13

CHRONIC COMPLICATIONS OF DIABETES

13.1 MACROVASCULAR DISEASE (ACCELERATED ATHEROSCLEROSIS)

Coronary artery disease (CAD), stroke and peripheral arterial disease are covered under the title of 'Macrovascular Diseases' and in general it is referred as 'cardiovascular diseases (CVD)'.
CVD is the leading cause of morbidity and mortality in individuals with diabetes. The risk of CAD is 2-4 times higher particularly in type 2 diabetes patients compared to non-diabetic individuals. Mortality estimates due to macrovascular events vary between 60-75%. Atherosclerosis occurs at a much younger age in patients with diabetes, and has multisegmental character and diffuse nature.

13.1.1 Risk Factors

- CAD is an independent risk factor for diabetes.
- Also HT, dyslipidemia, smoking, family history (<55 year old men and <65 year old women have CVD in first degree relatives) and obesity (particularly central obesity) are other important risk factors.

Patients with diabetes with the following characteristics should be considered at high risk for CAD:

- Men aged ≤45 year old, women aged ≤50 year old
- Men <45 year old and women <50 year old with one of the following risk factors;
  - Macrovascular disease (e.g. silent myocardial infarction or ischemia, evidence of peripheral arterial disease, carotid arterial disease or cerebrovascular accident)
  - Microvascular disease (especially nephropathy and retinopathy)
  - Multiple additional risk factors (a family history of premature coronary or cerebrovascular disease in a first-degree relative)
  - Extreme level of a single risk factor (e.g. LDL-cholesterol >200 mg/dL or systolic BP >180 mm Hg)
  - Long duration of diabetes (>15 years) with age over 40 years.

SEMT RECOMMENDATIONS FOR CHRONIC COMPLICATIONS

1. *Men aged ≥45 years, women aged ≥50 years with diabetes are at increased risk for CAD [Class B, Level 2 evidence (1)].*
2. *Also men <45 year old and women <50 year old with microvascular complications, multiple additional risk factors for CAD, extreme level of a single risk factor and long duration of diabetes are at increased risk for macrovascular disease (Class D, evidence-based consensus).*
3. *The patients with primary diagnosis of diabetes must be evaluated periodically with ECG, echocardiography and exercise (stress) test, if necessary, for CAD (Class D, evidence-based consensus). Patients with positive results and known CAD should be referred to a cardiology unit.*
4. *In contrast, patients with primary diagnosis of CAD should be investigated for FPG, OGTT, fasting lipid profile and A1C, if necessary, and normoglycemia must be provided in patients with ACS (acute coronary syndrome) or myocardial infarction; and patients with IGT, diabetes or metabolic syndrome should be referred to consultation with a cardiologist.*
5. *The patients with CAD along with known diabetes should be investigated for nephropathy and other complications, and optimal glycemic target should be obtained without increasing the risk of hypoglycemia.*
6. *Glycemic control, as well as multifactorial approach (life-style modification, lipid and BP control, use of antiaggregant drugs, and abstain from harmful factors such as tobacco) should be adopted to reduce the risk of CAD in type 2 diabetes.*

REFERENCE
1. Booth GL, Kapral MK, Fung K, et al. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006;368:29-36.

13.1.2 Coronary Artery Disease Screening

CV history (dyspnea, chest pain), life style derangements (smoking, sedentary lifestyle, unbalanced diet), long duration of diabetes, impotence, abdominal obesity, lipid profile, blood pressure, peripheral arterial disease, glycemic control level, retinopathy, ECG, ACR on first morning urine and eGFR should be taken into account to determine the patients at high risk for CAD.

SEMT RECOMMENDATIONS FOR SCREENING OF CORONARY ARTERY DISEASE

1. *A baseline resting ECG should be performed in individuals >40 years of age, with duration of diabetes >15 years, and with HT (Class D, evidence-based consensus).*
   - *A repeat testing ECG should be performed every 2 years in people considered at high risk for CAD (Class D, evidence-based consensus).*
2. *Persons with diabetes should undergo investigation for CAD by exercise ECG stress testing as the initial test in the presence of the following (Class D, evidence-based consensus):*
   - *Typical or atypical cardiac symptoms (e.g. unexplained dyspnea, chest discomfort) [Class C, Level 3 evidence (1)].*
   - *Resting abnormalities on ECG [Class D, evidence-based consensus].*
   - *Peripheral arterial disease (abnormal ankle-brachial ratio) [Class D, Level 4 evidence (2)].*
   - *Carotid bruits [Class D, evidence-based consensus].*
   - *Transient ischemic attack (Class D, evidence-based consensus).*
   - *Stroke [Class D, evidence-based consensus].*
3. *Pharmacologic stress echocardiography (e.g. dypiridamole) or nuclear myocardial imaging should be used in individuals with left bundle branch block or ST-T abnormalities (Class D, evidence-based consensus).*
   - *In addition, individuals who require stress testing and are unable to exercise due to obesity, sedentary lifestyle, neuropathy, peripheral arterial disease and diabetic foot¬ should undergo pharmacologic stress echocardiography or nuclear imaging [Class C, Level 3 evidence (3)].*
4. *Individuals with diabetes who demonstrate ischemia at low exercise capacity on stress testing should be referred to a cardiac specialist (Class D, evidence-based consensus).*

