Prevention of Microvascular Complications of Diabetes

Winston Crasto, MBBS, MRCP, MD[a,*],
Vinod Patel, MD, FRCP, DRCOG, MRCGP, FHEAA, RCPathME[a,b],
Melanie J. Davies, CBE, MBChB, MD, FRCP, FRCGP, FMedSci[c],
Kamlesh Khunti, FRCGP, FRCP, MD, PhD, FMedSci[c]

KEYWORDS

• Cardiovascular • Diabetes • Diabetic kidney disease • Diabetic retinopathy
• Diabetic neuropathy

KEY POINTS

- Microvascular complications of diabetes present with diverse clinical presentations, seem to be strongly intercorrelated, and are a cause of significant morbidity and cardiovascular mortality.
- Hyperglycemia mainly drives the development and progression of microvascular disease, whereas the synergistic effects of hypertension, dyslipidemia, smoking, and genetic and hereditary susceptibility also contribute.
- Preventative strategies should focus on tight control of modifiable cardiovascular risk factors including hypertension and dyslipidemia, with particular emphasis on individualized glycemic control.
- Increased awareness and education; pragmatic, low-cost screening; and affordable specialist care are important measures toward reducing the increasing global microvascular disease burden due to diabetes.

INTRODUCTION

Global prevalence estimates from 2019 suggest that the number of people diagnosed with diabetes was 463 million and is projected to increase to 700 million by the year 2045.[1] The growing prevalence and increase in life-years spent with diabetes has a significant impact on the development of macrovascular and microvascular complications and places a huge societal and financial burden on almost every health care system in the world.[2] Although, declining trends in cardiovascular complications, cardiovascular-related mortality and lower extremity amputation rates have been reported over the last 2 decades, particularly from high-income countries including

[a] Department of Diabetes and Endocrinology, George Eliot Hospitals NHS Trust, College street, Nuneaton CV10 7DJ, UK; [b] Warwick Medical School, University of Warwick, Coventry, UK; [c] Diabetes Research Centre, College of Life Sciences, University of Leicester, Leicester General Hospital, Leicester, LE5 4PW, UK
* Corresponding author.
E-mail address: winston.crasto@geh.nhs.uk

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Europe and North America, the global burden of cardiovascular disease, blindness due to retinopathy, and end-stage kidney disease (ESKD) in people with diabetes compared with those without has increased alarmingly.[3] The "DISCOVER" observational study program from 2014 to 2019 reported that the global crude prevalence of microvascular complications in people with type 2 diabetes was 18.8%, being highest in Europe (23.5%) and lowest in Africa (14.5%).[4] Among individuals with a median duration of type 2 diabetes of 4.1 years, the prevalence of peripheral neuropathy was 7.7%, chronic kidney disease 5.0%, and albuminuria 4.3%.

Epidemiologic studies suggest a strong correlation between the vascular related complications of diabetes.[5,6] For example, diabetic retinopathy (DR) is strongly associated with the risk of developing diabetic kidney disease (DKD) and is a strong predictor of stroke and cardiovascular disease.[5] Furthermore, in people with type 2 diabetes, individual microvascular complications indicate cardiovascular risk better than classic risk factors such as blood pressure, HbA1c, and LDL-cholesterol, whereas multiple complications are associated with doubling of cardiovascular risk and cardiovascular mortality.[7] These findings suggest that screening for microvascular complications offers a convenient and inexpensive tool to improve risk prediction in people with diabetes and that early use of cardioprotective therapies can prevent or delay these debilitating events with minimal impact.[8]

Microvascular complications typically develop over several years but can manifest even at diagnosis, particularly in people with type 2 diabetes. Although, hyperglycemia is the "sine qua non" in the causation of microvascular disease, the mechanisms by which it disrupts normal microvessel structure or function are multiple and not clearly defined.[9] In addition, the synergistic effects of hypertension, dyslipidemia (low HDL and often elevated triglycerides), smoking, and duration of diabetes, play an important role in its causation, development, and progression. In recent years, the interaction between genetic and environmental modifications (diet, lifestyle) is a plausible mechanism in the development of microvascular complications of diabetes.[10] Indeed, retinopathy and microalbuminuria are often present both in prediabetes states and prehypertension.[11]

This review discusses the pathogenesis, risk factors, diagnosis, and prevention of microvascular complications of diabetes mainly affecting the target organs including the eye, kidneys, and peripheral and autonomic nervous systems. It also summarizes best practice clinical care recommendations that can guide health care professionals to better manage people with these conditions.

DIABETES RETINOPATHY

Global prevalence estimates from 2015 suggest that nearly 2.6 million people had moderate or severe vision impairment due to DR, and the numbers are expected to increase to 3.2 million by 2020, which is approximately 1% of the total population with diabetes.[12] In high-income countries such as the United Kingdom, there has been a significant decline in DR prevalence due to improved surveillance and effective specialist care and is no longer the commonest cause of blindness.[13] Furthermore, it is estimated that between 2010 and 2030, the number of adults with diabetes will increase by 69% in low-income and middle-income countries compared with only 20% in high-income countries.

Pathogenesis

Increased pericyte loss, endothelial cell apoptosis, leaky retinal capillary endothelial cells, accumulation of advanced glycation end products, and thickening of the basement membrane occur early in DR.[14] Leukocyte adherence to retinal vascular

endothelium, vascular leakage, and capillary closure leads to the formation of microaneurysms, cotton wool spots, and hard exudates.[14] Occlusion of retinal capillaries and arterioles leads to retinal ischemia, which promotes increased intraocular production of vascular endothelial growth factor (VEGF). Subsequently, leakage of blood from fragile neoproliferative blood vessels, loss of retinal astrocytes and photoreceptors due to microglial fibrosis, leads on to loss of vision.[14]

RISK FACTORS FOR DIABETES RETINOPATHY

Poor glycemic control, longer duration of diabetes, hypertension, dyslipidemia (total cholesterol and low-density lipoprotein cholesterol), anemia, smoking, and microalbuminuria are recognized risk factors for DR.[15] Ethnicity is a complex, independent risk factor, and sight-threatening DR and diabetic macular oedema (DMO) are found to be higher in people of South Asian, African, Latin American, and indigenous tribal descent.[14] Genetic susceptibility has been linked to progression of DR, although validated genotype-phenotype associations have not yet been found. Interestingly, in people with type 2 diabetes and hypothyroidism, thyroid hormone replacement seems to have a protective effect on the development of DR.[16]

DIAGNOSIS AND CLASSIFICATION OF DIABETIC RETINOPATHY

Although grading systems vary across the world, the American Academy of Ophthalmology International Clinical Diabetic Retinopathy Disease Severity scale is a practical and valid method of grading DR and DMO and is being widely used.[14]

