Treatment priorities for patients with Type 2 Diabetes

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Highlights / Hoogtepunte

- Why should the diabetic patient, who has not had a cardiovascular event, be treated as aggressively as the non-diabetic patient who has already had a cardiovascular event?
- Treatment goals for hypertension and dyslipidaemia in the diabetic patient.
- Prevention and monitoring of microvascular complications.

- Waarom is dit belangrik om 'n tipe 2 diabeet, wat nog geen kardiovaskulêre insident gehad het nie, netso aggressief te behandel as 'n nie-diabeet met 'n vorige kardiovaskulêre insident?
- Mikpunte vir die behandeling van hipertensie en dislipidemie in die diabeet.
- Voorkoming en monitering van mikrovaskulêre komplikasies.

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I. MACROVASCULAR COMPLICATIONS

1. Diabetes and cardiovascular disease

Coronary artery disease (CAD) is a major cause of morbidity and mortality for any diabetic patient. A study published in the NEJM showed that patients with type 2 diabetes who had never had a cardiovascular event **were at the same risk** as non-diabetic patients, who had already had a vascular event, for having a cardiovascular event[1].

CAD occurs more frequently in the diabetic patient with up to 55% of diabetic patients being affected. In addition, the Framingham study[2] showed that diabetes was a **major independent risk factor** for CAD, even when adjustments were made for the known risk factors for CAD i.e. hypercholesterolaemia, smoking, HT, age and LVH. In the MRFIT trial, 9,7% of the diabetic patients died from CAD in a 12-year period[3]. The magnitude of this becomes evident when you appreciate that, in a comparable but non-diabetic group, only 2,6% of the patients died from CAD in the same period. This increased risk is magnified in the female diabetic who would normally be relatively protected in the pre-menopausal period. In patients undergoing elective PTCA or angiography, post thrombolysis, there was a higher incidence of multivessel disease amongst the diabetic patients[4]. This has been confirmed in autopsy studies. Diabetic patients are also more likely to infarct or require further intervention in the next 5 years.

Silent ischaemia, as evidenced by ST-depression and coronary perfusion abnormalities and even infarction, is also more common with respect to the non-diabetic patient. This is thought to be due to autonomic denervation of the heart[5,6]. Parasympathetic dysfunction precedes sympathetic system abnormalities. It results in a resting tachycardia, increased coronary vascular tone and reduced coronary perfusion pressure during hypotension. In addition, there is a prolongation in the time from the onset of ischaemic changes on the ECG to the perception of pain. Thus, a delayed warning system is combined with increased myocardial oxygen demand and reduced blood flow. Autonomic nerve supply to the left ventricle is not uniform, and in the presence of sympathetic dysfunction, myocardial electrical instability can cause life-threatening arrhythmias[7].

Diabetic patients have a higher post-infarct complication rate and mortality *per se*. One study demonstrated fewer collateral vessels with respect to non-diabetic control patients[8].

These factors suggest that the diabetic patient who has not had an event should be treated as aggressively as the non-diabetic patient who has already had a cardiovascular event.

Numerous factors contribute to this increased risk, including hyperlipidaemia, HT, hyperglycaemia, smoking, endothelial dysfunction and platelet function abnormalities. The patient with type 2 DM is often overweight, and thus it is not uncommon to find multiple risk factors present in this patient.

Diabetic patients have an increased incidence of:

- CAD, even in the absence of another risk factor.
- CAD for any given risk factor.
- Multivessel disease.

- Silent ischaemia and infarction.
- Complications post infarction.
- Ischaemia post revascularisation.

2. Dyslipidaemia

The Framingham study demonstrated that diabetic patients had the classic atherogenic lipid profile with raised VLDL and triglyceride levels and a lower HDL level with respect to the non-diabetic patient. This trial as well as the MRFIT trial demonstrated no significant differences in the LDL or total cholesterol concentrations[2,3]. However, for any given level of cholesterol, the diabetic patient fared worse. One possible explanation is increased concentrations of the more atherogenic Lp(a) and small dense LDL. Lipoprotein oxidation causes damage to the endothelium and vascular smooth muscle cells. This results in accelerated atherogenesis. Hypertriglyceridaemia potentiates lipid oxidation. Hyperglycaemia also facilitates LDL oxidation and aggravates hypertryglyceridaemia.