REFERENCES
1. Zellweger MJ, Hachamovitch R, Kang X, et al. Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients. Eur Heart J 2004;25:543-50.
2. Bacci S, Villella M, Villella A, et al. Screening for silent myocardial ischemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. Eur J Endocrinol 2002;147:649-54.
3. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004;11:171-85.

13.1.3 Clinical Findings

Some of the following clinical features can be seen together:

- Classic anginal symptoms (chest, left arm, shoulder and jaw pain, dyspnea, and cold sweating)
- Myocardial infarction: The likelihood of silent myocardial infarction is greater in patients with diabetes.
- Dyslipidemia: Diabetes is considered as the equivalent of primary CVD.
- HT: The goal of BP should be <130/80 mmHg in patients with diabetes.
- Peripheral vascular disease
- Cerebrovascular disease

Half of the patients, admitted to the intensive care unit because of ACS, are diagnosed as IGT or new onset diabetes. The algorithm to be followed during the investigation of the either disease in patients with diabetes or CAD can be seen in Figure 13.1.

Recommendations

- Asymptomatic patients should be treated according to the 10-year CVD risk.
- Glycemic targets should be tried to achieve in diabetic patients with CAD. The results of recent trials such as ACCORD, ADVANCE and VA-DT have shown that intensive glucose lowering in type 2 diabetes does not reduce major CV events, in contrast it can increase macrovascular event and mortality risk if hypoglycemia occurs (as shown in ACCORD-2007 and VA-DT-2008). Therefore, strict glycemic

control should not be targeted in type 2 diabetic patients with advanced age, long-term diabetes, comorbidities and at high risk of hypoglycemia.

■ Metformin is contraindicated in severe congestive heart failure. TZDs should not be used in patients with congestive heart failure, severe coronary insufficiency, or who are at risk of edema, and in patients using intensive insulin unless the benefits of therapy are believed to outweigh the risk.

■ β-blockers should be added to the treatment of patients with prior myocardial infarction or undergoing surgery.

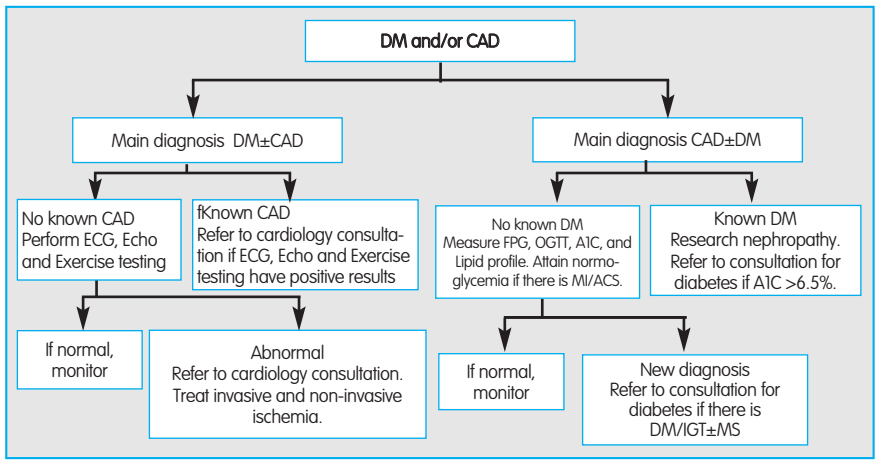

Figure 13.1 Screening Algorithms in Patients with Diabetes and Coronary Artery Disease

DM: Diabetes mellitus, CAD: Coronary artery disease, Echo: Echocardiography, FPG: Fasting plasma glucose, OGTT; Oral glucose tolerance test, A1C; Glycosylated HbA1C, MI; Myocardial infarction, ACS; Acute coronary syndrome, IGT; Impaired glucose tolerance, MS; Metabolic syndrome

