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Impact of Glycemic Control in Preventing Microvascular Complications of Diabetes

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Abstract: *A vital element of managing diabetes comprehensively is preventing microvascular problems. Microvascular disorders such as retinopathy, nephropathy, and neuropathy significantly raise the morbidity and mortality associated with diabetes. A complete preventative approach involves regular blood glucose tests, prescription treatments, and lifestyle modifications aimed at achieving rigorous glycemic control. Additionally, as hypertension and dyslipidemia exacerbate microvascular damage, it is essential to control these comorbidities. Raising awareness of the importance of routine medical exams, healthy diet, and medication adherence requires patient education. Early screening and detection of microvascular issues is necessary to enable timely intervention to impede their progression. Personalized healthcare solutions have the potential to enhance risk classification and facilitate targeted preventive measures, such genetic and biomarker analyses. Collaboration between medical experts, patients, and social support networks in the community is necessary to promote a comprehensive plan to prevent microvascular complications in individuals with diabetes. Making preventative care a priority not only improves the quality of life for those with diabetes but also lowers the overall cost of healthcare associated with these issues.*

Keywords: Diabetes, Microvascular complications

I. INTRODUCTION

Global prevalence estimates for 2019 indicated that 463 million individuals worldwide were believed to have diabetes; by 2045, that figure is predicted to increase to 700 million.1. The increasing prevalence and increased years of life ascribed to diabetes have a significant impact on the development of macro and microvascular problems. It also places a significant financial and social burden on almost all global healthcare systems.2. End-stage kidney disease (ESKD), blindness from retinopathy, and the burden of cardiovascular disease have all increased alarmingly in the world among individuals with diabetes, despite reported declines in cardiovascular-related mortality, lower extremity amputation rates, and cardiovascular complications over the past 20 years, especially in high-income nations like North America and Europe.3. The crude prevalence of microvascular complications in people with type 2 diabetes was 18.8% globally, with the highest rates found in Europe (23.5%) and the lowest rates found in Africa (14.5%), according to data from the "DISCOVER" observational research program, which ran from 2014 to 2019.4 Peripheral neuropathy was observed in 7.7% of cases, chronic renal disease in 5.0% of cases, and albuminuria in 4.3% of cases among individuals with a median duration of 4.1 years for type 2 diabetes.

A strong correlation has been shown by epidemiologic studies to link diabetes to vascular-related issues.5, 6 For example, diabetic retinopathy (DR) is strongly associated with the development of diabetic kidney disease (DKD) and is a strong predictor of stroke and cardiovascular disease.5. Compared to conventional risk factors like blood pressure, HbA1c, and LDL cholesterol, individual microvascular complications in type 2 diabetics also more accurately predict cardiovascular risk; multiple complications, however, are associated with a doubling of cardiovascular risk and cardiovascular mortality.7. These findings suggest that early administration of cardioprotective medications may prevent or delay these incapacitating events with little impact, and that screening for microvascular issues offers a useful and reasonably priced way to improve risk prediction in diabetic patients.8

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Even though they often take years to manifest, microvascular issues may arise as soon as a patient is diagnosed, particularly in individuals with type 2 diabetes. Although hyperglycemia is the "sine qua non" of microvascular disease, its effects on normal microvessel structure or function are not well understood.9. In addition, the conditions of smoking, long-term diabetes, dyslipidemia (low HDL and often elevated triglycerides), and hypertension all contribute to the development and exacerbation of the illness. The interaction of hereditary and environmental changes (diet, lifestyle) has been proposed as a likely mechanism in the development of microvascular complications of diabetes in recent years.10 In actuality, prehypertensive and prediabetic diseases often exhibit microalbuminuria and retinopathy.11

This research covers the pathogenesis, risk factors, diagnosis, and prevention of microvascular complications of diabetes that mainly affect the kidneys, eyes, and peripheral and autonomic nervous systems. It also contains an overview of clinical care best practices that may aid healthcare professionals in providing patients with these disorders with better treatment.

Diabetes Retinopathy

According to estimates of global prevalence from 2015, there were around 2.6 million individuals with moderate to severe visual impairment from DR; by 2020, that figure is predicted to rise to 3.2 million, or almost 1% of the world's total diabetes population.12 Due to enhanced monitoring and efficient specialized treatment, the frequency of DR has significantly decreased in high-income nations like the United Kingdom and is no longer the leading cause of blindness. Thirteen Moreover, it is projected that the proportion of adult diabetics would rise by 69% in low- and middle-income nations between 2010 and 2030, but it will only rise by 20% in high-income nations.

