UNIT NO. 5

COMPLICATIONS OF DIABETES MELLITUS

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ABSTRACT

Long-term complications are the major cause of morbidity and mortality in diabetes mellitus. In recent years, major advances have been made in the understanding of the pathophysiology of diabetic complications. Tight control of hyperglycemia and hypertension are important in preventing or delaying microvascular complications seen in both type 1 and type 2 diabetes. In type 2 diabetes, the major abnormality is loss of insulin sensitivity arising from central obesity. Weight control is therefore central to the control of this type of diabetes mellitus. Regular screening for complications for timely intervention is an important aspect of diabetes care.

INTRODUCTION

Long-term complications are the major cause of morbidity and mortality in diabetes mellitus. In recent years, major advances have been made in the understanding of the pathophysiology of diabetic complications. The major aim of diabetes management is to prevent complications.

The manifestation of diabetic complications is protean. The major complications include cardiovascular diseases, retinopathy, nephropathy and neuropathy. For a better understanding of the underlying pathophysiology, these complications are classified as macrovascular (affecting large arteries) and microvascular (affecting capillaries and small blood vessels) as shown in Table 1.

Table 1. Complications in diabetes

Macrovascular disease	Microvascular disease
o Coronary artery disease: angina, myocardial infarction, cardiac failure. o Peripheral vascular disease o Cerebrovascular disease: transient ischaemic attack; stroke	o Diabetic retinopathy: non-proliferative, proliferative, macular edema o Nephropathy: microalbuminuria, macroalbuminuria, end-stage renal disease o Amputation o Neuropathy: peripheral neuropathy, Autonomic neuropathy o Erectile dysfunction

The frequency and types of complications depends on the type of diabetes. In Type 2 diabetes, macrovascular complications are the major cause of morbidity and mortality[1]. Microvacular complications are also often present when diabetes is diagnosed, even in people with no symptoms. This clinical picture becomes apparent once we understand that the main pathogenic driving forces in type 2 diabetes mellitus are insulin resistance (and associated cardiovascular dysmetabolic syndrome) and hyperglycemia. Both factors contribute to profound alterations in metabolic and cell signaling pathways leading to abnormal tissue glyco-lipidation and enhanced oxidative stress. These insights form the foundation of our current therapy and will shape the future of the development of novel interventions. Attention to reduction of obesity restores the sensitivity to insulin for instance.

In Type 1 diabetes, the main driving force is hyperglycemia due to lack of insulin. Other risk factors, such as hypertension and dyslipidaemia, may occur secondary to uncontrolled hyperglycaemia or renal disease. Complications are therefore usually acquired only after diagnosis, unlike in type 2 diabetes where complications can be present at diagnosis[2].

MACROVASCULAR COMPLICATIONS

Macrovascular complications include coronary artery disease, peripheral artery disease (PAD), and strokes.

Coronary artery disease

Type 2 diabetes confers a two to four folds increase risk of coronary artery disease and abolishes the protectiveness of female sex observed in non-diabetic population[3]. In fact, the pre-diabetic state (manifesting as impaired fasting glucose or impaired glucose tolerance) is already associated with increased cardiovascular burden. In recent years, it is gaining acceptance to regard diabetes (type 2) per se as coronary artery disease risk equivalent. Therefore, aggressive risk factors interventions (blood pressure control and lipid level control) have been recommended once diabetes is present. An annual resting 12-lead electrocardiogram appears reasonable in asymptomatic subject. However, the best mode of screening for ischemic heart disease among asymptomatic subjects remains to be established.

Peripheral artery disease (PAD)

Peripheral artery disease (PAD) is a condition characterized by atherosclerotic occlusive disease of the lower extremities. Diabetes and smoking are the strongest risk factors for PAD. Other well known risk factors are advanced age, hypertension, and hyperlipidemia[4]. It is important to note that diabetes is most strongly associated with femoral-popliteal and tibial (below the knee) PAD, whereas other

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risk factors (e.g., smoking and hypertension) are associated with more proximal disease in the aorto-ilio-femoral vessels.