13.1.4 Cardiovascular Protection in Patients with Diabetes

SEMT RECOMMENDATIONS FOR PREVENTION OF CARDIOVASCULAR DISEASES

1. *The priority should be given to reduce CV risk by comprehensive and multifaceted approach in the prevention of diabetes complications [For all diabetic patients: Class D, evidence-based consensus; for type 2 diabetes patients over 40 years of age with microalbuminuria: Class A, Level 1A evidence (1)].*
2. *The approaches followed to reduce CV risk in all patients with diabetes are outlined below:*
   - *Lifestyle modifications (Maintenance of appropriate body weight, healthy diet, regular physical activity, smoking cessation)*
   - *Optimal BP control*
   - *Optimal glycemic control*
3. *Accompanied risk factors should be treated.*
   - *The goal of BP should be <130/80 mmHg in patients with diabetes. ACE-I or ARB should be preferred for the treatment of HT.*
   - *Lipid disorders in diabetic patients should be treated more aggressively compared to non-diabetic individuals. The target for patients with diabetes is an LDL-cholesterol <100 mg/dL (in diabetic patients with prior CVD 70 mg/dL), HDL-cholesterol >40 mg/dL in men and >50 mg/dL in women, and triglyceride <150 mg/dL. Statins should be used primarily in lipid lowering therapy.*
4. *Individuals at high risk of CV mortality should receive pharmacologic vascular protective measures such as ACE-I or ARB therapy [For patients with vascular disease: Class A, Level 1A evidence (2,3); for patients at high risk: Class B, Level 1A evidence (2,3)].*
5. *Low-dose aspirin therapy (80-150 mg/day) may be considered in patients with stable CVD (Class D, evidence based consensus).*
6. *Clopidogrel (75 mg/day) may be considered in people unable to tolerate aspirin (Class D, evidence based consensus).*
7. *The decision to prescribe antiplatelet therapy for primary prevention of CV events, however, should be based on individual clinical judgment (Class D, evidence based consensus).*

REFERENCES

1. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-93.
2. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-9.
3. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008385;15:1547-59.

13.2 MICROVASCULAR COMPLICATIONS

13.2.1 Retinopathy

Diabetic retinopathy is a leading cause of adult blindness.

Screening

1. Retinopathy screening should be performed yearly, starting at puberty or 5 years after diagnosis in type 1 diabetes.
2. Retinopathy screening should be performed in all individuals at diagnosis of type 2 diabetes, and the patients who at baseline had no diabetic retinopathy, or had mild retinopathy should be rescreened annually, who had advanced retinopathy in every 3 to 6 months.

Clinical evaluation

A fundus examination is performed by indirect ophthalmoscopy through dilated pupil.

1. Non-proliferative retinopathy: Microaneurysms and hard exudates.
2. Pre-proliferative: Exudates, bleedings, IRMA (Intraretinal microvascular abnormalities)
3. Proliferative retinopathy: Newly formed fragile capillaries replace with less functional blood vessels in the retinal circulation. Patients with neovascularization are at greater risk of developing retinal detachment and hemorrhage.
4. Macula edema is one of the leading causes of blindness along with tractional retinal detachment due to proliferative retinopathy, and neovascular glaucoma.

The guidelines in assessment of diabetic retinopathy in adult patients is summarized in Table 13.1.

Prevention and treatment

Optimal BP and glycemic control should be achieved.

People with abnormal lipid levels should be considered at high risk for retinopathy.

Laser photocoagulation, vitrectomy, and pharmacologic intervention with anti-vascular endothelial growth factor (anti-VEGF) agents can be considered.

Table 13.1 Diabetic retinopathy assessment in patients with type 2 diabetes

Routine follow-up methods	Referral to ophthalmologist	Urgent ophthalmology consultation needed
Fundus examination - At the time of diagnosis - Then annually Routine visual acuity tests should be performed. Alternatively, diabetic retinopathy can be screened through retinal photographs taken by experienced professionals using compatible devices.	I. If maculopathy is present - Exudates or retinal thickening within one disc diameter from the center of the fovea - Ring-shaped exudates or group of exudates within macula(*) - Visual acuity of 6/12 or less due to aneurysm or bleeding within one disc diameter from the center of the fovea II. If pre-proliferative retinopathy findings are present:(**) Venous beading - Venous ring or reduplication-Intraretinal microvascular abnormalities (IRMA) - Multiple deep-round or spot bleedings III. Any unexplained drop in visual acuity	The following cases must be examined immediately by an ophthalmologist: Sudden vision loss Rubeosis iridis Pre-retinal and vitreous hemorrhage Retinal detachment Neovascularization.