Pathogenesis

Early in diabetic retinal degeneration (DR), there is an increase in pericyte loss, endothelial cell apoptosis, leaky retinal capillary endothelial cells, accumulation of advanced glycation end products, and thickening of the basement membrane.14 Hard exudates, cotton wool patches, and micro-aneurysms are the results of leukocyte adhesion to the retinal vascular endothelium, vascular leakage, and capillary closure.14 Increased intraocular production of vascular endothelial growth factor (VEGF) is facilitated by retinal ischemia, which is caused by occlusion of retinal capillaries and arterioles. Loss of vision is thereafter caused by blood leaking from delicate neoproliferative blood vessels, loss of retinal astrocytes, and photoreceptor loss as a result of microglial fibrosis.14

Risk Factors for Diabetes Retinopathy

Risk factors for diabetic kidney disease (DR) include poor glycemic management, prolonged diabetes, hypertension, dyslipidemia (high total and low-density lipoprotein cholesterol), anemia, smoking, and microalbuminuria.15 People of South Asian, African, Latin American, and indigenous tribal heritage have been reported to have higher rates of diabetic macular oedema (DMO) and sight-threatening diabetic retinopathy (DR). Ethnicity is a complicated and independent risk factor.14 The development of DR has been associated with genetic vulnerability, albeit valid genotype-phenotype correlations have not yet been discovered. It's interesting to note that thyroid hormone replacement therapy seems to prevent the formation of diabetic reticulum (DR) in individuals with type 2 diabetes and hypothyroidism.16

Diagnosis and Classification of Diabetic Retinopathy

While grading schemes differ globally, the American Academy of Ophthalmology International Clinical Diabetic Retinopathy Disease Severity scale is a generally accepted, reliable, and useful way to grade DMO and DR.14

Nonproliferative Diabetic Retinopathy or Background Diabetic Retinopathy

The early, asymptomatic stage of diabetic retinopathy is known as nonproliferative diabetic retinopathy (NPDR). Increased vascular permeability, retinal ischemia, and capillary blockage are its defining features. Microaneurysms, intraretinal hemorrhages, venous anomalies including "beading" and "looping," and intraretinal microvascular anomalies are all seen on retinal examination. Additional characteristics include fluffy white "cotton wool spots," which

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are microinfarcts in the nerve fiber layer and hard exudates caused by lipid deposition in or outside the retina; however, they are often associated with preproliferative DR or DMO.14

Proliferative Diabetic Retinopathy

Neovascularization in reaction to severe ischemia is a characteristic of proliferative diabetic retinopathy (PDR). New blood vessels that proliferate along the vascular arcades and expand into the vitreous are prone to bleeding. These new vessels often form at or near the optic disc. Vitreous hemorrhage, vitreoretinal traction bands, retinal tears, and tractional retinal detachment are examples of funduscopic characteristics. Those who are affected may have significant visual impairment. A late PDR consequence is neovascular glaucoma, or new blood vessels in the iris.14

Diabetic Macular Oedema

The characteristic of DMO is the thickening or swelling of the macula as a result of intraretinal and subretinal fluid buildup in the macula brought on by the disruption of the blood–retinal barrier. DMO may induce visual distortion and a reduction in visual acuity at any point throughout the DR process. If left untreated, it might result in complete blindness (Fig. 1).14, 17

Fig.1. Funduscopic characteristics of various DR stages and photocoagulation of the retina. (A) Nonproliferative DR, including dot hemorrhages and microaneurysms. (B) Proliferative DR, which includes retinal hemorrhages and new disc vessels. (C) Proliferative DR, which includes exudates, retinal hemorrhages, preretinal fibrosis, and new arteries on the disc and elsewhere. (D) Diabetic maculopathy, which includes retinal hemorrhages, circinate hard exudates, and hard exudates within the macular region. Panoramic photocoagulation (E) reveals new laser burns on the superior retina and laser scars on the inferior retina.