Nonproliferative Diabetic Retinopathy or Background Diabetic Retinopathy

Nonproliferative diabetic retinopathy (NPDR) represents the early, asymptomatic stage of DR. It is characterized by increased vascular permeability, retinal ischemia, and capillary occlusion. Retinal examination shows microaneurysms, intraretinal hemorrhages, venous abnormalities such as “beading” and “looping,” and intraretinal microvascular abnormalities. Other features include hard exudates due to accumulation of lipid in or under the retina and fluffy white “cotton wool spots,” which are microinfarcts in the nerve fiber layer, although these are commonly a feature of preproliferative DR or DMO.[14]

Proliferative Diabetic Retinopathy

Proliferative diabetic retinopathy (PDR) is characterized by neovascularization in response to severe ischemia. New blood vessels grow into the vitreous, often at or near the optic disc or new vessels elsewhere along the vascular arcades, and are prone to bleeding. Funduscopic features include vitreous hemorrhage, vitreoretinal traction bands, retinal tears, and tractional retinal detachment. Affected individuals may experience severe vision impairment. Neovascular glaucoma (new blood vessels in the iris) is a late complication of PDR.[14]

Diabetic Macular Oedema

DMO is characterized by swelling or thickening of the macula due to subretinal and intraretinal accumulation of fluid in the macula triggered by the breakdown of the blood–retinal barrier. DMO can occur at any stage of DR and cause distortion of visual images and a decrease in visual acuity. Untreated it can lead to total loss of vision (**Fig. 1**).[14,17]

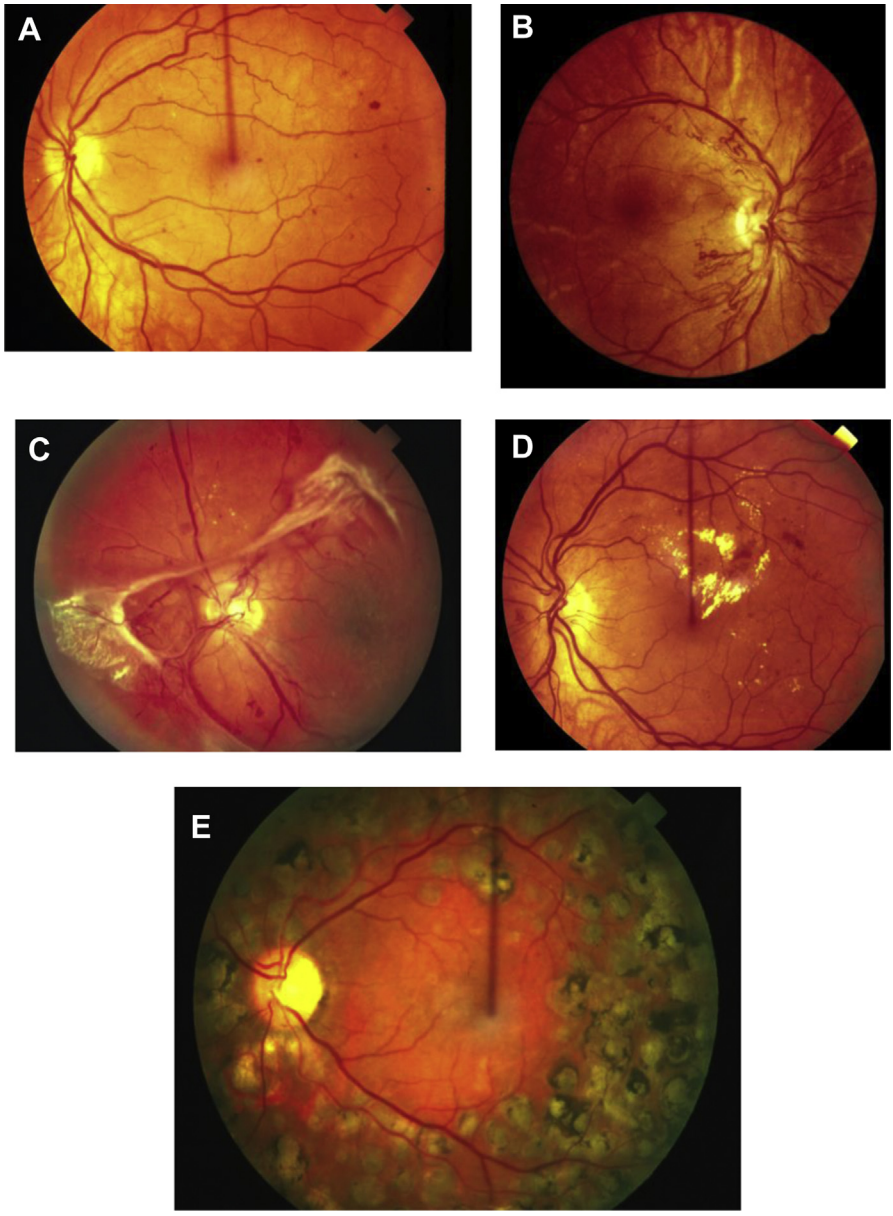

Fig. 1. Funduscopic features of different stages of DR and panretinal photocoagulation. (*A*) Nonproliferative DR (microaneurysms, dot hemorrhages. (*B*) Proliferative DR (new vessels on the disc, retinal hemorrhages). (*C*) Proliferative DR (new vessels on the disc and elsewhere, preretinal fibrosis, exudates, and retinal hemorrhages). (*D*) Diabetic maculopathy (hard exudates within the macular area, circinate hard exudates, MA, retinal hemorrhages). (*E*) Panretinal photocoagulation showing laser scars on the inferior retina and fresh laser burns on the superior retina.

RISK FACTOR CONTROL—EVIDENCE FROM CLINICAL TRIALS

Glycemic Control

The landmark DCCT (Diabetes Control and Complications Trial) and its subsequent, observational EDIC (Epidemiology of Diabetes Interventions and Complications) follow-up study in individuals with type 1 diabetes showed that intensive glycemic control reduced the development and progression of DR by 76% and 54%, respectively, over 6.5 years and diabetes-related eye surgery by 48% (95% confidence interval [CI]: 29–63, $P<.001$). Although, intensive glycemic control was associated with an initial worsening of DR, the beneficial "metabolic memory" effect of intensive glycemic control persisted for up to 23 years.[18]

In the seminal UKPDS study in people with type 2 diabetes, a 1% (approximately 10 mmol/mol) reduction in HbA1c equated to a 31% reduction in retinopathy. Improved glucose control showed significant ocular beneficial effects with a "legacy effect."[19] In the ACCORD eye study and its follow-up study, intensive glycemic control slowed the progression of DR compared with standard care, with a stronger treatment effect observed in individuals with mild DR. Intensive glycemic control conferred enduring protection even after ~4 years of completion of the study.[20,21]