ApoB acts as a carrier protein for LDL. Glycation of apoB prolongs the half-life of the LDL moiety, which is then taken up by macrophages in the endothelium. Here they are converted to foam cells. It is for this reason that the poorly controlled diabetic is at particularly increased risk. Glycated HDL has accelerated clearance and thus there is a situation of reduced HDL coupled with a raised LDL level.

Lipid abnormalities in diabetes

- Hypertriglyceridaemia/low HDL.
- LDL:
  - Predominance of small dense particles.
  - Raised LDL levels *per se*.
  - Predisposition to oxidation.
  - Prolonged half-life.
- Raid Lp(a) levels

To date, no trials have been performed specifically in the diabetic population and we rely on subgroup analysis of diabetic patients involved in the large trials. Two large secondary prevention trials were done. In the 4S-trial[9], the baseline total cholesterol was 6,8 mmol/l and the LDL averaged 4,8 mmol/l. After 5 years, there was a decreased incidence of new events and a trend towards decreased cardiovascular mortality in the treated group, as compared to the placebo group. These benefits were also noted in the patients with impaired fasting glucose.

In the CARE-study[10], the patients who were treated with pravastatin had an average total cholesterol of 5,4 mmol/l, with an LDL level of 3,6 mmol/l. Once again there was a decreased event rate, including those patients with impaired fasting glucose.

No primary prevention studies have been done in the diabetic population. Studies in **non-diabetic** patients were shown to be beneficial. These benefits most likely to extend to the diabetic patient.

Treatment of diabetic dyslipidaemia

Since the diabetic patient is at such increased risk for cardiovascular disease and has a poorer outcome therafter and since dyslipidaemia contributes significantly to this risk, there is no doubt that the dyslipidaemia should be treated aggressively.

All patients should be made aware of lifestyle modification at the time of diagnosis of the diabetes. They should thus be on a low cholesterol diet and be encouraged to exercise and lose weight. All of these result in an improved lipid profile, in addition to other benefits. Smoking cessation results in zero additional cardiovascular risk after stopping for 2 years.

The benefits of aspirin for macrovascular disease is widely accepted. A meta-analysis of secondary prevention trials showed that this benefit was greatest in the patient over the age of 65 years with diabetes or diastolic hypertension[11]. Since the majority of strokes are thrombotic in nature and the risk of haemorrhage is small, the ADA[12] have recommended the following:

All diabetic patients with evidence of macrovascular disease should be on aspirin. Aspirin should be used as primary prevention in all diabetics who have an additional risk factor. i.e HT, smoking, obesity, albuminuria, hyperlipidaemia or a family history of CAD. Only a minority will not require aspirin therapy or have a contraindication to its use.

Multiple lipid abnormalities exist, but the focus for the trials has been LDL cholesterol. The current goal level for LDL cholesterol is <3 mmol/l[13]. (American Diabetic Association (ADA) criteria[14] suggest an LDL of below 2,58 mmol/l, and starting drug therapy for an LDL of above 3,4 mmol/l). Furthermore, there is a growing amount of evidence that there is no threshold below which there is no longer a benefit to cholesterol lowering.

The Heart Protection Study looked at 20 000 patients who were either diabetic, had had a vascular event or were hypertensive[15]. The incidence of myocardial infarction and stroke was reduced in the simvastatin group with respect to the placebo group, even in those patients with LDL levels of less than 3 mmol/l. Based on this study, **all** diabetic patients should be on lipid lowering therapy, irrespective of their cholesterol levels. However, there would be major financial implications to this approach. This is not currently recommended. The drug of choice for predominant hypercholesterolaemia is a statin. Additional non-LDL lowering benefits have been documented.

Neither the CARE nor 4S trials addressed the hypertriglyceridaemia. Insulin resistance, relative insulin deficiency, obesity and poor glycaemic control are associated with hypertriglyceridaemia and a low HDL in patients with type 2 DM. These are known risk factors for CAD. Glycaemic control should therefore also be optimised.