It is important to diagnose PAD in patients with diabetes. In contrast to PAD in nondiabetic individuals, it is more prevalent, and because of the distal territory of vessel involvement and its association with peripheral neuropathy, it is more commonly asymptomatic. Patients with PAD and diabetes thus may present later with more severe disease and have a greater risk of amputation[4].

PAD should be screened by palpation of peripheral pulses. However, a high degree of inter-observer variability has been found. In contrast, the ankle brachial index is a reproducible and reasonably accurate, noninvasive measurement of for the detection of PAD. The diagnostic criteria for PAD based on the ABI are interpreted as follows: Normal if 0.91–1.30; Mild obstruction if 0.70–0.90; Moderate obstruction if 0.40–0.69; Severe obstruction if <0.40; Poorly compressible if >1.30. Referral for specialized assessment needs to be considered when subject is symptomatic or when ABI is abnormal. It is recommended that patients with diabetes who are 50 years or older have an ABI done. An ABI is also useful in patients with other PAD risk factors and in those with symptoms.

Stroke

The literature describing the relationship between diabetes and stroke has been reviewed in 1994 by Bell[5]. The conclusion is that most ischaemic strokes in diabetic patients are due to occlusion of small paramedical penetrating arteries. These occlusions cause small infarcts within the white matter of the brain.

Some idea of the contribution to diabetes to strokes can be seen in the Multiple Risk Factor Intervention Trial (MRFIT) in 1973-75 where a 12-year mortality was determined for 5,163 men age 35-37 years who reported taking medication for diabetes and 324,815 men without a history of diabetes[6]. The risk of mortality from stroke was increased 2.8-fold (95% confidence interval (CI) 2.0-3.7) among those with diabetes, even after adjusting for age, race, income and cardiovascular risk factors.

The Nurses Health Study showed the age-adjusted risk of stroke for diabetic versus non-diabetic women to be 4.1 (95% CI 2.8-6.1). The risk was similar for fatal (5.0) and nonfatal (3.8) strokes[7].

In the MRFIT study, the risk was also found to be increased among both diabetic and nondiabetic men with increasing blood pressure levels (systolic and diastolic), blood cholesterol level, and number of cigarettes smoked[8]. It is therefore important to regard stroke not as an inevitable consequence of diabetes and aging but take the view that aggressive efforts to prevent stroke will make a difference.

MICROVASCULAR COMPLICATIONS

The major mechanism of microvascular disease is the toxic effect of prolonged hyperglycaemia, with hypertension a further exacerbating factor. Microvascular complications seldom occur in isolation. Screening for microvascular disease enables intervention at the earliest possible stage. This will maximise the effectiveness of treatment. Data from trials over the past 10 years show that controlling hyperglycaemia and hypertension reduces microvascular complications not only in type 1 diabetes but in type 2 diabetes as well[2].

Retinopathy

Diabetic retinopathy is the leading cause of blindness in the adult population. In type 1 diabetes, almost all patients develop signs of retinopathy in the first 20 years. In type 2 diabetes, data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that more than one third of patients had signs of retinopathy at entry, with about 5% of the cases presenting with signs of advanced retinopathy[9]. This one-third prevalence of retinopathy increases to two- thirds within 20 years[2,10].

Table 2. International Clinical Diabetic Retinopathy Disease Severity Scale

Proposed Disease Severity Level	Findings Observable on Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Nonproliferative diabetic retinopathy (NPDR)	
o Mild	Microaneurysms only
o Moderate	More than just microaneurysms but less than severe nonproliferative diabetic retinopathy
o Severe	Any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants; definite venous beading in 2+ quadrants; Prominent intraretinal microvascular abnormalities in 1+ quadrant And no signs of proliferative retinopathy
Proliferative diabetic retinopathy (PDR)	One or more of the following: neovascularization, vitreous/preretinal hemorrhage

Source: Wilknson et al, American Academy of Ophthalmology, 2003

An international clinical classification system based on severity of diabetic retinopathy and diabetic macular edema is shown in Table 2. This is a five-stage disease severity classification made up of three stages of low risk, a fourth stage of severe nonproliferative retinopathy, and a fifth stage of proliferative retinopathy. Diabetic macular edema is classified as apparently present or apparently absent. This system is based on the Early Treatment Diabetic Retinopathy Study and Wisconsin Epidemiology Study of Diabetic Retinopathy classification and developed through a consensus process. The aims of this system are such that it could be used around the world, and to improve communication and coordination of care among physicians who care people with diabetes[11].