ROLE OF GLUCOSE-LOWERING DRUGS IN DIABETIC RETINOPATHY

The newer glucose-lowering agents (sodium-glucose co-transporter-2 inhibitors and glucagon-Like peptide 1[GLP-1] receptor agonists) provide no additional benefit beyond that of improving glycemic control. In the linagliptin outcomes study (CARMELINA trial),[22] Linagliptin, a selective dipeptidyl peptidase-4 inhibitor added to usual care, significantly reduced 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 (eGFR), and death from renal failure [hazard ratio [HR] 0.86 CI:0.78–0.95, $P = .003$]). Indeed, it seems that rapid improvements in glycemic control with subcutaneous semaglutide (once weekly GLP-1 receptor agonist) in the SUSTAIN 6 trial was associated with increased risk of DR and retinopathy complications.[23] Hence, it is important that physicians are alerted to the safety warning associated with the use of these drugs and monitoring for eye complications is recommended. A specific DR outcome study, the ongoing FOCUS trial, will establish the long-term effects of semaglutide on DR in subjects with type 2 diabetes.[24]

Blood Pressure Control

A systematic review by Do and colleagues reported that intensive blood pressure control is beneficial in reducing the combined outcome of DR incidence and progression (estimated risk ratio 0.78; 95% CI: 0.63–0.97), but it did not affect the 4- to 5-year progression of DR, progression to PDR or clinically significant Macular oedema (CSME), or moderate-to-severe loss of best-corrected visual acuity.[25] In the UKPDS studies, a 10 mm Hg decrement in systolic blood pressure equated to an 11% reduction in photocoagulation or vitreous hemorrhage.[19] There is some evidence that angiotensin-converting enzyme (ACE) inhibition may preferentially improve autoregulation in the retinal circulation when compared with other agents such as β-blockers.[26] A similar result was found in individuals with type 2 diabetes in the micro-HOPE study.[27] ACE inhibition may promote a hemodynamic milieu in the hypertensive, diabetic retinal circulation that serves to protect against the progression of DR.

Dyslipidemia

The FIELD study in people with type 2 diabetes showed 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%,[28] whereas the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study showed that fenofibrate and simvastatin treatment was associated with less progression of DR, although these benefits were not sustained at 4-year follow-up.[21] The mechanism of action seems to be independent of fenofibrate's lipid-lowering properties.[28]

Pregnancy

DR during pregnancy poses several challenges. Pregnant women with preexisting type 1 or type 2 diabetes (not gestational diabetes) are at a higher risk of development and progression of DR. Furthermore, the potential for DR to worsen rapidly either due to pregnancy itself, preexisting DR, or if rapid intensification of glycemic control is implemented.[29]

DIABETIC KIDNEY DISEASE

DKD suggests the presence of chronic kidney disease (CKD) due to diabetes, although the clinical spectrum can also extend to those with non-DKD or both. DKD is the global leading cause of ESKD, leading to significant morbidity and cardiovascular mortality.[30] The number of people receiving renal replacement therapy was around 2·6 million a decade ago and is likely to double by 2030.[30] However, only 10% of people with ESKD undergo hemodialysis and renal transplant therapies, whereas the remainder (~90%) succumb to cardiovascular disease or infection.[30] Large treatment gaps exist in low-income countries such as Asia and Africa where nearly 1·9 million and 432,000 people, respectively, do not receive renal replacement therapies despite needing it, which suggests the need for effective low-cost treatments and population-based prevention strategies.[31]

Pathogenesis

Metabolic and hemodynamic alterations caused by prolonged hyperglycemia, hypertension, and dyslipidemia promote inflammation, endothelial dysfunction, oxidative stress, and fibrosis.[32] Podocyte loss occurs early, followed by basement membrane thickening, mesangial expansion, reduced glomerular filtration surface density, and nodular sclerosis. Nodular glomerulosclerosis (the Kimmelstiel-Wilson lesion) of DKD is a pink hyaline material formation near the capillary loops in the glomerulus. It represents a marked increase in mesangial matrix damage as a result of nonenzymatic glycosylation of proteins. Late sequelae include arterial hyalinosis and tubulointerstitial fibrosis.[33]

RISK FACTORS FOR DIABETIC KIDNEY DISEASE

Prolonged hyperglycemia is a strong determinant of DKD. Other associated risk factors include hypertension, smoking, obesity, physical inactivity, and dyslipidaemia.[10] Genetic susceptibility seems to be a prerequisite to the development of DKD.[34]

DIAGNOSIS

DKD is clinically defined by abnormal increase in creatinine ratio excretion with or without a reduction in glomerular filtration function (eGFR), often associated with an increase in blood pressure but without evidence of other primary causes of kidney

disease.[33] The natural history of DKD includes glomerular hyperfiltration, progressive albuminuria, declining GFR, and ultimately ESKD (Fig. 2).

Albuminuria is diagnosed from a "spot" urine sample confirmed by 2 abnormal albuminuria creatinine ratio test results within a 3- to 6-month interval. The spectrum of albuminuria increases in severity from microalbuminuria (>2.5 mg/mmol in men; >3.5 mg/mmol in women) to macroalbuminuria (>30 mg/mmol). Microalbuminuria and macroalbuminuria are independent risk factors for cardiovascular morbidity and mortality in people with diabetes.[35] The eGFR is calculated from the abbreviated MDRD equation and is a more accurate measure of kidney function than serum creatinine. However, this may not be true in all populations. A study in India among healthy kidney donors and individuals with CKD showed that existing creatinine-based GFR estimating equations overestimate GFR by around 25%, because Indian subjects tend to have a lower protein intake and lower muscle mass.[36] Tracking an individual's creatinine level is therefore also important. The coexistence of albuminuria and CKD stages 3 to 5 is associated with a significantly increased risk of major adverse cardiovascular events independent of diabetes status.[37] Therefore, screening and monitoring with novel biomarkers such as cystatin C, which is an early predictor of DN, can also provide more accurate staging of DKD to improve health outcomes.[38]

Symptoms of DKD are usually absent until the advanced stages. Fatigue, anorexia, and swelling of the extremities are the main presenting complaints. The clinical symptoms of uremia in advanced DKD include nausea and vomiting, hiccoughs, and dysgeusia (altered taste). Signs of peripheral edema, hypertension, and concomitant presence of other microvascular complications (DR and neuropathy) can supervene.

GLYCEMIC CONTROL: EVIDENCE FROM CLINICAL TRIALS

Intensive glycemic control (HbA1c <53 mmol/mol [<7%]) offers small clinical benefits on the onset and progression of microalbuminuria but its effects on progression to

Prognosis of CKD by GFR and Albuminuria Categories KDIGO 2012				Persistent albuminuria categories Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately Increased	Severely increased
				< 30mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300mg/g >30 mg/mmol
eGFR Categories ml/min/1.73m^2	G1	Normal or High	≥ 90			
	G2	Mildly decreased	60-89			
Range and description	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney Failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk

Fig. 2. Prognosis of CKD by GFR and category of albuminuria. (*Adapted from* Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) [published correction appears in Kidney Int Suppl (2011). 2017 Dec;7(3):e1]. *Kidney Int Suppl (2011).* 2017;7(1):1-59; with permission).