Risk Factor Control Evidence from Clinical Trials

Glycemic Control

The groundbreaking Diabetes Control and Complications Trial and its observational follow-up study Epidemiology of Diabetes Interventions and Complications in people with type 1 diabetes demonstrated that rigorous glycemic control decreased the incidence of diabetes-related eye surgery by 48% (95% confidence interval and the development and progression of DR by 76% and 54%, respectively, over 6.5 years. Even while strict glycemic management was linked to a temporary deterioration of DR, the positive "metabolic memory" impact of strict glycemic control lasted for up to 23 years.18

In individuals with type 2 diabetes, a 1% decrease in HbA1c was associated with a 31% decrease in retinopathy in the landmark UKPDS trial. Significant benefits to the eyes were seen with improved glucose management, including a "legacy effect."19 Intense glycemic control, as opposed to conventional care, reduced the course of diabetic retinopathy in the ACCORD eye research and its follow-up study. This treatment benefit was more pronounced in patients with mild DR. Long-lasting protection was provided by strict glycemic management, even four years after the study's conclusion.20, 21

Role of Glucose-Lowering Drugs in Diabetic Retinopathy

Beyond enhancing glycemic control, the more recent glucose-lowering medications (glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors) provide no further advantages. The microvascular composite endpoint (time to retinal photocoagulation or anti-VEGF therapy for DR, vitreous hemorrhage or blindness, albuminuria progression, ESKD, greater than or equal to 50% reduction in estimated glomerular filtration rate, and death from renal failure [hazard ratio was significantly reduced in the linagliptin outcomes study.22 Linagliptin, a selective dipeptidyl peptidase-4 inhibitor added to usual care, significantly reduced this endpoint. In fact, it seems that the SUSTAIN 6 trial's quick gains in glycemic control with subcutaneous semaglutide—a once-weekly GLP-1 receptor agonist—were linked to a higher risk of DR and complications from retinopathy.23 As a result, it's critical that doctors be informed of the safety concern raised by using these medications, and it's advised that they keep an eye out for any eye complications. The current FOCUS trial is a particular DR outcome research that aims to determine the long-term impact of semaglutide on DR in people with type 2 diabetes.24

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Blood Pressure Control

Intense blood pressure control is helpful in lowering the combined outcome of DR incidence and progression, according to a systematic review by Do and colleagues. However, it had no effect on the progression of DR over the course of four to five years, the progression to PDR or clinically significant Macular oedema, or the moderate-to-severe loss of best-corrected visual acuity.25 According to the UKPDS research, a 10 mm Hg drop in systolic blood pressure corresponded to an 11% decrease in vitreous hemorrhage or photocoagulation.19 There is some indication that, as compared to other medications like b-blockers, angiotens in-converting enzyme inhibition may preferentially promote autoregulation in the retinal circulation.26 In the micro-HOPE research, those with type 2 diabetes had a similar outcome.27 The hemodynamic environment in the hypertensive, diabetic retinal circulation may be aided by ACE inhibition in preventing the advancement of diabetic retinal degeneration.

Dyslipidemia

The Action to Control Cardiovascular Risk in Diabetes Eye Study found that fenofibrate and simvastatin treatment was associated with less progression of DR, although these benefits were not sustained at 4-year follow-up. The FIELD study, which involved individuals with type 2 diabetes, demonstrated that treatment with fenofibrate over 5 years significantly slowed the progression of DR and reduced need for laser therapy for DMO and PDR by 31%.21 The lipid-lowering effects of fenofibrate do not seem to play a role in the mechanism of action.28

Pregnancy

Pregnancy and DR provide a number of complications. A increased risk of developing and worsening diabetic mellitus exists among pregnant women who have a history of type 1 or type 2 diabetes, not gestational diabetes. Additionally, there is a chance that DR will deteriorate quickly as a result of the pregnancy itself, if DR already existed, or if glycemic control is intensified quickly.29

Diabetic Kidney Disease

Although the clinical spectrum might include individuals without DKD or with both, DKD is associated with a higher likelihood of having chronic kidney disease as a result of diabetes. The primary cause of ESKD worldwide is DKD, which also significantly increases cardiovascular mortality and morbidity.30 By 2030, there will probably be twice as many patients undergoing renal replacement treatment as there were ten years ago roughly $26 million.30 However, only 10% of patients with ESKD get kidney transplant and hemodialysis; the other 90% pass away from infection or cardiovascular disease.30 There are significant treatment gaps in low-income regions like Asia and Africa, where 432,000 and approximately $19 million, respectively, of individuals do not obtain renal replacement therapy despite their need. These findings highlight the need for population-based preventative efforts and efficient, low-cost treatments.31