(*)Macula has been described as the circle with the center of fovea, and with the diameter between the temporal edge of the optic disk and the fovea

(**)Cotton wool spots do not indicate preproliferative retinopathy

SEMT RECOMMENDATIONS FOR DIABETIC RETINOPATHY

1. *In individuals with type 1 diabetes, screening for retinopathy should be performed starting at puberty or 5 years after the onset of diabetes [Class A, Level 1 evidence (1-3)], and in individuals with type 2 diabetes at the time of diagnosis (Class A, Level 1 evidence) and then annually [Class A, Level 1 evidence (2,4)]*
2. *To prevent the onset and delay the progression of diabetic retinopathy, people with diabetes should be treated to achieve optimal control of blood glucose and BP [For glycemia: Class A, Level 1A evidence (5); for BP: Class A, Level 1A evidence (5)].*
3. *Patients with severe retinopathy (preproliferative or proliferative) should be assessed by an ophthalmologist [Class D, evidence-based consensus].*
4. *Laser photocoagulation, vitrectomy and pharmacologic intervention should be considered in sight-threatening retinopathy [For laser and vitrectomy: Class A, Level 1 evidence (6-8); for pharmacologic interventions: Class B, Level 2 evidence (9)].*

REFERENCES
1. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1989;107:237-43.
2. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1984;102:520-6.
3. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. X. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. Arch Ophthalmol 1989;107:244-9.
4. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. VII. Diabetic nonproliferative retinal lesions. Ophthalmology 1987;94:1389-1400.
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
6. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796-806.
7. The Diabetic Retinopathy Study Research Group. Photocoagulation treatment Study findings. Ophthalmology 1978;85:82-106.
8. The Diabetic Retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Four-year results of a randomized trial: Diabetic Retinopathy Study report 5. Arch Ophthalmol 1990;108:958-64.
9. Cunningham ET Jr, Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112:1747-57.

13.2.2 Nephropathy

Nephropathy is one of the leading causes of morbidity and mortality in adults with diabetes.

Screening

To investigate the early nephropathy in adults, microalbuminuria and eGFR should be assessed together.

Serum creatinine is measured and GFR is estimated (eGFR) using MDRD or Cockcroft formulas. (Microalbuminuria assessment and eGFR calculation have been previously described in the chapter for guidelines of standard care in diabetic patients).

Diabetic nephropathy screening:

- Screening should be performed annually in adults with type 1 diabetes of >5 years' duration.
- Individuals with type 2 diabetes should be screened at diagnosis of diabetes and yearly thereafter.

Screening should be delayed when causes of transient albuminuria or low eGFR are present (e.g. uncontrolled HT, urinary tract infection, hypovolemia).

Staging

Diabetic nephropathy is the most important cause of end-stage renal disease. Chronic renal failure in patients with diabetes is assessed as in non-diabetic patients according to the following GFR stages based on kidney damage determined by urine and blood tests, imaging and/or pathological assessments.

Stage 1: eGFR ≥90 mL/min/1.73 m^2: normal/high GFR and kidney damage

Stage 2: eGFR 60-89 mL/min/1.73 m^2: mildly decreased GFR and kidney damage

Stage 3: eGFR 30-59 mL/min/1.73 m^2: moderately decreased GFR and kidney damage

Stage 4: eGFR 15-29 mL/min/1.73 m^2: severely decreased GFR and kidney damage

Stage 5: eGFR <15 mL/min/1.73 m^2 or dialysis: end-stage renal disease.

Serum creatinine levels should be measured to calculate albumin:creatinine ratio (ACR) in a first morning (spot) urine sample as well as eGFR in every 3-6 months in diabetic patients with chronic renal failure.

Clinical findings

- Diabetic nephropathy is characterized by HT, edema, proteinuria and renal failure.
- The patient reaching end-stage renal failure requires renal replacement treatment. Renal transplantation is treatment of choice for

young and middle age patients (<65 years of age) whereas elderly patients should be treated with hemodialysis, or with ambulatory peritoneal dialysis at home.

Prevention and treatment

■ **Glycemia control:** In patients with type 1 and type 2 diabetes optimal glucose control should be assessed to prevent or delay nephropathy. The progression of renal damage in diabetes can be slowed through intensive glycemic control.

■ **Microalbuminuria:** In people with persistent increased ACR (≥30 mg/g creatinine) with or without HT, an ACE-I or an ARB would be preferred for prevention of renal disease progression.

■ Individuals starting therapy with an ACE-I or an ARB should be monitored within 1 to 2 weeks of initiation or titration of treatment for serum creatinine and potassium levels.

■ **Renal failure:** The use of thiazide-like diuretics should be considered in individuals with CKD (chronic kidney disease) and diabetes for control of sodium and water retention, HT or hyperkalemia. Alternatively, furosemide can be substituted for or added to thiazide-like diuretics for individuals who fail monotherapy with thiazide-like diuretics or who have severe sodium and water retention or hyperkalemia.

■ Consideration should be given to stopping ACE-I, ARB and/or diuretic therapy during times of acute illness such as febrile illness or diarrhea, especially when intravascular volume contraction is present or suspected.

