CHAPTER 16
CHRONIC COMPLICATIONS OF DIABETES MELLITUS

- The chronic complications of diabetes mellitus are responsible for most of the morbidity and mortality associated with this disease.
- The prevention of the chronic complications of diabetes involves not only glucose control but also specific risk factor modification and treatment strategies aimed directly at the prevention and treatment of chronic complications.
- A detailed discussion of the pathogenesis of the chronic complications of diabetes is beyond the scope of these guidelines. What follows is a brief description of aspects of the prevention and management of diabetic complications.
- Diabetic complications are classified into:
  Macrovascular: Coronary artery disease, peripheral vascular disease , and cerebrovascular disease
  Microvascular: Retinopathy, nephropathy and neuropathy.

16.1 Macrovascular Complications

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- Atherosclerotic complications include coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD).
- They account for more than 70% of diabetic deaths.
- Etiology of atherosclerosis is multifactorial and includes:
  - Quantitative lipid abnormalities-primarily increases in VLDL-cholesterol (triglycerides) and decreases in HDL-cholesterol
  - Qualitative lipid abnormalities-Increases in glycated LDL and oxidized LDL
  - Increased insulin resistance/hyperinsulinemia
  - Increased procoagulant and decreased anticoagulant factors
  - Hyperglycemia itself

Coronary Artery Disease
- 2-3 fold more common in persons with DM
- Multiple and more diffuse atherosclerotic lesions
- Women with DM lose their usual premenopausal protection against atherosclerosis
- Increase in silent ischemia
- Worse prognosis following angioplasty/CABG

Peripheral Vascular Disease
- Peripheral vascular disease including intermittent claudication and gangrene is much more common in people with diabetes.
- The atherosclerosis tends to be more diffuse and involves small vessels.
- PVD, as well as diabetic neuropathy, leads to an increased risk for foot ulcers and amputation in those with DM.

Cerebrovascular Disease
- Diabetes increases the risk of stoke.

- Strategies aimed at primary and secondary prevention of stroke are similar to those aimed at coronary artery disease.

Preventive Maneuvers to Decrease Macrovascular Disease in DM

Vascular Protection including:

- High dose ACE inhibitor
- Antiplatelet therapy (e.g low dose ASA)
- Optimal control of Lipids:
  - For diabetic patients at high risk for vascular disease (vast majority): LDL<2.5 & TC/HDL<4
  - For diabetic patients at moderate risk (those with younger age and shorter duration of DM and no other diabetic complications and no other vascular risk factors): LDL<3.5 & TC/HDL<5
- Optimal control of blood pressure <130/80 mm Hg
- Optimal control of glucose
- Lifestyle modification
- Smoking cessation

16.2 Diabetic Retinopathy

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- Diabetes is the leading cause of blindness in North America in patients under the age of 60 years, and the second leading cause of blindness in patients over the age of 60 years.
- Although diabetic retinopathy itself cannot be prevented, in many cases its blinding complications can.
- In type 1 diabetes, retinopathy is rarely seen before 5 years from diagnosis, but in type 2 diabetes, some retinopathy is present in 17% of patients at the time of diagnosis.
- By 15 years, 98% of type 1 and 78% of type 2 diabetics have some retinopathy.

Classification of Diabetic Retinopathy

1. **Non-proliferative (NPDR):** Characterized by microaneurysms, dot & blot hemorrhages, hard exudates, and nerve fibre layer infarcts (NFLI).

2. **Pre-proliferative (Severe NPDR):** Characterized by increased NFLI and hemorrhages, presence of intraretinal microvascular abnormalities (IRMA), venous bleeding, and reduplication of vessels. 50% of patients will progress to proliferative disease within two years.

3. **Proliferative (PDR):** Characterized by neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE). Associated findings may include vitreous hemorrhage and/or tractional retinal detachment.

Prognosis

- In NPDR and Severe NPDR, visual loss can occur secondary to clinically significant macular edema (CSDME) and macular ischemia. While ischemia is irreversible, CSDME can be sometimes be treated with laser.
- In PDR, visual loss can occur similarly to NPDR, but can also occurs from vitreous hemorrhage or from tractional retinal detachment.