ESKD, death, and major cardiovascular events in people with DKD are unclear.[47] In the DCCT and EDIC studies, intensive glycemic control in people with type 1 diabetes slowed the decline in eGFR and development of albuminuria.[48] In people with type 2 diabetes, a meta-analysis by Zoungas and colleagues,[6] using patient level data from 4 large trials—UKPDS, Veteran Affairs Diabetes Trial (VADT), Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)—reported that 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.

ROLE OF GLUCOSE-LOWERING AGENTS IN DIABETIC KIDNEY DISEASE

A dose reduction with metformin is indicated with eGFR less than 45 mL/min, and metformin should be stopped when eGFR is less than 30 mL/min.[49] People with DKD receiving dialysis are preferentially treated with insulin. However, the initial dose must be reduced by half due to reduced drug clearance. Low-dose oral sulfonylureas can be used alone or added to insulin therapy. The roles of glucose-lowering agents in DKD are summarized in **Table 1**. The specific renal outcomes of 2 SGLT-2 inhibitor studies in people with diabetes and CKD are summarized in **Table 2**.

Hypertension

Adequate blood pressure control reduces the progression of DKD. ACE inhibitors and angiotensin-receptor blockers (ARBs) reduce the incidence of moderately increased albuminuria in people with diabetes and hypertension. In addition, the use of ACE inhibitors or ARBs in people with normal blood pressure (<130/80 mm Hg) who have moderately or severely increased albuminuria stabilizes albuminuria and may reduce progression of DKD, ESKD, and death.[49] The most important trial data in people with type 1 diabetes come from the EUCLID study that randomized 530 men and women, aged 20 to 59 years, with normoalbuminuria or microalbuminuria to lisinopril.[51] Over a 2-year follow-up period, albumin excretion rate (AER) was lower by 12.7% and 49.7% in normoalbuminuric and microalbuminuric individuals, respectively (both $P = .1$). Pooled data revealed significant lowering of AER by 18.8% ($P = .03$). In people with type 2 diabetes, losartan, 50 to 100 mg, once daily was associated with a significant 28% reduction in progression to ESKD in individuals with proteinuria.[52]

Dyslipidemia

People with diabetes mellitus and CKD are at a high risk of cardiovascular events.[35] Statin therapy in DKD exerts pleiotropic effects beyond lipid lowering, including modest improvements in proteinuria, renal function, and reduced risk for major vascular events.[53]

DIABETIC NEUROPATHY

Diabetic neuropathy is a clinically diverse group of conditions that can affect both peripheral and autonomic nervous systems. Diabetic peripheral neuropathy (DPN) is the commonest form resulting in pain, reduced quality of life, gait disturbances, and depressive symptoms, in nearly 30% of affected people with type 2 diabetes.[54] Remission from pain albeit transient usually occurs when sensory deficits are complete or when metabolic control improves after a prolonged period of suboptimal metabolic control. Diabetic foot ulcers and nontraumatic lower extremity amputations that develop as a consequence of DPN have a major impact on health-related quality of life, health care utilization, and costs.[55,56] Autonomic neuropathies can cause

Table 1
Glucose-lowering agents in diabetes kidney disease

Glucose-Lowering Agent	Indications/Benefits	Clinical Trial Evidence	Dose Adjustment	Side Effects
Metformin (MF)	1. First-line agent in T2DM 2. ↑ insulin sensitivity 3. ↑ peripheral glucose uptake 4. ↓hepatic gluconeogenesis 5. ↓ weight	1. UKPDS: intensive control with MF showed a 32% reduction in any diabetes-related endpoint, 36% for all-cause mortality in individuals with T2DM.[39] 2. MF usage in T2DM and CKD 3b is associated with lower all-cause mortality (HR 0.65; 95% CI 0.57–0.73[a]) and ESRD progression (HR 0.67; 95% CI 0.58–0.77[a]).[40]	1. Half the dose of MF if eGFR is < 45 mL/min. 2. Stop MF and do not initiate, if eGFR <30 mL/min.	Risk of lactic acidosis
Sodium glucose cotransporter 2 (SGLT-2) inhibitors	1. Useful second-line glucose-lowering agent (as add-on to MF) in T2DM and DKD. 2. ↓renal tubular glucose reabsorption 3. ↓ weight 4. ↓systemic blood pressure 5. ↓intraglomerular pressure 6. ↓albuminuria 7. ↓reduction in GFR	1. Canagliflozin in patients with albuminuric CKD (CREDENCE study), reduced the renal composite risk of ESKD, doubling of the creatinine, or death by 34% (HR, 0.66; 95% CI, 0.53–0.81[a]); ESKD reduced by 32% (HR, 0.68; 95% CI, 0.54–0.86[a]).[41] 2. Lower risk of CV death, MI, stroke, hospitalization for heart failure.[6] 3. The EMPA-REG OUTCOME trial,[42] the CANVAS Program[43] and the DECLARE-TIMI 58 cardiovascular outcomes	Dapagliflozin, empagliflozin, and ertugliflozin should be avoided if eGFR >45 mL/min. (For each agent, use licensed dose for the specific therapeutic indication) Canagliflozin is safe at low eGFR (<45 to <30 mL/min).[41]	Risk of genitourinary infections especially candidiasis. Ketoacidosis has been reported and concomitant use of diuretics with SGLT-2 inhibitor drugs is best avoided due to the risk of dehydration.

(*continued on next page*)

Table 1
(*continued*)

Glucose-Lowering Agent	Indications/Benefits	Clinical Trial Evidence	Dose Adjustment	Side Effects
		trial[44] were RCTs in people with T2DM and CVD or CV risk factors in patients on SGLT-2 inhibitors. SGLT-2 inhibitors reduce decline in renal function with reduced progression of DKD.		
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)	1. Useful second-line glucose-lowering agent (as add-on to MF) in T2DM and DKD. 2. Stimulate glucose-dependent insulin secretion 3. ↓ weight 4. ↓systemic blood pressure 5. ↓intraglomerular pressure 6. ↓albuminuria 7. ↓reduction in GFR	1. Meta-analysis of LEADER (liraglutide), SUSTAIN-6 (semaglutide), REWIND (dulaglutide), EXSCEL (exenatide), ELIXA (lixisenatide), harmony outcomes (albiglutide), and PIONEER-6 (oral semaglutide): treatment with GLP-1 RAs reduced the composite kidney outcome (development of new-onset macroalbuminuria, decline in eGFR or increase in creatinine, ESRD, or renal death by 17% (HR0.83 [95% CI: 0.78–0.89])[a].[45] 2. Effects mainly driven by reduction in albuminuria.[45]	1. Avoid exenatide if eGFR <30 mL/min. 2. Liraglutide, dulaglutide, and semaglutide are not recommended with eGFR < 15 mL/min. 3. Exenatide QW not recommended with eGFR < 50 mL/min.[46]	Gastrointestinal side effects can occur when treatment is initiated.