There are no South African guidelines regarding treatment of the hypertriglyceridaemia. The ADA recommends that treatment be instituted if the triglyceride level is above 4,5 mmol/l. Therapy of triglyceride levels of between 2,3 mmol/l and 4,5 mmol/l is left to the discretion of the doctor. Whilst the statins reduce tryglyceride levels by approximately 33%, marked hypertriglyceridaemia is best treated with a fibrate[16]. Often combination therapy is required with a statin. Whilst they are not primary hypolipidaemic agents, thiazolidinediones promote correction of the lipid abnormalities caused by the insulin resistance state.

Nicotinic acid is not appropriate therapy for the type 2 diabetic patient, as it aggravates insulin resistance. Bile acid sequestrants are not well-tolerated and cause raised triglyceride levels. Omega-3-fatty acids can lower

triglyceride levels but can cause raised levels of small dense LDL and glucose and should be used with caution in this population. The use of antioxidants was controversial until the publication of the Heart Protection Study, in which patients in one arm of the trial were given vitamin E, vitamin C and beta-carotene supplementation or a placebo. After 5 years, no benefit in any end point was demonstrated.[15]

Initial observations suggested a benefit with the use of HRT for both primary and secondary prevention of CAD. Large trials have not confirmed this benefit. This might be in part to 'healthy-user bias'. The Women's Health Initiative (WHI) is a series of clinical trials looking at the healthy postmenopausal woman. One of the arms looked at **continuous combined** oestrogen-progestin therapy vs placebo. This arm only was discontinued early due to an increased risk of stroke, CAD, thromboembolism and breast cancer.[17] There is much debate surrounding this finding, but suffice to say that this form of therapy should not be used for primary or secondary prevention. Combination therapy should be discontinued if an acute CHD event occurs and should not be restarted as secondary prevention therapy[16]. Current recommendations for oestrogen therapy alone are as for combination therapy.[18,19]

The HOPE-study looked at patients who were at risk of CAD. Some had DM and dyslipidaemia.[20] The group using the ACE inhibitor had a lower incidence of MI, stroke and total mortality, particularly in the group who were older than 55 years with established CAD or more than 2 risk factors for it. Based on this study, the FDA has approved the use of ramipril in high-risk patients. Once again, this has financial implications.

The UKPDS was a large randomised trial involving patients with type 2 DM. The effects of tight glycaemic and BP control were assessed[21]. Improved glucose control alone showed little benefit in cardiovascular events and mortality in the UKPDS trial, compared to the improvement in microvascular complications. This was possibly due to inadequate control of other risk factors. However, epidemiological analysis show that for every 1% decrease in HbA1c, there is a 25% reduction in diabetes-related deaths and an 18% reduction in combined fatal and nonfatal MI.

Management for Atherosclerosis risk

- Stop smoking.
- Low cholesterol diet.
- Exercise.
- Weight loss.
- Improved glucose control.
- Aspirin.
- Statins.
- Fibrates.
- Ace inhibitor.

3. Hypertension and diabetes

Hypertension is **the major risk factor for premature atherosclerosis,** since it is the most common. Thirty five percent of males and 46% of females have HT at the time of diagnosis of the diabetes. When combined with DM, dyslipidaemia and the other risks, there is an additive effect. The type 2 diabetic patient often has a multitude of risks. The risk for CAD and stroke increases progressively with incremental BP[22] and pulse pressure[23], and evidence of target organ damage[24].

Treatment of hypertension

Lifestyle modification is recommended in all patients as part of the initial treatment for the diabetes, or in any non-diabetic patient who has a blood pressure above 140/ 90 mmHg. Anti-hypertensive drug therapy should be instituted if the blood pressure remains above this level. Due to the increased macro- and microvascular risk posed by the diabetes itself, the goal level is 130/ 85 mmHg. Patients with micro-albuminuria should be treated to a goal blood pressure of 125/75 mmHg.