■ Women should avoid becoming pregnant when receiving ACE-I or ARB therapy, as the use of medications has been associated with adverse fetal outcomes, and if pregnancy is planning the medication should be stopped two months before conception.

Evaluation of kidney damage in adult patients with diabetes is summarized in Figure 13.2.

A referral to a nephrologist should be considered in the following situations:

- Progressive loss of kidney function
- eGFR <30 mL/min,
- ACR >300 mg/g creatinine
- Uncontrolled HT
- Hyperkalemia or a >30% increase in serum creatinine within three months of starting an ACE-I or an ARB.

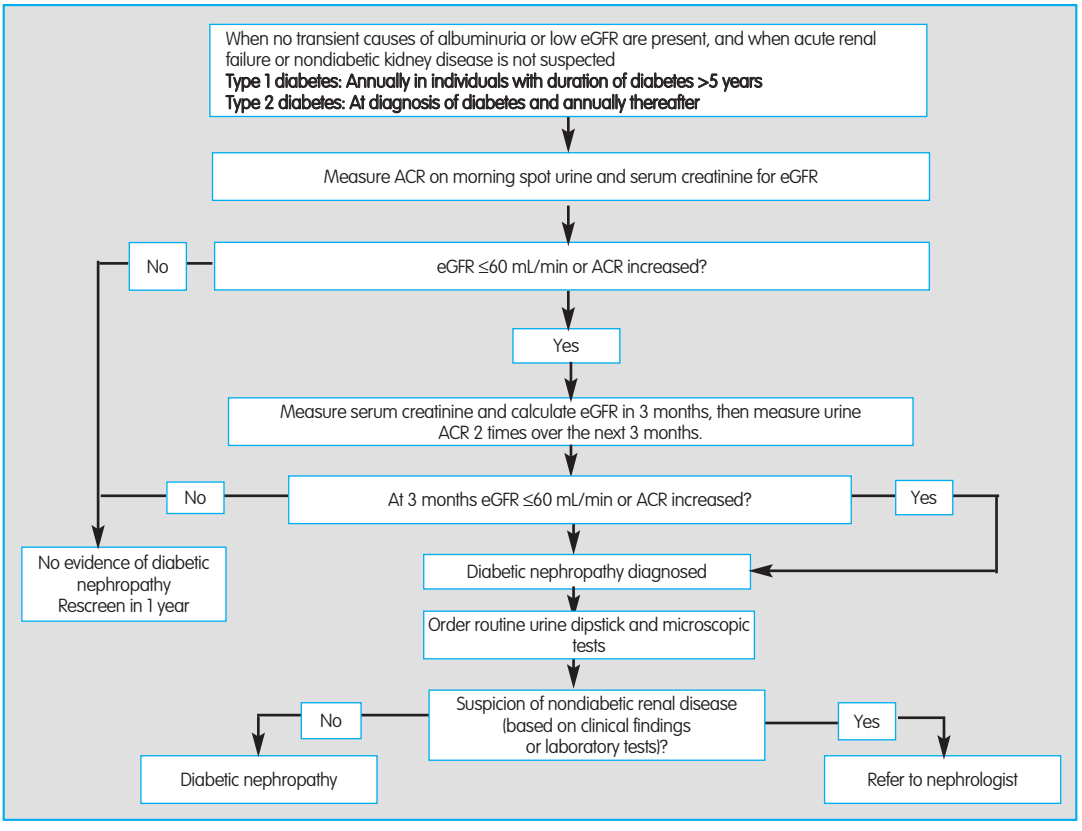

Figure 13.2 Evaluation of kidney damage in adult patients with diabetes

SEMT RECOMMENDATIONS FOR DIABETIC KIDNEY DISEASE

1. *The best possible glycemic control should be instituted in people with type 1 or type 2 diabetes for the prevention of onset and delay in progression to CKD [Class A, Level 1A evidence (1-3)].*
2. *In adults, screening for CKD in diabetes should be conducted using ACR and eGFR [Class D, evidence-based consensus]. Screening should be performed:*
   - *Annually in adults with type 1 diabetes of >5 years' duration.*
   - *At diagnosis of diabetes and yearly thereafter in individuals with type 2 diabetes [Class D, evidence-based consensus].*
3. *People with diabetes and CKD should have a random urine ACR and serum creatinine for calculated eGFR at least every 3 to 6 months [Class D, evidence-based consensus].*
4. *Adults with diabetes and persistent albuminuria should receive an ACE-I or an ARB to delay the progression of CKD, even in the absence of HT [for ACE-I use in type 1 and type 2 diabetes, and for ARB use in type 2 diabetes: Class A, Level 1A evidence (4-11); for ARB use in type 1 diabetes Class D, evidence-based consensus].*
5. *People with diabetes on an ACE-I or an ARB should have their serum creatinine and potassium levels checked [Class D, evidence-based consensus].*
6. *The use of thiazide-like diuretics and/or furosemide should be considered in individuals with CKD and diabetes [Class D, evidence-based consensus].*
7. *Consideration should be given to stopping ACE-I, ARB and/or diuretic therapy when intravascular volume contraction is suspected [Class D, evidence-based consensus].*
8. *Women should avoid becoming pregnant when receiving ACE-I or ARB therapy [Class D, evidence-based consensus].*
9. *A referral to a nephrologist should be considered if eGFR is <30 mL/min or ACR is >300 mg/g creatinine, or the individual is unable to achieve BP targets or if the patient has hyperkalemia or a >30% increase in serum creatinine after starting an ACE-I or ARB [Class D, evidence-based consensus].*