Table 3. Eye Examination Schedule*

Type of diabetes mellitus	Recommended Initial Eye Examination	Routine Follow-Up
Type 1	5 years after onset or during puberty	Yearly
Type 2	At time of diagnosis	Yearly
Pregnancy with pre-existing DM		Early in first trimester Each trimester or more frequently as indicated Six weeks postpartum

Source: Aiello, 2003. Note: = Abnormal findings will dictate more frequent follow-up examinations (Table 2).*

In the earliest stages of diabetic retinopathy, the characteristic abnormality is increased vascular permeability. Without treatment, microvascular occlusions occur, resulting in retinal ischaemia and, eventually, the growth of new vessels, namely, proliferative retinopathy. Macular oedema, caused by increased vascular permeability, may occur at any stage.

Screening for retinopathy should be regularly taken. Otherwise, diabetic retinopathy progresses silently until visual loss occurs. Table 3 shows such an eye examination schedule[12]. Patients with type 2 diabetes should have an initial dilated eye examination at time of diagnosis and also yearly. For a type 2 diabetes patient, the recommended initial eye examination is 5 years after onset or during puberty and yearly thereafter.

Referral to ophthalmologist needs to be considered when moderate NPDR or higher grade retinopathy is detected. Retinopathy is treated with laser photocoagulation, which usually prevents further loss but generally does not restore vision. For proliferative and severe non-proliferative retinopathy, pan-retinal laser photocoagulation is used. The greatest benefit is in patients with high-risk changes (new vessels on the optic disc or vitreous haemorrhage). Clinically significant macular oedema is treated with focal laser photocoagulation therapy.

Diabetic Nephropathy

The most common cause of end-stage renal disease (ESRD) is diabetic nephropathy. About 20%–30% of patients with diabetes have evidence of overt diabetic nephropathy, defined as persistent clinically detectable proteinuria in association with hypertension and reduced glomerular filtration rate[2].

The earliest clinical evidence of nephropathynis the appearance of low but abnormal levels (>30 mg/day) of albumin in the urine, referred to as microalbuminuria, and patients with microalbuminuria are referred to as having incipient nephropathy. A test for the presence of microalbumin should be performed at diagnosis in patients with type 2 diabetes. Microalbuminuria rarely occurs with short duration of type 1 diabetes; therefore, screening in individuals with type 1 diabetes should begin after 5 years' disease duration.

Screening for microalbuminuria can be performed by three methods: 1) measurement of the albumin-to-creatinine ratio in a random spot collection; 2) 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance; and 3) timed (e.g., 4-h or overnight) collection. The first method is often found to be the easiest to carry out in an office setting, generally provides accurate information, and is therefore preferred; first-void or other morning collections are best because of the known diurnal variation in albumin excretion, but if this timing cannot be used, uniformity of timing for different collections in the same individual should be employed.

Microalbuminuria is said to be present if urinary albumin excretion is > 30 mg/g creatinine on a random sample (equivalent to 20 mg/min on a timed specimen or > 30 mg/24 h). All positive tests by reagent strips or tablets should be confirmed by more specific methods. There is also marked day-to-day variability in albumin excretion, so at least two of three collections done in a 3- to 6-month period should show elevated levels before designating a patient as having microalbuminuria.

Peripheral Neuropathy

The presence of peripheral neuropathy is one of the three major risk factors for foot ulcers and amputations in people with diabetes. The other two are altered biomechanics in the foot and peripheral vascular disease. An important point to note is about half of all lower-limb amputations in people with diabetes are preventable. Amitryptyline, carbamazepine and gabapentin are helpful in the symptomatic management of painful neuropathy.

Controlling hyperglycaemia and hypertension and identifying patients with peripheral neuropathy or peripheral vascular disease are the mainstays of preventing foot complications. All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions. This examination should include assessment of protective sensation, foot structure and biomechanics, vascular status, and skin integrity. People with one or more high-risk foot conditions should be evaluated more frequently for the development of additional risk factors.