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; LEADER, The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; RCT, randomized controlled trial; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes; SUSTAIN-6, ; T2DM, type 2 diabetes mellitus.

SUSTAIN-6 (Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes); REWIND (Dulaglutide and cardiovascular outcomes in type 2 diabetes).

[a] $P < .001$.

Table 2
Summary of the published sodium glucose cotransporter 2 inhibitor cardiovascular and renal outcomes trials

RCT	CREDENCE[43]	DAPA-CKD[50]
Patients Studied	DM with CKD	CKD±DM
Patients Enrolled, n (Mean Age, y)	4401 (63.0)	4304 (62)
Drug	**Canagliflozin**	**Dapagliflozin**
Dose: Daily Oral (mg)	100	10
Median Follow-up (y)	2.6	2.4
Baseline HbA1c mmol /(%)[a]	67/8.3	62/7.8
Mean DM (y)	15.8	15.0
Baseline Statin Use (%)	69	65
Baseline Prevalence of CV Disease/HF (%)	50	37.4 10.9
Baseline Prevalence of HF (%)	15	10.9
Outcomes[b]		
MACE Outcome (%)	−20	—
Hospitalization for HF or CV Death (%)	−31	−29
CV Death (%)	−22	—
Fatal or Nonfatal MI	Not reported	Not reported
Fatal or Nonfatal Stroke	Not reported	Not reported
All-cause Mortality (%)	0.83 (0.68–1.02)	−31
HF Hospitalization (%)	−39	—
Renal Composite End Point (%)	−30	−39
End-stage Kidney Disease (%)	−42	−36

Definition of CKD and Inclusion Criteria

CREDENCE:

1. T2 DM: ≥30 years of age; HbA1c 6.5% – 12.0%
2. eGFR: 30-89 mL/min/1.73 m^2;
3. UACR >33.9 – ≤565.6 mg/mmol
4. Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Exclusion criteria included: other kidney diseases, dialysis or kidney transplant; treatment with dual ACEi and ARB, direct renin inhibitor or MRA; serum K^+ >5.5 mmol/L; CV events within 12 weeks of screening; NYHA class IV heart failure; diabetic ketoacidosis or T1DM.

DAPA-CKD

1. T2 DM or No DM
2. ≥18 years of age
3. **eGFR ≥25 to ≤75** mL/min/1.73m^2
4. UACR ≥ 22.6 to ≤ 565mg/mmol
5. Stable max tolerated dose of ACEi/ARB for ≥4 weeks
6.

Exclusion criteria included: T1DM, Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, Immunosuppressive therapy ≤6 months prior to enrolment

Abbreviations: ACEi, ACE inhibitor; ANCA, antineutrophil cytoplasmic antibodies; ARB, angiotensin receptor blocker; DM, diabetes mellitus; HF, heart failure; MACE, major adverse cardiac event; NYHA, New York Heart Association; T1DM, type 1 DM; UACR, urine albumin/creatinine ratio.

[a] DM.

[b] All outcomes given as HR (95% CI).

Adapted from Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL Jr, Kalyani RR, Kosiborod M, Magwire M, Morris PB, Neumiller JJ, Sperling LS. 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020 Sep 1;76(9):1117-1145; with permission.

severe morbidity depending on the organ site of involvement and are linked to increased cardiovascular mortality.[54,56]

Pathogenesis

A unifying hypothesis for the pathogenesis of diabetic neuropathy remains elusive. It is plausible that several factors induced by the deleterious effects of hyperglycemia, nerve ischemia, segmental demyelination, and axonal degeneration of peripheral nerves acting in concert lead on to the progressive changes of DPN.[55]

RISK FACTORS FOR DIABETIC PERIPHERAL NEUROPATHY

Recognized risk factors for DPN in people with type 2 diabetes are duration of diabetes, age, glycemic control, and presence of DR.[57] Similar risk factors as well as smoking and dyslipidemia have been identified in youth with type 1 diabetes.[58]

Diagnosis

DPN or chronic distal symmetric polyneuropathy is the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other cause.[54] Other clinical manifestations of autonomic neuropathy include hypoglycemic unawareness, gastroparesis, constipation, diarrhea, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction[54] (refer to **Table 3**).

GLYCEMIC CONTROL

Evidence from Clinical Trials

Early intensive glycemic control delays and prevents the development of clinically manifest DPN and cardiovascular autonomic neuropathy (CAN) in patients with type 1 diabetes; however, its effects in people with type 2 diabetes are modest.[60]

OTHER CONSIDERATIONS IN DIABETIC NEUROPATHY

Diabetic Foot Ulcer

Diabetic foot ulcer (DFU) is most often caused by a combined result of reduced sensation; vascular compromise; functional changes in the microcirculation; or stimulus factors such as abnormal foot anatomy, plantar callous, or ill-fitting footwear and is associated with prolonged hospitalization, significant morbidity due to increased risk of falls and loss of work productivity, and cardiovascular mortality.[54]

Risk factors for recurrence of foot include male gender, smoking, duration of diabetes previous ulceration, peripheral artery disease, and PDN.[61] The cornerstone of foot ulcer management is a multidisciplinary approach aimed at control of hyperglycemia, pressure offloading with specialized therapeutic footwear, removable devices, or total contact casts. In people with DFU and high-risk feet undergoing dialysis, Charcot foot, or prior history of amputation, the aim is not only to preserve the limb but also to reduce cardiovascular risk.[54]

PREVENTION OF MICROVASCULAR COMPLICATIONS OF DIABETES

Primary Prevention

Primary prevention of microvascular complications should address intensive management of modifiable risk factors, lifestyle modification, and system-level measures such as systematic screening, education, and awareness. A summary of screening schedules is outlined in **Table 4**. Pragmatic approaches to screening intervals are also being

