

Everyday Practice: Diabetes Mellitus

Treatment of diabetes mellitus: Beyond glycaemic control

RANJIT UNNIKRISHNAN I., V. MOHAN

INTRODUCTION

Type 2 diabetes mellitus has emerged as the leading metabolic disorder worldwide, affecting more than 350 million individuals as of 2007. India is the 'diabetic capital' of the world, with 41 million people afflicted with the disease. The clinical importance of diabetes lies mainly in its propensity to produce macrovascular and microvascular complications, leading to cardiovascular disease, cerebrovascular disease, retinopathy, nephropathy, neuropathy and foot problems, which account for considerable morbidity and mortality throughout the world.

Two landmark clinical trials—the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS)—established beyond doubt the importance of tight glycaemic control in preventing or delaying the complications of diabetes. Maintaining good control of blood sugar, as evidenced by a glycated haemoglobin level of <7%, can reduce the risk of diabetic retinopathy and nephropathy to negligible levels. However, in these trials, a similar impressive reduction was not found in the case of macrovascular complications, namely, cardiovascular and cerebrovascular disease. This leads one to presume that a comprehensive programme of risk reduction, looking beyond just glycaemic control, would be needed in order to reduce cardiovascular events in people with diabetes. This is of particular relevance to India as Asian Indians have been found to have an extremely high prevalence of cardiovascular disease.

THE CONCEPT OF GLOBAL CARDIOVASCULAR RISK

An individual's risk of developing cardiovascular disease depends on the presence or absence of a number of risk factors, hyperglycaemia being only one of them. These factors act either additively or multiplicatively to determine the global cardiovascular risk of the individual. The most important of these risk factors have been included in the definition of the metabolic syndrome. These are central obesity, dyslipidaemia, fasting hyperglycaemia and hypertension. In addition to these conventional risk factors, newer markers such as C-reactive protein and platelet activator inhibitor-1 (PAI-1) have also been the subject of intense study. No less important are behavioural factors such as smoking and physical activity. Any programme to reduce cardiovascular risk must target all these factors if it is to succeed.

We focus on the control of 'conventional' risk factors in people with diabetes, as these have been found to contribute to >90% of the cardiovascular burden of risk.

Madras Diabetes Research Foundation and Dr Mohan's Diabetes Specialities Centre, 4, Conran Smith Road, Gopalapuram, Chennai 600086, Tamil Nadu, India

RANJIT UNNIKRISHNAN I., V. MOHAN

Correspondence to RANJIT UNNIKRISHNAN I.;
unnikrishnan_ranjit@yahoo.com

© The National Medical Journal of India 2007

LIPIDS

As a result of defects in insulin secretion and insulin action, patients with type 2 diabetes are at risk of developing an atherogenic lipid profile. The main features of the so-called 'diabetic dyslipidaemia' are:

1. Elevated levels of triglycerides
2. Low levels of high density lipoprotein (HDL) cholesterol
3. High, normal or low levels of low density lipoprotein (LDL) cholesterol, associated with an increase in the highly atherogenic small dense LDL particles.

The lipid profile should be checked at least annually in persons with diabetes, and more often if not at the target levels (Table I).

Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol and lowering triglycerides has been shown to reduce macrovascular disease and mortality in people with type 2 diabetes, particularly in those who have had prior cardiovascular events. Recent trials suggest that aggressive lowering of LDL to <70 mg/dl can lead to significant reduction in cardiovascular events. The following points may be kept in mind when treating diabetic dyslipidaemia.

1. Any patient with dyslipidaemia should be offered a trial of therapeutic lifestyle change. Exceptions include those with prior cardiovascular or cerebrovascular disease and an LDL >100 mg/dl, or those at risk of acute complications of hyperlipidaemia (e.g. acute pancreatitis from hypertriglyceridaemia). In such people, pharmacotherapy should be initiated at the same time as therapeutic lifestyle change.
2. Improvement in glycaemic control can in itself lead to improvement in certain lipid levels (e.g. triglycerides).
3. Patients who fail to respond to a therapeutic lifestyle change are candidates for drug therapy. The primary goal of drug therapy is to reduce LDL to target levels. Statins are the drug of choice for this purpose. Other drugs that lower LDL include nicotinic acid, ezetimibe, bile acid sequestrants and fenofibrate.
4. If the HDL is low, niacin may be added to the regimen.
5. In those with elevated triglycerides and normal cholesterol levels, a fibrate would be the drug of choice.