Screening

- Those with **Type I DM** of at least 5 years duration should have an annual eye examination by an ophthalmologist.
- Those with **Type 2 DM** should be examined by an ophthalmologist at the time of diagnosis, or shortly thereafter, and then annually.
- More frequent examinations may be required depending on severity of retinopathy, at the discretion of the ophthalmologist.
- **In Pregnancy**, a retinal examination should be performed in the first trimester and then every 3 months, or sooner if retinopathy is active.

Diagnosis

- Diabetic retinopathy is evaluated with visual acuity, slit lamp biomicroscopy, dilated retinal examination with binocular direct and indirect ophthalmoscopy.
- If significant retinopathy is present, fundus photography and fluorescein angiography may be indicated.
- If media opacity is present precluding visual retinal examination, A and B scan ultrasonography can be extremely helpful in diagnosis.

Risk Factors

- Risk factors for diabetic retinopathy include duration of disease, elevated glycosylated hemoglobin, hypertension, hyperlipidemia, puberty, smoking, as well as a genetic predisposition for retinopathy.
- The DCCT and UKPDS have demonstrated a significant reduction in visual complications with tight control of blood sugar, blood pressure, and lipids.
- There may be an initial worsening of retinopathy when poorly controlled patients initiate intensive treatment protocols, but retinopathy usually improves within 2-3 years, and long-term benefits of tight control usually exceed the risk of initial deterioration.

Management

- An important part of managing diabetic retinopathy is informing patients of the natural history of the disease, and their current status with respect to severity.
- Risk factors should be reviewed, and patients should be encouraged to monitor and optimize controllable factors such as glycemic control, hypertension, lipid status, and smoking.
- The mainstay of treatment for CSDME in NPDR is focal or grid laser photocoagulation, as reported by the ETDRS.
- The mainstay for PDR is panretinal photocoagulation (PRP), as reported by the DRS.
- Treatment of a non-clearing vitreous hemorrhage or traction retinal detachment may require a vitrectomy with possible endolaser enhancement.
- With timely application of each form of treatment, visual loss from diabetic retinopathy can be reduced significantly.
- People with DM should optimize their vision with appropriate visual aids such as spectacles or contact lenses.
- It is important to have stable glycemic control for at least 2 months prior to refraction to get an accurate result.
- Low vision aids, such as hand-held magnifiers, may be extremely helpful in patients with moderate to severe visual loss.
- Referral to the Canadian National Institute for the Blind (CNIB) forms an integral role in the support and management of patients with severe visual loss.

Other Diabetic Eye Complications

- Diabetes is also associated with increased prevalence of cataracts, and glaucoma.
- Best results from cataract surgery are achieved when diabetic retinopathy has been treated optimally pre-operatively to minimize macular edema and/or proliferative disease.
- Glaucoma must be managed aggressively, to minimize its contributory effects.
- Neuropathy affecting corneal sensation can affect the ability of the corneal epithelium to heal.
- Diabetic cranial nerve palsies can cause diplopia.
- Optic neuropathy can occur suddenly and severely decrease vision even though retinopathy may be quite mild. Optic Neuropathy is sometimes reversible in those under 50 years of age, if put on a course of high dose corticosteroid.

16.3 Diabetic Nephropathy

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- Diabetes is the leading cause of end stage renal disease in Canada, the USA and Europe accounting for 35-40% of incident cases. In patients, the development of diabetic renal disease is associated with a magnified risk of all the long-term complications of diabetes.
- In people with type 1 diabetes, 25-45% will develop clinical nephropathy (stage 4, see below).
- In people with type 2 diabetes, the risk of end-stage renal disease is less due to increased cardiac mortality at stage 4. However, in some sub-groups, such as the Pima Indians, the incidence is similar to that in type 1 diabetes.
- In type 1 diabetes, nephropathy is rarely seen before 5 years, but in type 2 diabetes, microalbuminuria is often present at the time of diagnosis.
- Hypertension is extremely common affecting 20-60% of patients with diabetes. In type 2 diabetes, it is part of the metabolic syndrome and is often present at diagnosis of diabetes. In type 1 diabetes, blood pressure starts to rise early during the course of diabetes and may progress to reach hypertensive levels.