Pathogenesis

Prolonged hyperglycemia, hypertension, and dyslipidemia induce metabolic and hemodynamic changes that enhance oxidative stress, fibrosis, endothelial dysfunction, and inflammation.32 Early podocyte loss is accompanied by thickening of the basement membrane, enlargement of the mesangial cells, decreased density of the glomerular filtration surface, and nodular sclerosis. A pink hyaline material deposition next to the glomerulus's capillary loops is known as nodular glomerulosclerosis, or the Kimmelstiel-Wilson lesion, in diabetic kidney disease. This indicates a significant rise in damage to the mesangial matrix due to nonenzymatic protein glycosylation. Tubulo-interstitial fibrosis and arterial hyalinosis are examples of late sequelae.33

Risk Factors for Diabetic Kidney Disease

Extended hyperglycemia is a significant DKD predictor. Hypertension, smoking, obesity, physical inactivity, and dyslipidemia are additional risk factors.10 It seems that genetic vulnerability is a need for DKD development.34

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Diagnosis

DKD is defined clinically as an excessive elevation in creatinine ratio excretion with or without a deterioration in glomerular filtration function when there is no sign of any other primary cause of kidney disease. Frequently, this illness is accompanied with elevated blood pressure.33 The natural course of DKD includes glomerular hyperfiltration, rising albuminuria, falling GFR, and ultimately ESKD.

The diagnosis of albuminuria based on a "spot" urine sample is confirmed by two abnormal results from an albuminuria creatinine ratio test performed over a period of three to six months. The spectrum of albuminuria gradually increases in severity from microalbuminuria to macroalbuminuria. Microalbuminuria and macroalbuminuria are independent risk factors for cardiovascular morbidity and mortality in people with diabetes.35 The eGFR is calculated using the condensed MDRD equation and is a more accurate measure of renal function than serum creatinine. But this may not apply to every group. According to a study done in India among healthy kidney donors and those with CKD, existing creatinine-based GFR calculation equations tend to overstate GFR by around 25% since Indian respondents often consume less protein and have less muscle mass.36 Therefore, it is equally important to check an individual's creatinine level. The combination of CKD stages 3 to 5 with albuminuria is associated with a significantly increased risk of severe adverse cardiovascular events, independent of diabetes.37 Therefore, by allowing more accurate DKD staging, the use of novel biomarkers for screening and monitoring such as cystatin C, an early DN predictor can assist improve health outcomes.38 DKD symptoms often don't show up until the condition is much worse. Anorexia, exhaustion, and limb edema are the main symptoms that occur. The clinical manifestations of uremia in severe DKD include dysgeusia, hiccoughs, nausea, and vomiting. It is possible to develop peripheral edema symptoms, hypertension, and coexisting microvascular issues (DR and neuropathy).

Glycemic Control: Evidence from Clinical Trials

The beginning and advancement of microalbuminuria may be somewhat improved clinically by strict glycemic management; nevertheless, the impact on progression to about DKD patients, there is uncertainty about mortality, severe cardiovascular events, and ESKD.47 Strict glycemic control prevented the development of albuminuria and the decline in eGFR in people with type 1 diabetes in the DCCT and EDIC trials.48 According to a meta-analysis by Zoungas and colleagues6 using patient level data from four large trials: the UKPDS, Veteran Affairs Diabetes Trial (VADT), Action to Control Cardio-vascular Risk in Diabetes (ACCORD), and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), intensive glycemic control offers a 20% risk reduction (HR 0$80, 95% CI 0$72–0$88; P<0$0001) for the composite of macroalbuminuria, ESKD, and death in people with type 2 diabetes.

Hypertension

The evolution of DKD is slowed down by adequate blood pressure regulation. In patients with diabetes and hypertension, the incidence of moderately elevated albuminuria is decreased by ACE inhibitors and angiotensin-receptor blockers (ARBs). Furthermore, in patients with moderately to severely elevated albuminuria and normal blood pressure (<130/80 mm Hg), the administration of ACE inhibitors or ARBs stabilizes albuminuria and may slow the course of DKD, ESKD, and mortality.49 The most significant trial findings pertaining to individuals with type 1 diabetes are from the EUCLID research, which randomized 530 individuals with normoalbuminuria or microalbuminuria, aged 20 to 59, to lisinopril.51 Normoalbuminuric and microalbuminuric people had reduced albumin excretion rate (AER) after a 2-year follow-up period by 12.7% and 49.7%, respectively (both P <.1). AER was significantly lowered by 18.8% (P 5.03) according to pooled data. Losartan, 50–100 mg once daily, was linked to a substantial 28% decrease in the development of ESKD in adults with proteinuria who had type 2 diabetes.52

