of individuals diagnosed with Diabetic Peripheral Neuropathy (DPN) exhibit symptoms such as burning, tingling, numbness, electric shock sensations, and stabbing pains. It is common for patients to initially feel these symptoms in their toes and then gradually spread towards more central areas of the body. Typically, these sensations are at their peak severity during nighttime, often disrupting the quality of sleep for affected individuals. The significant prevalence of diabetic neuropathy results in a considerable amount of suffering, including an increased susceptibility to recurring infections in the lower extremities, development of ulcers, feelings of depression, as well as a higher likelihood of experiencing fractures in the foot and ankle, along with undergoing amputations in the lower limbs.[16]

The multifactorial nature of diabetic peripheral neuropathy (DPN) is attributed to a complex interplay of various elements, including metabolic, vascular, and hormonal factors, which collectively influence the delicate equilibrium between nerve fiber damage and regeneration. The direct impact of hyperglycemia, endothelial damage, and dysfunction in the microvasculature contributes significantly to the initiation of nerve injury within the affected individuals. Consequently, the development of nerve ischemia is a direct consequence of this interplay of factors. Furthermore, the presence of nerve ischemia and subsequent hypoxia, along with elevated levels of cytokines, can also play a crucial role in the pathogenesis of diabetic peripheral neuropathy.[17]

Many questionnaires have been developed to aid physicians in evaluating the diagnosis of Diabetic Polyneuropathy (DPN). The Douleur Neuropathique 4 Questions (DN4) questionnaire is a tool that can be swiftly completed, proving to be easy to use with high sensitivity and specificity. There exist numerous uncomplicated clinical tests that are recommended for screening patients for DPN. It is essential for individuals with both type 1 and type 2 diabetes to undergo DPN screening annually. Evaluation of pinprick sensation and light touch perception should involve the use of a 10-gram monofilament. Furthermore, the assessment of vibratory threshold is conducted by employing a 128-Hz tuning fork. Research indicates that combining appropriate tools with clinical examination and inspection yields a specificity rate exceeding 87% in detecting DPN. Evidence suggests that optimizing glycemic control can enhance nerve function in diabetic patients. Intensive glycemic management has also been proven to lower the risk of developing diabetic neuropathy in type 1 diabetes patients and potentially in type 2 diabetes patients. However, the evidence supporting the relationship between glycemic control and neuropathy prevention in type 2 diabetes patients is not as robust. The UK Prospective Diabetes Study (UKPDS) investigators documented a 25% reduction in the risk of microvascular complications after 10 years of intensive treatment, primarily driven by a decrease in retinopathy. Studies have demonstrated a deceleration in the progression of diabetic neuropathy with improved glycemic control among type 2 diabetes patients. Intensive glycemic control, especially when initiated early in the disease course, appears to offer long-term advantages in preventing diabetic neuropathy. The Epidemiology of Diabetes Interventions and Complications (EDIC) trial monitored around 95% of the participants from the Diabetes Control and Complications Trial (DCCT) cohort for numerous years. Throughout the EDIC trial, the initial glycemic gap between the intensively treated group and the standard treatment group vanished.

Diabetic Nephropathy:

Nephropathy is regarded as one of the most common complications of both type 1 and type 2 diabetes, with an estimated prevalence of diabetic nephropathy standing at 15% to 25% and 30% to 40% of patients, respectively. The UKPDS trial analysis showed that 24.9% of patients with type 2 diabetes progressed to microalbuminuria, 5.3% developed microalbuminuria, and 0.8% experienced increased creatinine levels or needed dialysis within the initial 10 years post-diagnosis. Diabetes stands out as the primary cause of end-stage renal disease (ESRD) in both developed and emerging nations. The clinical manifestations of diabetic nephropathy, such as proteinuria, elevated blood pressure, and reduced glomerular filtration rate (GFR), appear similar in patients with type 1 and type 2 diabetes; however, by the time the laboratory or clinical abnormalities of diabetic nephropathy become apparent, significant pathological changes are already underway within the kidney.