Diagnosis

- The earliest clinical evidence of nephropathy is the appearance of low levels of albumin in the urine.
- Clinical diabetic nephropathy is present when there is >500 mg proteinuria/day.
- Urinalysis demonstrates a bland sediment (i.e. usually hematuria is **not** present).
- 90% of patients with clinical nephropathy have diabetic retinopathy.
- Although the 'gold standard' for diabetic nephropathy is renal histology, when the clinical course and the above noted features are present, a renal biopsy is not generally necessary to make the diagnosis.
- The presence of renovascular disease deserves consideration in light of the diffuse macrovascular disease that can be seen in patients with diabetes.

Stages of Disease

Stage 1 ***Functional changes*** at the onset of diabetes are marked by hyperfiltration and transient microalbuminuria. These changes may be reversed or attenuated with improved glycemic control.

Stage 2 ***Clinically silent***, though pathological changes of diabetic renal disease are evolving.

Stage 3 ***Incipient nephropathy-persistent microalbuminuria*** of 30-300 mg albumin/day or 20-200 μg/min demonstrated in 2 out of 3 samples collected over a 6-month period. Urine samples must be collected when other causes of elevated microalbuminuria are absent (see Screening).

Stage 4 ***Clinical nephropathy-proteinuria*** with a decline in glomerular filtration rate with or without hypertension. This is the stage classically referred to as 'diabetic nephropathy'.

Stage 5 ***End-stage renal disease*** requiring renal replacement therapy with dialysis or kidney transplantation.

Risk factors

- **Hypertension**: Increased risk of nephropathy with increased systolic blood pressures.
- **Glomerular filtration rate:** GFR > 150 mls/min associated with a greater risk of stage 4 nephropathy or of stage 3 disease if GFR > 125 mls/min.
- **Glycemic Control:** In both type 1 and type 2 diabetes, improved glycemic control is associated with a reduced risk of developing stage 3 or stage 4 disease as demonstrated in the DCCT and the UKPDS studies, respectively.
- **Genetics and Race:** Risk increased in aboriginal people, blacks (4-6 fold compared to Caucasians) and people of Hispanic descent.

Screening

- Type 1: Annual screen for microalbuminuria in patients >15 years of age and after 5 years duration of diabetes.
- Type 2: Urinalysis at diagnosis: if positive for protein, quantitate; if negative for protein, screen for microalbuminuria.
- Spot collection or first morning void should be assessed for albumin/creatinine ratio as a screening test. Confirmation with timed samples (either 4 hour or overnight) should then be continued for ongoing monitoring. For positive samples, repeat a timed collection twice more over a 6-month period to diagnose stage 3 diabetic nephropathy.
- Screening tests should be scheduled when other causes of transient increases in microalbuminuria are not present (i.e. transient loss of glycemic control, intercurrent febrile illness, urinary tract infections, heart failure, marked hypertension and vigorous exercise). Except for exercise, allow 4-6 weeks for their effects on albumin excretion to abate.

Disease Treatment

The emphasis of management is on prevention of progressive disease through screening and early detection and on having aggressive targets for glycemic, lipemic and blood pressure control, dietary protein and the modifiable cardiovascular risk factors.