Table 3
Diabetic neuropathies: classification and clinical features

Type	Symptoms	Clinical Features	Other Considerations
Generalized Neuropathies			
Hyperglycemic neuropathy	Peripheral limb tingling, numbness, pain, or hyperesthesia	As for DPN	Can occur with poor glycemic control, or rapid improvements in glycemic control
Distal symmetric sensorimotor polyneuropathy	Burning and tingling, deep aching, electric shock–like, and lancinating Exaggerated response to painful stimuli or allodynia (increased pain from an innocuous stimulus such as daytime or bedtime clothes)	Absent ankle reflexes Mild muscle weakness in both feet Loss of vibration sense, pin prick, temperature, light touch in a stocking distribution	Symptoms are typically worse at night DR or DKD may be present Treatment: antineuropathic drugs, good glycemic control
Insulin neuritis	Severe painful sensory symptoms (as descried in DPN)	Clinical signs are commonly minimal or even absent	Usually recovers in 6–12 mo
Painful neuropathy with severe weight loss	Severe painful sensory symptoms (as described in DPN)	Significant weight loss	Usually occurs in people with inadequately controlled type 1 diabetes
Focal and Multifocal Neuropathies			
Cranial neuropathies: Third, fourth, and sixth nerve palsy	Onset is abrupt. Can present with retro-orbital pain and diplopia	Third nerve palsy: ptosis, pupillary sparing	Usually recovers in 3–6 mo
Focal limb neuropathies: Carpal tunnel syndrome Ulnar neuropathy Common peroneal neuropathy	Sensorimotor symptoms, including muscle weakness depending on site of involvement	Sensorimotor signs depending on site of involvement	Decompressive surgery may be needed
Lumbosacral radiculoplexus neuropathy (previously termed diabetic amyotrophy)	Usually asymmetric; severe pain around lower back or anterior thigh Proximal weakness, weight loss	Nerve conduction shows denervation changes in affected muscle groups	Slow recovery, but muscle strength may not improve completely

(*continued on next page*)

Table 3
(*continued*)

Type	Symptoms	Clinical Features	Other Considerations
Autonomic Neuropathies			
Cardiovascular autonomic neuropathy	Postural syncope, dizziness, falls, and fatigue	Resting tachycardia is often presenting sign. Heart rate variability on lying and with deep breathing. Orthostatic hypotension	Good glycemic control; treatment of orthostatic hypotension in symptomatic individuals
Gastroparesis	Early satiety, ·nausea/vomiting, bloating, ·upper abdominal pain, weight loss	Delayed gastric emptying confirmed by scintigraphy, 13C breath tests, or wireless motility capsule	Treatment: dietary modifications, supplemental nutrition, antiemetic and prokinetic drugs. Surgical treatment is a last resort[59]
ED	Persistent inability to attain or maintain an erection sufficient for satisfactory sexual performance (lasting for ~6 mo) Lower urinary tract symptoms may be present	Sexual Health Inventory for Men questionnaire: used to evaluate severity of ED Assessment for hypogonadism	Treatment: replacement testosterone for hypogonadism ED treatment: psychosexual counseling, phosphodiesterase-5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, penile prostheses
Sudomotor dysfunction (reduced sweating)	Dry foot with increased inflammation of the skin	Reduced normal foot odour, increased dryness, increased fissuring (especially heel areas)	Maintain hydration of dry skin (especially hyperkeratosis) with consideration of daily application of a urea-based emollient

Abbreviation: ED, erectile dysfunction.

Table 4
Screening schedule for microvascular complications in type 1 and type 2 diabetes

	Diabetic Retinopathy	Diabetic Kidney Disease	Diabetic Neuropathy
Initial screening	1. Type 1 DM: 3–5 y after diagnosis 2. Type 2 DM: at the time of diagnosis 3. Pregnant women (T1DM or T2DM) before conception and in each trimester	a. Type 1 DM: 3–5 y after diagnosis b. Type 2 DM: at the time of diagnosis	Type 1 DM: $\geq$5 y after diagnosis Type 2 DM: at the time of diagnosis
Screening method/examination	a. Direct or indirect ophthalmoscopy or slit-lamp examination through dilated pupils b. Retinal (fundus) photography (preferred option) c. Optical coherence tomography (OCT) scanning is a sensitive method to identify DME and can be combined with funduscopy	1. Urine albumin-creatinine ratio (ACR) 2. Estimated glomerular filtration rate (eGFR) 3. Tracking an increase in the creatinine level in individual patients	a. Pinprick sensation (small fiber) b. Vibration perception (128 Hz tuning fork); 10 g monofilament pressure sensation at the distal plantar aspect of both great toes and metatarsal joints; assessment of ankle reflex Symptom scoring systems in neuropathy Diabetic neuropathy symptom score Neuropathy impairment score Michigan neuropathy screening instrument
If microvascular complication present	1. Type 1 and type 2 diabetes: screen annually, or 2. Depending on the severity of retinopathy, monitoring intervals determined by eye specialist. 3. If there is rapid improvement in glycemic control—locally defined 4. Screen for other complications—especially DKD	ACR >3 mg/mol (urine albumin >30 mg/g creatinine) $\pm$ eGFR <60 mL/min/1.73 m^2 Type 1 and type 2 diabetes: screen twice a year, or depending on the severity, monitoring intervals determined by clinician Screen for other complications	a. Type 1 and type 2 diabetes: screen every year or b. Screen for other diabetes complications

(*continued on next page*)

Table 4
(*continued*)

	Diabetic Retinopathy	Diabetic Kidney Disease	Diabetic Neuropathy
If microvascular complication not present	1. Type 1 and type 2 diabetes: screen every 2 y (a new COVID-19 contingency measure for some screening services) 2. Type 2 diabetes with risk factors: annual screening only for people with long duration of diabetes ~15 y, suboptimal glycaemic control (HbA1c 64 mmol/mol (>8%), poor BP control, rapid improvement in glycaemic control 3. Screen for other complications	a. Type 1 and type 2 diabetes: screen annually b. Type 2 diabetes with risk factors: annual screening ONLY for long duration of diabetes ~15 y, suboptimal glycaemic control (HbA1c >8% or 64 mmol/mol), poor BP control, other diabetes microvascular complications c. Screen for other complications	a. Type 1 and type 2 diabetes: screen every 2 y b. Screen for other diabetes complications

Abbreviation: BP, blood pressure.

considered in many health care systems due to the COVID-19 pandemic. For example, people with stable DR can be screened at 18- to 24-month interval.[62]

Secondary Prevention

As with primary prevention, regular monitoring and aggressive management of risk factors is important to prevent and reduce the progression of dreaded complications including vision-threatening retinopathy, ESKD, painful DPN, foot ulceration, and limb (or digit) amputation.