REFERENCES

1. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. Lancet 1993;341:1306-9.
2. The Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney Int 1995;47:1703-20.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
4. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;329:1456-62.
5. Strippoli GF, Craig MC, Schena FP, et al. Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy and delay its progression. J Am Soc Nephrol 2006;17(suppl 2):S153-S155.
6. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
7. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.
8. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. Am J Med 1995;99:497-504.
9. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 2001;134:370-9.
10. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Int Med 1993;118:577-81.
11. Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 2002;106:672-8.

13.2.3 Neuropathy

Neuropathy may affect any system of the body. Distal symmetrical sensory disorder of the lower-extremity is the major cause of foot amputation with infection and ischemia. In recent years it is recommended to conduct screening for neuropathy annually in adults with type 1 diabetes of 5 years duration, and at diagnosis of diabetes and yearly thereafter in individuals with type 2 diabetes.

A. Peripheral polyneuropathy

1. Distal polyneuropathy

The most common presentation is a progressive distal polyneuropathy.

- Unsteadiness of the gait, ataxic gait, muscle weakness in hands and feet
- It is associated with loss of proprioception and tactile hypoesthesia
- There is also loss of pain and heat sensation
- Abnormal changes in tactile sensory (allodynia, pain) may progress to the sensory loss
- Stocking glove distribution of sensory loss with a distal to proximal gradient is typical.
- Diabetic polyneuropathy causes contact-induced discomfort, superficial burning, dull aching, deep aching pains, and jabbing pain especially at nights.
- Foot ulcers, infections and neuro-osteoarthropathy (Charcot foot: characterized by bone erosions, undetected recurrent fractures, foot edema due to bone demineralization disorders, increase of heat and deformities) may develop. Proper foot care can reduce the risk.
- Sometimes it is asymptomatic. When symptomatic it may show a self-limiting or a progressive clinical course.

2. Focal neuropathies

Focal neuropathy usually has a sudden onset and shows a spontaneous regression within a few weeks or months.

- **Third cranial nerve paralysis:** It is characterized by unilateral eye pain, diplopia and ptosis.
- **Radiculopathy:** Diabetic radiculopathy involving the nerve roots causes thoracic, abdominal and truncal pain with band-style spread.
- **Plexopathy:** Diabetic plexopathy typically affects the lumbosacral plexus and brachial plexus and causes pain spreading to extremities.

Treatment of neuropathy

- Immediate and accurate diagnosis is needed.
- Treatment should be directed at symptoms
- Painful neuropathies should be treated with non-specific analgesics initially, specific pain treatment should be performed in non-responsive cases (Table 13.2).

Table 13.2 Management of neuropathic pain in diabetes

Class	Example	Recommended doses(*)
Tricyclic antidepressants	Amitriptyline	10-75 mg at night
	Nortriptyline	25-75 mg at night
	Imipramine	25-75 mg at night
Anticonvulsants	Gabapentin	3x300-1200 mg
	Carbamazepine	3x200-400 mg
	Pregabalin	3x100 mg(**)
5-Hydroxytryptamine and Norepinephrine reuptake inhibitors	Duloxetine	1x60-120 mg
Alpha lipoic acid(**)	Thioctacid ampoule	600-1200 i.v. infusion
Substance-P inhibitor	Capsaicin cream	0.025-0.075% externally 1 to 3 times per day
Isosorbide dinitrate(**)	Isosorbide topical cream	Externally 1 to 2 times per day

(*)Dose response is variable. The therapy is started at the lowest dosage and titrated gradually
(**)Not available in our country

Treatment algorithm of pain neuropathy is shown in Figure 13.3. It has been known for many years that alpha lipoic acid may partially improve subjective findings, such as paresthesia, burning, pricking, and numbness. However, the oral form of alpha lipoic acid is not useful in the treatment of neuropathic pain. On the other hand, small pilot studies using parenteral form of this drug, which is not available in our country, have been proposed some beneficial effects in the pain relief.

Prevention

- Optimum glycemic control should be achieved.
- Foot care should not be neglected.