People with neuropathy should have a visual inspection of their feet at every visit with a health care professional. Evaluation of neurological status in the low-risk foot should include a quantitative somatosensory threshold test, using the Semmes-Weinstein 5.07 (10-g) monofilament. Patients with diabetes with increased and high-risk foot conditions should be educated regarding their risk factors and appropriate management. One useful quick reference guide on prevention and management of foot problems in type 2 diabetes is that produced by the College of General Physicians and updated by by the National Institute for Clinical Excellence in the United Kingdom[13].

All patients should be educated about daily foot care namely, inspection, washing and careful drying, moisturizer use for dry skin and cracked heels, nail-care and use of practical footwear. Particular care should be taken with new footwear.

INTERVENTIONS

Preventing macrovascular complications

Reduction of the global vascular risk factors is the key to the prevention of macrovascular diabetic complications in type 2 diabetes. This has been borne out by a Danish study which found that macrovascular complications in patients at high risk can be reduced through a multifactorial approach involving behaviour modification and pharmacological therapy targeting hyperglycaemia, hypertension, dyslipidaemia, microalbuminuria, and also low-dose aspirin[1]. This treatment was associated with an impressive reduction in cardiovascular events, equivalent to a number needed to treat for 5 years of 3.2, as well as significant reductions in diabetic nephropathy and retinopathy. The targets shown in Table 4 are recommended for most subjects with diabetes.

Table 4. Summary of recommendations for adults with diabetes

Glycemic control	
AIC	<7.0%
Blood pressure	<130/80 mmHg
Lipids	
LDL	<100 mg/dl (2.6 mmol/l)
Triglycerides	<150 mg/dl (1.7 mmol/l)
HDL	<40 mg/dl (1.1 mmol/l)

Control of hyperglycemia

The UKPDS showed that intensive control of hyperglycaemia with sulfonylurea or insulin did not significantly reduce the risk of myocardial infarction or stroke ($P = 0.05$)[14,15]. However, subgroup analysis of 342 obese patients suggested that metformin therapy reduced the risk of myocardial infarction. Thus, metformin is the drug of first choice in overweight patients with type 2 diabetes[16].

Control of hypertension

At diagnosis of patients with type 2 diabetes, a proportion of them have either a raised blood pressure or were already receiving treatment for hypertension. The Hypertension in Diabetes Study (HDS) which was a nested substudy within the main UKPDS showed that for each 10 mm Hg reduction in mean systolic blood pressure there was a 11% reduction in myocardial infarctions, and a 15% reduction of deaths related to diabetes. There was also a 13% reduction in microvascular end-points[17].

Treatment of hypertension should be prioritized and stressed as the most important intervention for the average population of persons with type 2 diabetes. Blood pressure targets should be 135/80 mm Hg. First choice agents should probably be thiazide diurectics, angiotensin II receptor blockers, or ACE inhibitors. Second choice agents should be beta-blockers or calcium channel blockers. Aggressive control of blood pressure in patients with type 2 diabetes has dramatic benefits and should be the first priority in diabetes care[18].

Controlling dyslipidemia

Given the two to four folds increase for cardiovascular events in most persons with type diabetes, preventing cardiovascular disease through aggressive management of cardiovascular risk factors is of great importance. Optimising treatment for hypertension as described above, smoking cessation, and lipid control provides substantial benefit, at least to the average patient with type 2 diabetes. The evidence suggests that lipid-lowering leads to a 22% to 24% reduction in major cardiovascular events with patients with diabetes. Statins are the agents of choice[19].