Dyslipidemia

Individuals who have both CKD and diabetes mellitus are more vulnerable to cardiovascular events.35 Beyond decreasing cholesterol, statin treatment for DKD has pleiotropic effects that include minor improvements in renal function, proteinuria, and the risk of severe vascular events.53

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Diabetic Neuropathy

A clinically varied set of diseases known as diabetic neuropathy may damage the autonomic and peripheral nerve systems. Diabetic peripheral neuropathy (DPN) is the most prevalent kind of peripheral neuropathy in adults with type 2 diabetes. About 30% of afflicted individuals experience discomfort, a decreased quality of life, gait abnormalities, and depressed symptoms.54 Even though it is only temporary, remission from pain often happens when all sensory impairments are addressed or when metabolic control returns to normal after an extended period of subpar metabolic control. The development of diabetic foot ulcers and subsequent nontraumatic lower limb amputations resulting from DPN has a significant effect on health-related quality of life, health care usage, and expenditures.55, 56 In T2DM and DKD, autonomic neuropathies may result in a useful adjunctive glucose-lowering medication (MF).

Pathogenesis

There is still no consensus on the pathophysiology of diabetic neuropathy. It is possible that a number of variables brought on by the harmful effects of nerve ischemia, segmental demyelination, axonal degeneration of peripheral nerves, and hyperglycemia work in concert to cause the gradual alterations associated with diabetic peripheral neuropathy.55

Risk Factors For Diabetic Peripheral Neuropathy

Age, glycemic control, existence of DR, and length of diabetes are known risk factors for diabetic peripheral neuropathy (DPN) in individuals with type 2 diabetes.57 For young people with type 1 diabetes, smoking and dyslipidemia have been linked to similar risk factors.58

Other Considerations in Diabetic Neuropathy

Diabetic Foot Ulcer

Reduced sensitivity, vascular compromise, functional changes in the microcirculation, or stimulus factors like abnormal foot anatomy, plantar callous, or ill-fitting footwear are the most common causes of diabetic foot ulcers (DFUs). DFUs are linked to extended hospital stays, significant morbidity from increased risk of falls and lost productivity at work, and cardiovascular mortality.54 Male gender, smoking, diabetes duration, history of ulceration, peripheral artery disease, and PDN are risk factors for foot recurrence.61 A multidisciplinary strategy is the cornerstone of managing foot ulcers; it aims to control hyperglycemia and pressure unload the ulcer using complete contact casts, customized therapeutic footwear, or detachable devices. Not only is limb preservation important in individuals with DFU and high-risk feet receiving dialysis, Charcot foot, or a history of previous amputations, but cardiovascular risk reduction is also a goal.54

Secondary Prevention

Similar to primary prevention, the advancement of feared consequences such as painful DPN, limb (or digit) amputation, ESKD, vision-threatening retinopathy, and foot ulceration may be prevented and reduced by rigorous risk factor control and routine monitoring.

Clinical Considerations

History Taking and Examination

The length of diabetes, smoking history, medication history (including aspirin, antihypertensives, lipid-lowering medications, and glucose-lowering agents [particularly insulin]), and pregnancy were all covered in depth in the history. Inquiries about visual impairment symptoms, floaters in the eyes, the existence of DR, visual acuity testing, and lens and retinal exams should all be part of the evaluation process for DR. Anemia and a propensity for bleeding are frequent in ESKD and should be closely watched. The rule out of reversible conditions such renal artery stenosis, obstructive nephropathy, and medication evaluation for nephrotoxic medicines should be prompted by a sudden drop in eGFR or hyperkalemia. An examination of the foot should involve skin inspection, assessment of foot abnormalities, and evaluation of the lower limbs' neurologic and vascular systems. All diabetics should learn about risk factors, be

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instructed how to periodically check and evaluate their feet, and be sent to the appropriate health care provider in accordance with local standards if they have high-risk feet (such as foot deformities).63

Management of Dyslipidemia

We encourage lifestyle changes and greater physical exercise to lose weight. Lipid lowering with a moderate-intensity statin (e.g., atorvastatin, 20 mg, once daily) can improve DR, DKD, and cardiovascular outcomes in adults aged 40-75. A target of less than 1.8 mmol/L (<70 mg/dL) or a 50% reduction from baseline (between 1.8 and 3.5 mmol/L [70 and 135 mg/dL]) is recommended.Fenofibrate may aid DR patients.28

Smoking

To slow retinopathy, quit smoking. It offers broader health benefits and should be promoted regardless of diabetes or other chronic diseases.