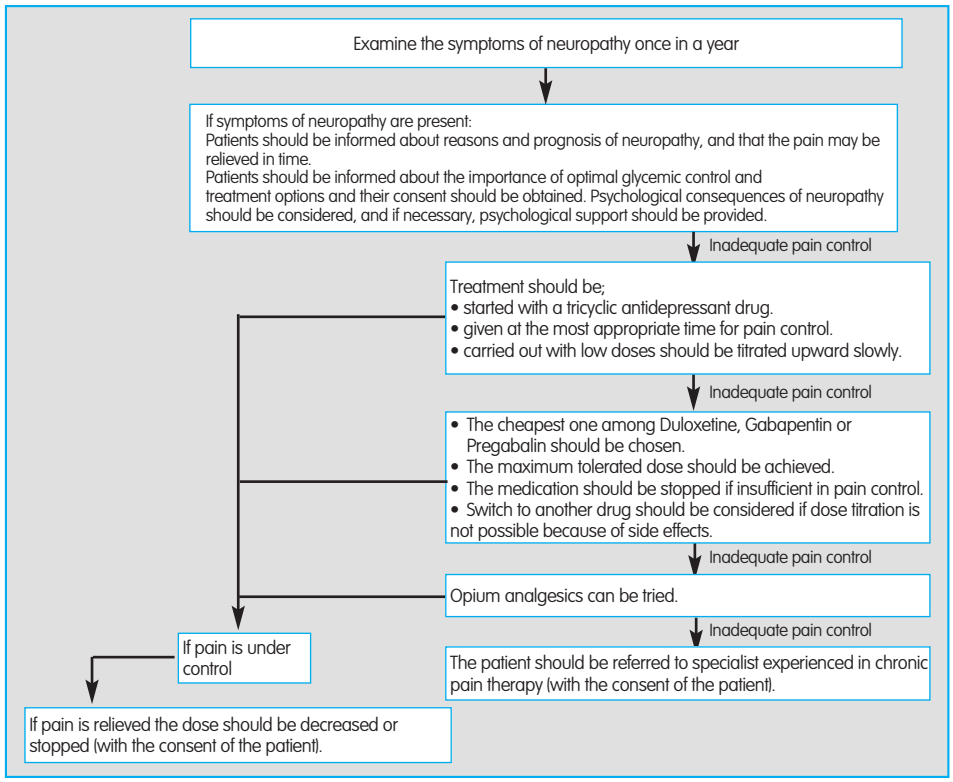

Figure 13.3 Treatment of neuropathic pain in adult patients with diabetes

SEMT RECOMMENDATIONS FOR PERIPHERAL NEUROPATHY

1. *In people with type 1 diabetes, annual screening for peripheral neuropathy should commence after 5 years' postpubertal duration of diabetes. In people with type 2 diabetes, screening should begin at diagnosis of diabetes and occur annually thereafter. [Class D, evidence-based consensus].*
2. *Screening for peripheral neuropathy should be conducted by assessing loss of sensitivity to the 10-g monofilament or loss of sensitivity to vibration at the dorsum of the great toe [Class A, Level 1 evidence (1)].*
3. *People with diabetes should be treated with intensified glycemic control to prevent onset and delay progression of neuropathy [For type 1 diabetes Class A, Level 1A evidence, (2, 3); for type 2 diabetes Class B, Level 2 evidence (4)].*
4. *For the relief of painful peripheral neuropathy:*
   - *Antidepressants [Class A, Level 1A evidence (5,6)],*
   - *Anticonvulsants [Class A, Level 1A evidence (7-10)], and*
   - *Opioid analgesics [Class A, Level 1A evidence (9)] should be considered alone or in combination.*

REFERENCES

1. Perkins BA, Olaleye D, Zinman B, et al. Simple screening tests for peripheral neuropathy in the diabetes clinic. Diabetes Care 2001;24:250-6.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
3. Reichard P, Berglund B, Britz A, et al. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. J Intern Med 1991;230:101-8.
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-53.
5. Rowbotham MC, Goli V, Kunz NR, et al. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004;110:697-706.
6. Raskin J, Smith TR, Wong K, et al. Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. J Palliat Med 2006;9:29-40.
7. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA1998;280:1831-6.
8. Richter RW, Portenoy R, Sharma U, et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 2005;6:253-60.
9. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005;352:1324-34.
10. Dogra S, Beydoun S, Mazzola J, et al. Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. Eur J Pain 2005;9:543-54.