- **Glycemic control:** Best possible glucose control. In light of the emerging appreciation for the reversibility of diabetic nephropathy, the importance of glycemic control at any stage of the disease cannot be overstated.
- **Blood pressure:** Target of <130/80 in all patients or $\leq$125/75 in patients with greater than 1-2 grams/day of proteinuria. Lifestyle modifications are introduced for mild hypertension (<140/90). Use of multiple antihypertensive medications is often required. Initial therapy with an ACE-I or an ARB (Angiotensin Receptor Blocker) followed by the addition of a diuretic (indapamide or low dose hydrochlothiazide, up to 25 mg) often achieves the target. Other drug classes including β-blockers, α-blockers and calcium channel blockers (CCBs) should be added and guided by the presence of comorbid conditions. The dihydropyridine CCBs are suggested as additions to ACE-I and β-blockers whereas the non-dihydropyridine CCBs may reduce proteinuria per se.
- **Angiotensin-converting enzyme inhibitors (ACE-I)*:** In type 1 diabetes with stage 3 disease or stage 4 disease to delay the progression of proteinuria or clinical nephropathy, respectively; in type 2 diabetes, in stage 3 or stage 4 disease. They are contraindicated in pregnancy and this requires emphasis in women of childbearing potential.
- **Angiotensin II receptor blockers*:** If ACE-I are not tolerated in type 1 diabetes. They may be used as first line in type 2 diabetes with stage 3 or 4 nephropathy. If in spite of maximum ACE-I and

blood pressure control, overt proteinuria persists, further reductions in proteinuria to targets of <500mg/d may be seen with the addition of ARBs, but this effect has only been assessed in short term studies.

- **Dietary protein restriction:** To 0.8g/kg/day in the presence of clinical nephropathy (stage 3 or 4 disease) or if hyperfiltration (creatinine clearance >130 mls/min) is present.
- **Lipid control:** Target levels as in the presence of cardiovascular disease.
- **Smoking cessation**

***Note of Caution:** check the serum potassium and creatinine at 1-2 weeks after starting these medications or after adjusting the dosage upwards.

- **Refer to a nephrologist**: At the latest when the creatinine clearance is approximately 50% of normal for timely planning of renal replacement therapy and management of the other features of progressive renal insufficiency including anemia. Pre-emptive living renal transplantation followed by pancreas transplantation or simultaneous cadaveric kidney-pancreas transplantation is the treatment of choice for type 1 diabetes ESRD.

Patient Management

- An important part of managing diabetic nephropathy is educating patients about the natural history of the disease and treatment options for end-stage renal disease.
- Risk factors should be reviewed, and patients should be encouraged to be vigilant with controllable factors such as glycemic control, hypertension, lipid status, and smoking. Importance of lifestyle factors for control of hypertension requires emphasis as therapies that partner with the medications.
- Referral to the Kidney Foundation of Canada for information and peer support surrounding the needs of renal replacement therapy by dialysis or transplantation is encouraged.

16.4 Diabetic Neuropathy

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- The term "diabetic neuropathy" refers to a set of clinical conditions in patients with diabetes that share as a common feature abnormalities in the structure and the function of peripheral nerves.
- The metabolic derangement in diabetes leads to generalized subclinical nerve injury that may itself progress to clinical disease, or, in the setting of nerve entrapment (as in the carpal tunnel, for example), this underlying injury may increase the likelihood of clinical mononeuropathies.
- Diabetic Neuropathy may affect sensory, motor, and autonomic neurons of the peripheral nervous system
- Hyperglycemia is associated with activation of the polyol pathway, auto-oxidation of glucose, non-enzymatic glycation of proteins (advanced glycation endproduct formation), and inappropriate activation of protein kinase which all share the common end result of oxidative stress to the peripheral nerve.
- The most common form of neuropathy is "diabetic sensorimotor polyneuropathy", affecting up to 50% of patients. It is an insidious, progressive, and diffuse process that eventually involves all nerve types and for which the pathological severity is poorly linked with the development of symptoms. It is the cause of extreme morbidity and health care costs arising from pain, sensory ataxia, deformity, and the late stage sequelae of infection, ulceration and amputation. Consequently, diabetic polyneuropathy necessitates routine screening in the clinic.

Classification

- Although several classification schemes exist, the most broadly accepted one considers all diabetic neuropathies as being categorized as diffuse (anatomically symmetrical) or focal (anatomically asymmetrical).
- While diffuse and focal neuropathies may involve any nerve fiber type, involvement of the autonomic nervous system is often classified separately.