CLINICAL CONSIDERATIONS

History Taking and Examination

A detailed history focused on duration of diabetes, smoking history, medication history (glucose-lowering agents [especially insulin], antihypertensives, lipid-lowering drugs, and aspirin), existing comorbidities, and pregnancy. Evaluation of DR should enquire about symptoms of visual impairment, floaters in the eye, presence of existing DR, assessment of visual acuity, and lens and retinal examination. Bleeding tendency due to platelet dysfunction and anemia are common in ESKD and should be monitored. An abrupt decline in eGFR or hyperkalemia should prompt exclusion of reversible conditions such as renal artery stenosis, obstructive nephropathy, and medication review for nephrotoxic drugs. Foot examination should include inspection of the skin, assessment of foot deformities, and neurologic and vascular assessment of both lower limbs. All people with diabetes, especially those with high-risk feet (eg, foot deformity), should be educated about risk factors and shown how to regularly inspect and examine their feet and refer themselves to the right health care professional according to local protocols.[63]

Recommendations for Glycemic Control

Glycemic monitoring and individualization of targets is key to the management of people with microvascular complications of diabetes. Broad principles include the following:

1. Aim for HbA1c target of less than 7% (53 mmol/mol) generally in people with microvascular complications of diabetes (note: HbA1c measurements may not be reliable in people with DKD on hemodialysis, and self-monitoring of blood glucose is also advised).[49]
2. Aim for HbA1c target of less than 6.5% (48 mmol/mol) in select empowered individuals in whom this can be achieved safely with little or no risk of hypoglycemia.
3. Aim for HbA1c target of less than 7.5% (58 mmol/mol) in older healthy adults with few coexisting comorbidities and intact cognitive and functional status.
4. Aim for HbA1c target of less than 8% (64 mmol/mol) or pursue less stringent targets in people with a history of severe hypoglycemia, long-standing diabetes, multiple coexisting comorbidities, limited life expectancy, cognitive impairment or functional dependence, or in whom stringent HbA1c targets are difficult to achieve despite optimal management.[63]

Newer glucose-lowering drugs

Although more than 50,000 subjects have been studied in various outcome trials with the use of SGLT-2 inhibitors in people with type 2 diabetes, none have specifically reported DR outcomes, and this is despite SGLT-2 inhibitors showing beneficial rates in DR progression.[23] These studies therefore draw toward the conclusion that glycemic control is of principal importance in the prevention and progression of DR. In contrast,

the body of evidence from cardiovascular outcome trials suggests that treatment with an SGLT2 inhibitor in most patients with DKD (and eGFR $\geq$ 30) results in substantial improvements in cardiorenal outcomes (refer to **Table 2**). KDIGO guidelines 2020 also recommend first-line treatment with metformin and an SGLT2 inhibitor and additional treatment as needed to achieve glycemic targets. GLP-1 agonists also demonstrate cardiorenal benefits among people with existing atherosclerotic cardiovascular disease, prevent onset of severely increased albuminuria, and preserve renal function.[49]

Recommendations for Blood Pressure Control

A blood pressure (BP) target of less than 140/90 mm Hg should be aimed for in all adults with microvascular complications of diabetes.[8] However, a tighter BP target of less than or equal to 130/80 mm Hg can be pursued in high-risk, young people with DKD with urinary albumin excretion greater than or equal to 30 mg/24 hours (urinary ACR $\geq$3). ACE inhibitors or ARBs (also, if ACE inhibitors are not tolerated) are preferred first-line agents for blood pressure control (proven benefits on reducing DKD progression).[64] Combination therapy with ACE inhibitor and ARB increases the risk of hyperkalemia and acute kidney injury and is not recommended.[65]

Management of Dyslipidemia

Weight loss with lifestyle modification and increased physical activity (if appropriate) are strongly recommended. In adults aged between 40 and 75 years, lipid lowering with a moderate-intensity statin (eg, atorvastatin, 20 mg, once daily) aiming for an LDL-cholesterol (LDL-C) target of less than 1.8 mmol/L (<70 mg/dL) or a 50% reduction from baseline (if LDL-C is between 1.8 and 3.5 mmol/L [70 and 135 mg/dL]) has beneficial effects on DR, DKD, and cardiovascular outcomes.[63] Fenofibrate may have potential benefits for people with DR and should be considered.[28]

Smoking

Smoking cessation is important to halt the progression of retinopathy. It has wider health implications and should be encouraged irrespective of the presence of diabetes or any other chronic disease.

SPECIAL SITUATIONS

Pregnancy

The ideal HbA1c target in pregnancy is 42 mmol/mol (<6%), if achieved without significant hypoglycemia.[8] Rapid, intensive glycemic control in pregnancy should be avoided. All women of child-bearing age should be counseled regarding the effects of pregnancy and ocular complications in the presence of poor glycemic control.[8] Pregnant women with preexisting diabetes should be screened for DR before conception, following the first antenatal visit and again at 28 weeks if the first assessment is normal. If any features of DR are present, additional retinal assessment should be performed at 16 to 20 weeks. Further screening in the first year of postpartum is advised.[66] Severe NPDR or PDR before pregnancy should be treated with scatter laser photocoagulation.[66] Anti-VEGF treatments for DMO during pregnancy should only be considered if the potential benefits of treatment outweigh the potential harm to the mother and/or developing fetus.[67]

TERTIARY PREVENTION

As discussed earlier, include specialist treatments as outlined in the following section.

Specialist Treatments and Other Considerations in Diabetic Retinopathy

1. Panretinal photocoagulation (PRP)
   PRP involves application of laser burns on the retinal surface, sparing the central macula. The landmark Diabetic Retinopathy Study and The Early Treatment Diabetic Retinopathy Study effectively demonstrated the benefits of scatter laser photocoagulation in patients with severe NPDR and PDR and focal laser treatment in patients with DMO.[17] PRP is indicated high-risk PDR and severe NPDR to reduce the risk of vision loss.
2. Anti-VEGF therapies
   Intravitreal anti-VEGF injection, ranibizumab, aflibercept, and bevacizumab, are evidence-based effective treatments in the management of PDR. They are effective over standard laser in patients with visual impairment due to DMO.[17] Anti-VEGF therapy may be used to inhibit neovascularization before completion of PRP or as an adjuvant to prevent the aggravation of DMO after PRP. For patients with advanced PDR, anti-VEGF therapy is recommended before vitrectomy to reduce the probability of intraoperative and postoperative hemorrhage.[17]
3. Vitrectomy: the aim of vitrectomy is to evacuate blood in the vitreous space due to vitreous hemorrhage, treat retinal detachment, and to remove the scaffolding of neovascular growth. The factors that determine the need for surgery include duration of hemorrhage, the amount of previous PRP, status of the other eye, and glycemic control.[17]