TABLE I. Targets for lipid levels in people with diabetes

Lipid level (mg/dl)	People with diabetes	
	without vascular complications	with vascular complications
Triglyceride	<150	<120
<i>Cholesterol</i>		
Total	<200	<180
Low density lipoprotein	<100	<70
High density lipoprotein	>45	>45

TABLE II. Doses, side-effects and contraindications of commonly used lipid-lowering drugs

Class of drug	Effect on lipids	Drug and daily dose	Side-effects	Contraindications
HMG-CoA reductase inhibitors (statins)	↓TC ↓↓LDL	Simvastatin (5–40 mg) Atorvastatin (5–80 mg) Rosuvastatin (5–20 mg)	Myopathy, altered liver function tests, nausea, vomiting	Pregnancy, impaired liver function
Fibric acid derivatives (Fibrates)	↓↓TG ↑HDL	Gemfibrozil (900–1500 mg) Bezafibrate (600–800 mg) Fenofibrate (67–200 mg)	Myopathy, altered liver function tests, increase in serum creatinine (fenofibrate)	Pregnancy, impaired liver function, gallstones
Niacin	↓TC ↓TG ↑↑HDL	Niacin (375 mg–6 g)	Flushing, activation of peptic ulcer, hyperglycaemia	Pregnancy, hepatic disease, active peptic ulcer
Ezetimibe	↓LDL	Ezetimibe (10 mg)	Diarrhoea, abdominal pain	Pregnancy

HMG CoA hydroxymethyl glutaryl coenzyme A TC total cholesterol TG triglycerides LDL low density lipoprotein HDL high density lipoprotein

6. Combination therapy with a statin and a fibrate or statin and niacin, may be efficacious for those needing treatment for all 3 lipid fractions, but this combination is associated with an increased risk of elevated liver enzymes and myopathy. Data are not available on reduction of vascular events with such combinations.

The usual doses, contraindications and side-effects of the commonly used lipid-lowering agents are listed in Table II.

In addition to their cholesterol-lowering effect, statins also have other beneficial ('pleiotropic') effects on atherogenesis (Table III).

HYPERTENSION

Hypertension is twice as common in persons with diabetes compared with those who do not have diabetes. In addition to contributing to cardiovascular risk, hypertension is also a major risk factor for stroke as well as in the development and progression of diabetic retinopathy and nephropathy.

Randomized clinical trials have demonstrated the benefit of lowering blood pressure to <140 mmHg systolic and <80 mmHg diastolic in people with diabetes. Epidemiological analyses show that blood pressure >115/75 mmHg is associated with increased rates of cardiovascular events and mortality in people with diabetes. Therefore, a target blood pressure of <130/80 mmHg is desirable in all persons with diabetes. In those with proteinuria, a goal of 125/75 mmHg should be set.

The blood pressure should be measured at every follow up visit. Those who have a systolic blood pressure ≥130 mmHg or diastolic blood pressure 80 mmHg should have a confirmation of their blood pressure on a separate day.

Lifestyle modifications include reducing sodium intake and body weight; increasing consumption of fruits, vegetables and low-fat dairy products; exercise, moderation in consumption of alcohol and increasing activity levels can be tried for 3 months in those presenting with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg (pre-hypertension as per the Seventh Report of the Joint National Committee [JNC-7]). Those who fail to respond to lifestyle modification or those presenting with a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg should be started on drug therapy. The following points should be kept in mind while prescribing antihypertensive agents for people with diabetes.

1. Most patients need more than one drug to achieve target levels of blood pressure.
2. Initial drug therapy should be with a class of drugs proven to

TABLE III. Pleiotropic effects of statins

1. Improvement of endothelial dysfunction
2. Increased nitric oxide bioavailability
3. Antioxidant properties
4. Inhibition of inflammatory responses
5. Stabilization of atherosclerotic plaques

reduce cardiovascular events (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARB], beta-blockers, diuretics and calcium-channel blockers).

3. All regimens should contain an ACE inhibitor or an ARB. Not only have these agents been shown to reduce the risk of cardiovascular disease, but they also prevent and retard the development of diabetic nephropathy.
4. A thiazide diuretic can be added if needed to achieve the target blood pressure levels.
5. Blood pressure should be reduced gradually in elderly patients.
6. Check the blood pressure in the supine and erect positions separately if orthostatic hypotension is suspected.

The dosage, side-effects and contraindications of the 5 common classes of antihypertensive drugs are listed in Table IV.

ANTIPLATELET AGENTS

Aspirin is recommended for all people with diabetes as primary or secondary prevention for cardiovascular events. Several trials have shown an up to 30% reduction in myocardial infarction rates and 20% reduction in stroke rates when aspirin is used.