Diffuse (Symmetrical)

- Diabetic Sensorimotor Polyneuropathy (by far the most common form of diabetic neuropathy)
- Small fiber polyneuropathy associated with weight loss and cachexia.
- Hypoglycemic polyneuropathy.

Focal (Asymmetrical)

- Proximal diabetic neuropathy (the so-called "diabetic amyotrophy")
- Truncal Radiculoneuropathy
- Limb mononeuropathies
    - Median neuropathy ("Carpal Tunnel Syndrome")
    - Ulnar neuropathy
    - Brachial plexus neuropathy
    - Peroneal neuropathy
- Cranial neuropathies
    - Ocular neuropathies (Third and Sixth Cranial Nerves)

Autonomic Neuropathies

- Cardiac Autonomic Neuropathy
- Gastropathy/Enteropathy
- Cystopathy
- Sexual Dysfunction
- Sweating irregularities (sudomotor neuropathy)
- Hypoglycemia-associated autonomic failure
- Although involvement of the autonomic nervous system is generally diffuse (as in diabetic pandysautonomia listed above), symptoms may be confined to a single target organ or organ system.

Prevention

- The Diabetes Control and Complications Trial demonstrated a dramatic 5-year risk reduction (57-69%) in the onset of diabetic polyneuropathy in those free of this complication at baseline.
- Furthermore, the United Kingdom Prospective Diabetes Study in patients with type 2 diabetes showed that a policy of intensive glycemic control compared with more standard therapy maintained for 9 years resulted in improved markers of diabetic polyneuropathy.
- Glycemic control is the only proven modality for the prevention of the onset and the progression of diabetic polyneuropathy. Clinical trial evidence for therapy against the other forms of diabetic neuropathy does not exist.

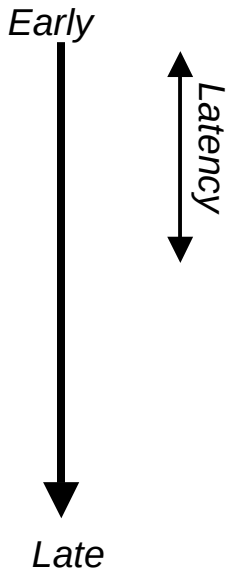
Clinical Presentation and Management

Diabetic Sensorimotor Polyneuropathy

The natural history of diabetic sensorimotor polyneuropathy is described in **Figure 16.1**. Clinically, this presents as progressive sensory loss (diabetic sensory polyneuropathy) in a stocking-and-glove distribution often associated with pain, and eventually complicated by motor impairment (diabetic sensorimotor polyneuropathy)and the late-stage sequelae of infection, ulceration, deformity, amputation, and Charcot deformity. Autonomic dysfunction frequently accompanies late-stage polyneuropathy.

FIGURE 16.1 Diabetic Sensorimotor Polyneuropathy: Classical Features

- Generalized asymptomatic dysfunction of peripheral nerve fibers
- Detectable by NCS, heartbeat deep-breathing and valsalva abnormality
- Decrease or loss of vibration sensation at the great toes
- Panmodality sensory loss of the toes, feet, distal legs
- Abnormal tendon reflexes
- Autonomic abnormalities
- Weakness of small foot muscles and of ankle dorsiflexion



- Given the latency phase seen in Figure 16.1, screening is important for the identification of diabetic sensorimotor polyneuropathy, for intervention with improved glycemic control, and for institution of foot care programs to prevent the late-stage complications.
- In atypical presentations, neuropathies due to uremia, toxins, nutritional deficiencies, neoplasia, drugs, autoimmune and genetic factors should be considered.
- Charcot deformity is a condition that occurs in patients with advanced polyneuropathy and leads to damage of the joint's architecture. A team approach (orthopaedic surgeon, chiropodist, endocrinologist and diabetes educators) is required for successful management.
- At present, the only proven disease-modifying therapy for polyneuropathy is glycemic control,
- Small fiber polyneuropathy associated with weight loss and cachexia and Hypoglycemic polyneuropathy.
- These conditions share the differential diagnosis of diabetic sensorimotor polyneuropathy. Nerve dysfunction is frequently more rapidly progressive and severe than with diabetic sensorimotor polyneuropathy.