B. Autonomous polyneuropathy

- **Orthostatic hypotension**
- **Cardiac denervation syndrome:**
  - It affects CV reflexes.
  - Heart becomes hypersensitive to catecholamine.
  - Dysrhythmia (mostly tachycardia)
  - Exercise intolerance
  - Silent (painless) myocardial infarction
  - Sudden death
- **Gastrointestinal neuropathy**
  - Delayed gastric emptying (Gastroparesis)
  - Motility is reduced (swallowing difficulty, quick full feeling, nausea-vomiting)
  - Delayed absorption of food (Brittle diabetes: Episodes of hypoglycemia or hyperglycemia which constantly disrupt regulation of diabetes.
  - Constipation (colonic atony)
  - Nocturnal diarrhea
  - Cholecystitis, biliary sludge (gallbladder atony)
- **Genitourinary neuropathy**
  - Erectile dysfunction
  - Retrograde ejaculation and infertility
  - Sexual arousal difficulties and dyspareunia in women
  - Bladder dysfunction (incontinence due to neurogenic bladder, infection)
- **Hypoglycemia unawareness**
  - Counterregulatory hormone (epinephrine, glucagon) responses to hypoglycemia are blunted.
  - Autonomous sudomotor dysfunction
  - Uncontrolled hypohidrosis in extremities
  - Gustatory sweating (central hyperhidrosis): Sweating on the forehead, face, and neck occurring soon after ingesting food.

The approach to autonomous neuropathy in diabetic patients is summarized in Table 13.3.

Table 13.3 The approach to autonomous neuropathy in diabetic patients

Involved system	Treatment approach	Suggestions
Gastroparesis - Impaired glucose control due to hypo- and hyperglycemia -Unexplained stomach bloating and vomiting	- Metoclopramid - Domperidone - Erythromicin	- Suspicion in the differential diagnosis - In case of continuous and severe vomiting patient should be referred to a gastroenterologist.
Erectile dysfunction - Diabetic men should be examined once in a year	- Necessary assessments should be performed. - Patients should be informed about contributing factors and treatment options - Phosphodiesterase-5 inhibitors should be given unless there is some contraindication to their use.	If a phosphodiesterase-5 inhibitor is insufficient the next step will be: - Medical treatment - Surgical treatment - Patient should be referred to a specialist for psychological support.
Hypoglycemia unawareness The absence of hypoglycemic symptoms	Sympathetic nervous system damage must be considered	Further investigations and specific treatment should be applied
Nocturnal diarrhea Unexplained diarrhea especially at night	Intestinal autonomic neuropathy	
Neurogenic bladder Impaired bladder emptying	Autonomic neuropathy involving the bladder	

Erectile dysfunction

SEMT approach and recommendations on this issue are summarized below:

SEMT RECOMMENDATIONS FOR ERECTILE DYSFUNCTION

1. *Adult males with diabetes should be regularly screened for erectile dysfunction along with sexual function history (Class D, evidence-based consensus).*
2. *A phosphodiesterase-5 inhibitor is recommended as first-line therapy for treating erectile dysfunction in men with diabetes (Class A, Level 1A evidence (1-8)).*
3. *Referral to a specialist in erectile dysfunction should be considered for eugonadal men who do not respond to phosphodiesterase-5 inhibitors, or for whom the use of phosphodiesterase-5 inhibitors is contraindicated (Class D, evidence-based consensus).*
4. *Men with diabetes and erectile dysfunction who do not respond to phosphodiesterase-5 inhibitors should be investigated for hypogonadism (Class D, Level 4 evidence (9-12)).*
5. *Men with diabetes and retrograde ejaculation who desire fertility should be referred to a specialist experienced in the treatment of ejaculatory dysfunction (Class D, evidence-based consensus).*

REFERENCES

1. Fonseca V, Seftel A, Denne J, et al. Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. Diabetologia 2004;47:1914-23.
2. Rendell MS, Rajfer J, Wicker PA, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. JAMA 1999;281:421-6.
3. Boulton AJM, Selam J-L, Sweeney M, et al. Sildenafil citrate for the treatment of erectile dysfunction in men with type II diabetes mellitus. Diabetologia 2001;44:1296-301.
4. Goldstein I, Young JM, Fischer J, et al. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 2003;26:777-83.
5. Sáenz de Tejada I, Anglin G, Knight JR, et al. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 2002;25:2159-64.
6. Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU Int 2005;96:257-80.
7. Briganti A, Salonia A, Gallina A, et al. Drug insight: oral phosphodiesterase type 5 inhibitors for erectile dysfunction. Nat Clin Pract Urol 2005;2:239-47.
8. DeBusk R, Drory Y, Goldstein I, et al. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. Am J Cardiol 2000;86:175-81.
9. Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004;89:5462-68.
10. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male 2003;6:1-7.
11. Shabsigh R, Kaufman JM, Steidle C, et al. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 2004;172:658-63.
12. Kalinchenko SY, Kozlov GI, Gontcharov NP, et al. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male 2003;6:94-9.