Specialist Treatments and Other Considerations in Diabetic Kidney Disease

1. Physical activity: people with DKD should incorporate moderate-intensity physical activity for at least 150 min/wk individual cardiovascular and physical tolerance.[49]
2. Diet: salt intake should be restricted to less than 2 g/d. Dietary protein intake should be approximately 0.8 g/kg body weight per day. However, people on dialysis need more dietary protein intake to prevent malnutrition.[49]
3. Blood potassium monitoring: recommended for people with DKD treated with ACE inhibitors, ARBs, or diuretics because these drugs can induce hyperkalemia or hypokalemia.[35]
4. Nephrotoxins: liberal use of nonsteroidal antiinflammatory drugs should be avoided in people with DKD.[35]
5. Hypoglycemia: people with DKD on hemodialysis are at high risk of hypoglycemia, and regular monitoring is advised. Regular inspection of feet and retinopathy screening should be undertaken.[49]
6. Metabolic abnormalities: monitoring and treatment of hypocalcemia and vitamin D deficiency with vitamin D supplements, dietary phosphate restrictions or use of phosphate binders for hyperphosphatemia, and monitoring of parathyroid hormone are important considerations in the management of people with stage 3 to 5 CKD. Chronic anemia is managed with iron replacement and erythropoietin.[32]
7. Renal replacement therapy comprises either transplantation or dialysis. A detailed discussion is out of the scope of this review. Dialysis is conventionally grouped under hemodialysis and peritoneal dialysis. Dialysis is a planned procedure and is usually started in symptomatic ESKD or in asymptomatic individuals with an eGFR of ~5 to 7 mL/min/1.73 m.[49]

Management of Neuropathic Pain in Diabetic Neuropathy

No compelling evidence exists in support of glycemic control or lifestyle management.[60] For reducing neuropathy-related pain, tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors (eg duloxetine), pregabalin, and gabapentin are

strongly recommended as first-line therapies; second-line agents include lidocaine patches, capsaicin cream high-concentration patches, and tramadol; and third-line agents include strong opioids and botulinum toxin A.[54]

CRITERIA FOR SPECIALIST REFERRAL

For people with DR, specialist referral is indicated if visual acuity is less than 6/12 (20/40) or if there is symptomatic vision impairment, central macular edema (noncentral macular edema, if laser resources are available), severe nonproliferative DR, or any PD. People with diabetes and CKD should be referred to a nephrologist if eGFR is less than 30 mL/min, persistent significant albuminuria greater than or equal to $\geq$30 mg/mmol, CKD with hypertension despite use of 3 antihypertensive agents, and/or sustained decrease in eGFR of greater than or equal to 25% or $\sim$15 mL/min in the last 12 months.[49] Referral to a neurologist for DPN should be considered for atypical or asymmetrical presentations or if motor symptoms predominate. Foot ulcers and wound care may require intervention by a podiatrist, foot surgeon, physiotherapist, and occupational therapist.[54]

DISCUSSION

Microvascular complications of diabetes both individually and collectively present a significant challenge, not only in terms of morbidity and diverse presentations but also as strong predictors of cardiovascular disease. Hence, increased awareness and education, universal access to low-cost screening, and affordable specialist treatment are important strategies in reducing the disease burden. A patient-centered approach and health care professional education strategy such as the ALPHABET strategy,[68] based on multifactorial intervention aiming for tight glycemic, blood pressure and lipid control, smoking cessation, and patient self-management education with individualized care plans, should be pursued vigorously in these high-risk individuals.[69]

In recent years, the newer glucose-lowering agents such as SGLT-2 inhibitors and GLP-1 agonists have made transformative changes in the treatment algorithm of people with type 2 diabetes at high risk of atherosclerotic disease. Early use of SGLT-2 inhibitors in DKD offers substantial renal and cardiovascular protection independent of their beneficial effects on hyperglycemia, BP, and weight loss. Other pleiotropic effects include glycosuria, natriuresis, restoring intraglomerular pressure, improvements in cardiac metabolism via shifts in fuel metabolism, and ketone oxidization as an alternative fuel to fatty acids.[70]

Although it would seem, anecdotally at least, that the evidence for the use of fenofibrate and ACE inhibitors is not widely appreciated in DR, some national guidelines do advocate the use of these agents, and in 2013, Australia became the first country in the world to approve the use of fenofibrate to reduce the progression of DR in people with type 2 diabetes.[63]

Finally, telemedicine based on digital imaging techniques, automated analyzers, and deep learning artificial systems applied to retinal image datasets in DR holds great promise for early detection and accurate treatment.

SUMMARY

The burden and costs of managing microvascular complications of diabetes are enormous to the individual and the society. Primary prevention must focus on promoting healthy eating habits, exercise and physical activity, and tobacco abstinence from an early age. Health care professionals must address risk factors specifically aiming for tight glycemic and blood pressure control with judicious use of ACE inhibitors,

ARBs, SGLT-2 inhibitors, statin, and fibrate therapies. Finally, improved technology and communication systems using innovative digitized health care systems, including diagnostic instruments and seamless data transfer, more universal screening, early aggressive risk factor management, and coordinated efforts to implement policies and programs, that promote a healthy environment, improve education, and support self-management with easy and low-cost access to specialist care are needed. The implementation of these strategies will provide greater opportunities for greater patient empowerment, reduced costs, and improved health outcomes.

CLINICAL PEARLS IN THE PREVENTION OF MICROVASCULAR COMPLICATIONS OF DIABETES

1. Multifactorial intervention including tight control of hyperglycemia, BP, dyslipidemia, and smoking cessation alongside structured patient self-management education is the cornerstone of good management to improve microvascular and cardiovascular health.
2. People with diabetes are at high risk of DR and any symptom of new visual impairment should be assessed with priority.
3. Worsening of existing DR can occur with intensive glycemic control but should not be a contraindication to achieving it. Similar effects in pregnancy and with injectable semaglutide warrants close retina monitoring.
4. SGLT2 inhibitors in people with type 2 diabetes and CKD offers substantial cardiorenal protection and must be strongly considered (with metformin) as first-line treatment.
5. Timely screening and specialist referral are important considerations in the management of people with vascular complications of diabetes.

CONFLICT OF INTEREST

W. Crasto has received lecture fees and educational grants from Sanofi-Aventis, Eli Lily, Boehringer Ingelheim, Novo Nordisk, Napp pharmaceuticals, Internis, and MSD. He has received grants in support of investigator and investigator-initiated trials from BHR pharmaceuticals. V. Patel has received lecture fees and educational grants from most large companies in diabetes care, including Sanofi-Aventis, Boehringer Ingelheim, Eli Lily, AZ, Novo Nordisk, Napp pharmaceuticals, Internis, and MSD. He has been on the Advisory Board for some of these companies. M.J. Davies has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, Astra Zeneca and Janssen, an advisory board member for Servier and Gilead Sciences Ltd, and as a speaker for NAPP, Mitsubishi Tanabe Pharma Corporation, and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, Astrazeneca, and Janssen. K. Khunti has acted as a consultant and speaker for Amgen, Astra Zeneca, Boehringer Ingelheim, Novartis, Janssen, Roche, Servier, Berlin-Chemie AG, Novo Nordisk, Sanofi-Aventis, Lilly, and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Janssen, Roche, Astra Zeneca Boehringer Ingelheim, and Merck Sharp & Dohme.

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