Truncal Radiculoneuopathy and Proximal Neuropathy

- Truncal radiculoneuropathy presents with pain in the distribution of a nerve root on the torso of the body.
- Proximal neuropathy presents with marked pain and muscle wasting of the thighs.
- Both conditions are hypothesized to have an inflammatory and/or ischemic etiology.
- These occur primarily in older men with type 2 diabetes, and do not appear to accompany other complications.
- In striking contrast to diabetic polyneuropathy, these conditions have a relatively acute onset, run a clearly-defined course with remission occurring within 6-18 months, generally without further recurrence.
- Treatment is supportive and aimed at optimization of glycemic control.

Limb and Cranial Mononeuropathies

- The most common upper limb mononeuropathy is median nerve impairment (the "carpal tunnel syndrome".
- Entrapment of a susceptible nerve, as a result of underlying subclinical diffuse nerve injury, likely explains the increased incidence in diabetes patients.
- Treatment includes a trial of conservative measures (splints), and surgical release when conservative measures fail.
- Third nerve cranial mononeuropathy typically presents with diplopia and ptosis (and sparing of pupillary responses) occurring with acute onset usually over hours and associated with ipsilateral headache.
- Therapy is aimed at optimization of glycemic control and eye patch for suppressing diplopia during the recovery phase.

Autonomic Neuropathy

- Cardiac autonomic neuropathy often accompanies diabetic sensorimotor polyneuropathy, and results in abnormalities in heart rate control and vascular dynamics. These are manifested by exercise intolerance, intra-operative cardiovascular lability, orthostatic hypotension, and silent myocardial ischemia.
- Further clinical manifestations of autonomic neuropathy include gustatory sweating, gastroparesis, diarrhea, fecal incontinence, urinary retention, retrograde ejaculation, and impotence.
- Hypoglycemia associated autonomic failure is characterized by defective glucose counter-regulation and hypoglycemia unawareness.

Clinical Practice Recommendations

- Screening for diabetic sensorimotor polyneuropathy should be carried out annually to identify those at high risk of developing foot ulcers.
- Detection of diabetic sensorimotor polyneuropathy should be done by assessing loss of sensitivity to the 10-g monofilament at the great toe or loss of sensitivity to vibration at the great toe. A protocol for these screening maneuvers can be found in Perkins et al. 2002, cited below.
- People with type 1 and type 2 diabetes should be treated with intensive glycemic control management to delay the onset and slow the progression of polyneuropathy.
- Tricyclic antidepressants and/or anticonvulsants should be considered for relief of painful polyneuropathy. An example is the use of amitriptyline 10 mg taken nightly and increased by 10mg per week titrating for treatment effect and the development of side effects.
- Carpal tunnel syndrome should be diagnosed on clinical grounds and managed accordingly with supplementary electrophysiological testing as needed in patients with diabetes.
- People with clinically significant autonomic dysfunction should be appropriately assessed and referred to a specialist experienced in managing the affected body system.

16.5 The Diabetic Foot

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- A strategy to prevent lower limb amputation should be developed by each diabetes team.
- Prevention of foot ulcers should start with patient education.
- For those who are unable to perform such care, ongoing chiropody or podiatry care should be implemented.

- Aggressive treatment of foot injuries, infections and ulcers can lead to decreased possibility of amputation.
- A multidisciplinary approach is required, where a chiropodist or podiatrist will work in concert with the diabetes health care team, an orthopaedic surgeon, a vascular surgeon, orthotics technician and other disciplines.
- Patients at a higher risk for lower extremity amputation include those with peripheral vascular disease, neuropathy, cigarette smoking, and anatomical deformities of the feet and abnormal gait.
- Encourage frequent self-inspection of feet by subjects to detect injury, minor ulcers, or abrasion.

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