Based on a systematic review of the currently available evidence in the management in people with type 2 diabetes mellitus, the American College of Physicians has developed a clinical practice guideline for lipid control in the management of type 2 diabetes mellitus. The target audience for this guideline is all internists and primary care physicians who care for patients with type 2 diabetes. The target patient population is all persons with type 2 diabetes, including those who already have some form of microvascular complication and, of particular importance, premenopausal women[19]. There are four recommendations in this guideline, namely:

- Recommendation 1: Lipid-lowering therapy should be used for secondary prevention of cardiovascular mortality and morbidity for all patients (both men and women) with known coronary artery disease and type 2 diabetes.
- Recommendation 2: Statins should be used for primary prevention against macrovascular complications in patients (both men and women) with type 2 diabetes and other cardiovascular risk factors.
- Recommendation 3: Once lipid-lowering is initiated, patients with type 2 diabetes mellitus should be taking moderate doses of a statin (Table 5).
- Recommendation 4: For those patients with type 2 diabetes who are taking statins, routine monitoring of liver function tests or muscle enzymes is not recommended except in specific circumstances. These are patients who have symptoms of statin-associated myopathy, have baseline abnormalities of liver function tests or myopathy, or are taking other drugs that interact with statins to increase the risk for adverse events.

Table 5. Treatments Used in the Trials Reviewed

Primary prevention trials
Atorvastatin, 10-20 mg/d
Lovastatin, 20-40 mg/d
Pravastatin, 40 mg/d
Simvastatin, 40 mg/d
Secondary prevention trials
Fluvastatin, 80 mg/d
Lovastatin, 40-80 mg/d
Pravastatin, 40 mg/d
Simvastatin, 20 mg/d and 40 mg/d
Gemfibrozil, 1200 mg/d (for secondary prevention in patients with low levels of both low-density and high-density lipoprotein cholesterol)

Source: Snow et al, 2004

Smoking cessation

Smoking result in increase in insulin resistance. Prospectively, the increased risk for complications in type 2 diabetes is around 50%. Cigarette smoking increase the risk for diabetic nephropathy, retinopathy, and neuropathy, probably via its metabolic effects in combination with increased inflammation and endothelial dysfunction. This association is strongest in type 1 diabetic patients. The increased risk for macrovascular complications, namely, coronary heart disease (HD), stroke and peripheral vascular disease, is most pronounced in type 2 diabetic patients. The development of type 2 diabetes is another possible consequence of cigarette smoking, besides the better known increased risk for CHD. Hence, in diabetes care, smoking cessation is of utmost importance to facilitate glycaemic control and limit the development of diabetic complications[20].

Aspirin

Low-dose aspirin therapy is recommended for all people with diabetes and another risk factor, such as hypertension[21,22].

Preventing microvascular complications

The strategy for preventing microvascular complication lies in the tight control of hyperglycemia and hypertension.

Control of hyperglycaemia

The Diabetes Control and Complications Trial[23] and the UKPDS[24] established the importance of intensive blood-glucose control in reducing the risk of microvascular complications (target HbA1c level ≤7%). For both diabetic retinopathy and nephropathy, the benefit of good glycaemic control appears to be greatest in the early stages.

Control of hypertension

Treatment of hypertension reduces the development and progression of microvascular complications in diabetes. Most of the supporting evidence comes from trials of the effects of inhibitors of the renin-angiotensin system on diabetic nephropathy. Drugs inhibiting this system, such as ACE inhibitors and angiotensin II receptor antagonists, generally have a greater benefit than other classes of anti-hypertensive drugs[2].

CONCLUSION

Type 1 and type 2 diabetes mellitus have different pathophysiological pathways. As such the complications are different. Tight control of hyperglyecemia and hypertention are important in preventing or delaying microvascular complications seen in both type 1 and type 2 diabetes. In type 2 diabetes, the major abnormality is loss of insulin sensitivity arising from central obesity. Weight control is therefore central to the control of this type of diabetes mellitus. Regular screening for complications for timely intervention is an important aspect of diabetes care.

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FURTHER READING

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LEARNING POINTS

- **Microvascular complications are the major risk in type 1 diabetes, while macrovascular complications are the major cause of morbidity and mortality in type 2 diabetes.**
- **A multifactorial approach, comprising behaviour modification and pharmacological therapy for all risk factors, reduces the development of micro- and macrovascular complications in type 2 diabetes.**
- **The benefit of treating dyslipidaemia is at least as great in the diabetic population as in the non-diabetic population.**
- **Regular annual screening for diabetes complications allows treatable disease to be identified.**