1. Aspirin is indicated for secondary prevention in people with diabetes with a history of cardiovascular and cerebrovascular disease.
2. It is also recommended as primary prevention in people with type 2 diabetes who are above 40 years of age and in those who have additional cardiovascular risk factors such as family history, smoking, hypertension or dyslipidaemia.
3. Aspirin is not recommended for people below the age of 21 years due to the risk of Reye syndrome.
4. Doses of aspirin from 75 to 325 mg/day have been used. It is best to treat with lower doses in order to minimize side-effects.
5. Those who are unable to tolerate aspirin may be candidates for other antiplatelet agents (e.g. clopidogrel).
6. Combination therapy with aspirin and clopidogrel may be considered in those with severe and progressive cardiovascular or cerebrovascular disease.

TABLE IV. Doses, side-effects and contraindications of commonly used antihypertensive drugs

Class of drug	Drug and daily dose	Side-effects	Contraindications
Diuretics	Hydrochlorothiazide (25–50 mg) Indapamide (1.5–2.5 mg)	Hypokalaemia, hyponatraemia, hyperuricaemia, hyperglycaemia	Anuric renal failure, hepatic failure, hypercalcaemia, pregnancy
Beta-blockers	Atenolol (50–200 mg) Metoprolol (100–450 mg) Bisoprolol (5–10 mg) Nebivolol (2.5–5 mg)	Bradycardia, fatigue	Bronchial asthma, heart block, peripheral vascular disease, severe heart failure
Angiotensin-converting enzyme inhibitors	Enalapril (2.5–40 mg) Ramipril (1.25–20 mg) Lisinopril (2.5–40 mg) Perindopril (2–4 mg)	Dry cough, hyperkalaemia, renal failure	Bilateral renal artery stenosis, pregnancy
Angiotensin receptor blockers	Losartan (25–100 mg) Irbesartan (150–300 mg) Valsartan (40–160 mg) Telmisartan (20–80 mg)	Headache Dizziness Hyperkalaemia	Bilateral renal artery stenosis, pregnancy
Calcium-channel blockers (dihydropyridines are preferred as antihypertensives)	<i>Dihydropyridines</i> Amlodipine (2.5–10 mg) Nifedipine (5–40 mg) <i>Non-dihydropyridines</i> Verapamil (40–480 mg) Diltiazem (60–240 mg)	Headache, pedal oedema, flushing, palpitation Nausea, constipation	Cardiogenic shock, acute myocardial infarction Congestive cardiac failure, heart block

CESSATION OF SMOKING

Smoking is the most important modifiable cause of premature death. A large body of evidence links smoking with heightened risk of premature morbidity and mortality. In persons with diabetes, not only does smoking accelerate the development of macrovascular complications, but it has also been shown to adversely affect microvascular complications such as nephropathy. Cessation of smoking is one of the most cost-effective means of reducing the cardiovascular risk in people with diabetes.

A history of tobacco use should be asked for and those who smoke should be strongly advised to quit. Counselling for cessation of smoking should be made an integral part of diabetes care.

SCREENING FOR COMPLICATIONS OF DIABETES

Complications of diabetes account for most of the morbidity and mortality due to the disease. An important aspect of diabetes care beyond glycaemic control is to screen for these complications, so as to detect them at a stage when effective treatment can be instituted. Comprehensive screening for these complications includes the following:

1. Regular assessment of cardiovascular risk factors as described above.
2. Diagnostic cardiac stress testing in individuals with symptoms

of cardiovascular disease or those with abnormal resting ECG. The role of stress testing in asymptomatic individuals with normal ECG is controversial.

3. Estimation of microalbuminuria, serum creatinine and estimated glomerular filtration rate (eGFR) at least annually, starting from 5 years after diagnosis for those with type 1 and at diagnosis for those with type 2 diabetes.
4. Annual dilated retinal examinations starting at diagnosis in type 2 diabetes and at 5 years after diagnosis in type 1 diabetes.
5. Detailed foot examination with assessment of sensation and pedal pulses at each visit.

Any of these screening procedures should be performed more frequently if any abnormality is detected.

CONCLUSION

Type 2 diabetes has reached epidemic proportions in India. The large number of people with diabetes in India translates into a huge population at risk for complications of diabetes. The most important aspect of diabetes care is the maintenance of tight glycaemic control. Nevertheless, to be successful, a diabetes care programme must look beyond glycaemic control and address each of the cardiovascular risk factors prevalent in the community. Such an approach alone can bring about a long-lasting reduction in the prevalence of complications of diabetes.