Special Situations

Pregnancy

The optimal pregnant HbA1c goal is 42 mmol/mol (<6%) without significant hypoglycemia.8 Avoid rapid, intense glycemic control during pregnancy. All childbearing women should be advised about pregnancy and ocular risks from inadequate glycemic management.8 Pregnant women with diabetes should be checked for DR before concep-tion, after the first prenatal appointment, and at 28 weeks if normal. If DR symptoms are apparent, retinal evaluation should occur at 16–20 weeks. Screening should continue throughout the first year postpartum.66 Scatter laser photocoagulation treats severe NPDR or PDR before pregnancy.66 Anti-VEGF therapy for DMO during pregnancy should only be undertaken if the benefits exceed the risks.67

Specialist Treatments and Other Considerations in Diabetic Kidney Disease

1. Physical activity: DKD patients should engage in 150 minutes of moderate-intensity exercise each week, depending on their cardiovascular and physical tolerance.49
2. Limit salt consumption to fewer than 2 g/d in diet. About 0.8 g/kg body weight of protein should be eaten daily. Dialysis patients must consume extra protein to avoid malnutrition.49
3. Monitor blood potassium levels for DKD patients on ACE inhibitors, ARBs, or diuretics, since these medicines may cause hyperkalemia or hypokalemia.35
4. Avoid excessive use of nonsteroidal anti-inflammatory medicines in DKD patients due to nephrotoxins.Those with DKD on hemodialysis are at significant risk for hypoglycemia and should be monitored regularly. Foot examination and retinopathy screening should be done regularly.49

Management of Neuropathic Pain in Diabetic Neuropathy

No convincing data supports lifestyle or glycemic control. First-line treatments for neuropathy-related pain include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (e.g. duloxetine), pregabalin, gabapentin, lidocaine patches, capsaicin cream high-concentration patches, tramadol, and strong opioids and botulinum toxin A (54).

Criteria for Specialist Referral

Visual acuity less than 6/12 (20/40), symptomatic vision impairment, central macular edema (noncentral, if laser resources are available), severe nonproliferative DR, or any PD need expert referral. Diabetes and CKD patients should see a nephrologist if their eGFR is less than 30 mL/min, they have persistent significant albuminuria greater than 30 mg/mmol, they have hypertension despite using 3 antihypertensive agents, and/or they have had a 25% or w15 mL/min decrease in eGFR in the past year.49 The presence of motor symptoms or unusual or asymmetrical presentations should prompt referral to a neurologist for DPN. Foot ulcers and wound care may need podiatrist, foot surgeon, physiotherapist, and occupational therapist involvement.

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II. DISCUSSION

Microvascular consequences of diabetes are a major health issue due to their morbidity, diversity, and ability to predict cardiovascular disease. Thus, illness burden reduction requires enhanced awareness and education, universal access to low-cost screening, and cheap specialized treatment. These high-risk patients should be aggressively treated with a patient-centered approach and health care professional education strategy like the ALPHABET strategy68, which emphasizes multifactorial intervention for tight glycemic, blood pressure, and lipid control, smoking cessation, and patient self-management education with individualized care plans.

Recent glucose-lowering medications like SGLT-2 inhibitors and GLP-1 agonists have transformed the treatment strategy for type 2 diabetics at high risk of atherosclerotic disease. Without affecting hyperglycemia, BP, or weight loss, early SGLT-2 inhibitor usage in DKD protects the kidneys and heart. Glycosuria, natriuresis, intraglomerular pressure restoration, fuel metabolism alterations, and ketone oxidization as an alternative fuel to fatty acids are further pleiotropic effects. Anecdotally, fenofibrate and ACE inhibitors seem to be underappreciated in DR, but some national guidelines recommend their use, and in 2013, Australia became the first country to approve their use to slow DR progression in type 2 diabetics.63 Telemedicine using digital imaging, automated analyzers, and deep learning artificial systems on retinal image datasets in DR has enormous potential for early identification and accurate therapy.

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