Pathological alterations like glomerulosclerosis, thickening of the glomerular basement membrane, expansion of mesangial cells, loss of podocytes, renal cell hypertrophy, and tubulointerstitial fibrosis are the primary changes witnessed during the progression of diabetic nephropathy. These changes lead to escalating albuminuria, declining GFR, rising blood pressure, and fluid retention. Chronic kidney disease is associated with a substantially heightened risk for cardiovascular disease, independent of the conventional cardiovascular disease risk factors. Screening for diabetic nephropathy should involve evaluating increased urinary albumin excretion through an albumin/creatinine ratio in a random spot urine sample. It is recommended to conduct an albumin/creatinine ratio test in patients with type 1 diabetes after five years and in all patients with type 2 diabetes at the time of diagnosis.[18]

Healthcare providers should obtain a yearly serum creatinine level with estimated GFR for all diabetes patients regardless of their urine albumin excretion status. Studies have uncovered reduced GFR in patients lacking signs of increased urine albumin excretion. The necessity of ongoing annual assessment of urine albumin excretion post-albuminuria diagnosis remains uncertain. The American Diabetes Association advises continual monitoring of urine albumin excretion to gauge both treatment response and disease progression. The emergence of complications from chronic kidney disease is closely tied to kidney function level, particularly GFR. It is strongly recommended that physicians

commence screening for chronic kidney disease complications in patients with an estimated GFR below 60 mL/min/1.73m2.[18]

The optimal strategy for managing patients with diabetic nephropathy entails addressing multiple factors, including hypertension, hyperglycemia, and dyslipidemia. By initiating early interventions targeting these risk factors, the onset or progression of diabetic nephropathy can be delayed or even prevented. The UKPDS trial demonstrated that intensive control of blood pressure was linked to a significant 30% reduction in the risk of developing microalbuminuria. However, the precise lower threshold for systolic blood pressure that is most effective in preventing diabetic nephropathy remains to be definitively established. Studies have shown that maintaining adequate blood pressure levels using medications that impact the renin-angiotensin system can significantly decrease both the incidence and advancement of diabetic nephropathy. In individuals with type 1 diabetes and diabetic nephropathy, it is possible to achieve remission or regression through effective control of systemic blood pressure, especially with the use of ACE inhibitors. Various large-scale, prospective, randomized trials involving type 1 diabetes patients have indicated that reducing systolic blood pressure levels to below 140 mm Hg results in a notable reduction in both blood pressure and the occurrence of new-onset microalbuminuria over a four-year monitoring period. The beneficial effects of ACE inhibitors and ARBs appear promising, suggesting a direct protective effect on the kidneys that is independent of their blood pressure-lowering properties. Numerous clinical trials have concluded that ARBs can slow down the progression of albuminuria and end-stage renal disease (ESRD) in individuals with type 2 diabetes and diabetic nephropathy. In cases where patients are unable to tolerate ACE inhibitors or ARBs, or if further reduction in blood pressure is necessary, other classes of antihypertensive medications may be considered as adjunct therapies.

Maintaining strict control over blood glucose levels has been shown to mitigate the risk of developing and slow down the advancement of diabetic nephropathy. Findings from the DCCT and its subsequent long-term investigation, the EDIC trial, revealed that intensive glucose management was effective in preventing the progression of microalbuminuria in individuals with type 1 diabetes. Similarly, the UKPDS study involving type 2 diabetes patients demonstrated that intensive glucose control led to a 33% reduction in the risk of developing microalbuminuria or proteinuria. Physicians should contemplate referring patients to a nephrologist if there are uncertainties regarding the underlying cause of the individual's kidney disease. Collaboration with a nephrologist in cases involving stage IV chronic kidney disease has been shown to reduce costs, enhance the quality of care provided, and postpone the necessity for dialysis. Additional factors that may warrant consideration for referral to a nephrologist include the presence of anemia, secondary hyperparathyroidism, or disturbances in electrolyte levels.

Conclusions:

Diabetes is widely recognized as the primary underlying factor leading to end-stage renal disease, vision loss, and nontraumatic lower-limb amputation. It has been observed that the most significant reductions in cardiovascular complications occur when various risk factors such as high blood pressure, abnormal lipid levels, and elevated blood sugar are effectively addressed simultaneously. Extensive research has been conducted on the benefits of using aspirin for secondary prevention in individuals who have previously experienced a stroke or heart attack. Regular dilated eye exams play a crucial role in the early detection of sight-threatening diabetic retinopathy, ultimately helping to prevent vision loss. By combining the appropriate diagnostic tools with thorough clinical examination and inspection, healthcare providers can achieve a specificity of over eighty percent in identifying diabetic peripheral neuropathy. Timely intervention to manage risk factors like hypertension, high blood sugar, and abnormal lipid levels can significantly delay or even prevent the onset of diabetic kidney disease.

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