In the UKPDS a mean BP of 144/82 mmHg was achieved. Yet it still showed an 11% reduction in MI, a 15% reduction in diabetes related deaths and a 13% reduction in micvrovascular complications for every 10mmHg decrease in BP. The study demonstrated that blood pressure lowering was beneficial, irrespective of the drug used. However, the ACE inhibitors have been shown to retard the progression of diabetic renal disease independent of the blood pressure lowering effect. For patients with microalbuminuria who are intolerant of this class of drug, irbesartan[25] and losartan[26] have been shown to be beneficial in the patient with type 2 diabetes.

In general, most patients require combination therapy with an average of 3 agents to achieve goal BP levels. ACE inhibitors and beta-blockers should not be used as monotherapy in black patients due to the poor response rate. The addition of low dose thiazide diuretics improves the response rate. The metabolic derangements seen with this class are insignificant at low doses. Indapamide is a useful alternative. In addition, beta-blockers mask hypo-glycaemic symptoms and may aggrevate PVD and hyperlipidaemia. However, their benefit in the patient with established CAD is unquestionable and thus the benefits and risks need to be assessed for each patient. The alpha-blockers are lipid neutral but postural hypotension can be a problem in the patient with autonomic neuropathy. The long-acting non-dihydropyridine calcium channel blockers, verapamil and diltiazem are a useful addition. Both have antiproteinuric benefits in addition to BP lowering, and are useful as add-on therapy to the ACE inhibitor.

II. MICROVASCULAR COMPLICATIONS

The microvascular complications are retinopathy, nephropathy and neuro-pathy. The UKPDS study showed that the overall microvascular complication rate was decreased by 35% for every 1% decrease in HbA1c.

1. Diabetic nephropathy

There are a number of risk factors for nephropathy in patients with type 2 diabetes: genetic susceptibility[27], HT, glycaemic control[21] and race.

The presence of persistent micro-albuminuria, defined as 30-300mg albumin/24hrs, strongly predicts the development of dipstick positive macroproteinuria. It is a marker of increased morbidity and mortality from CAD, and definite progression to end-stage renal failure. The relationship between nephropathy and retinopathy is not as clear-cut as for the patient with type 1 DM.

Treatment

Strict blood pressure control, as defined above, and the addition of an ACE inhibitor for microproteinuria together

with improved glycaemic control delay, the progression of nephropathy. A low protein diet is also indicated.

2. Diabetic retinopathy

Retinopathy is a major cause of morbidity in the diabetic patient. The presence of severe retinopathy may be a risk factor for death due to IHD[28]. The pathogenesis is multifactorial with alterations in autoregulation of retinal blood flow, sorbitol, glycation end-products, microthrombosis and genetic factors being implicated. Smoking and HT aggravate the problem and should be addressed. ACE inhibitors may slow the progression of retinopathy[29].

3. Diabetic neuropathy

The most common form of neuropathy is distal symmetrical sensory polyneuropathy with relative sparing of the motor axons. The autonomic nervous system is also commonly involved and the spinal cord can also be affected. Endothelial dysfunction is of particular importance in the patient with type 2 diabetes. It is most likely that both ischaemia and metabolic factors operate together. The exact nature of this interaction is unclear.

Animal studies have demonstrated impaired nerve repair and regeneration, due to decreased levels of neurotrophic peptides.

Pathogenesis of diabetic neuropathy

- Nerve ischaemia.
- Metabolic factors:
  - Hyperglycaemia.
  - Diminished intracellular sorbitol levels.
  - Decreased nerve repair and regeneration.

Prevention of diabetic neuropathy

Hyperglycaemia or insulin deficiency has been shown to be the major risk factor in the pathogenesis of diabetic neuropathy[30]. Improved glycaemic control delays the onset of neuropathy and its progression, if already present.

CONCLUSION

As can be seen from the above the diabetic patient is at risk for many complications. But prevention and early intervention are beneficial. There should thus be active screening for these complications. A good clinical examination (to exclude HT, cataracts, retinopathy, neuropathy and vascular disease) should be done at 6 monthly intervals. Hypertension should be treated to goal level. Screening for nephropathy should be done at the time of diagnosis and then six to twelve monthly thereafter. Fundoscopy should be done at the time of diagnosis and annually thereafter. The pupils must be dilated for adequate visualisation. Early referral to an ophthalmologist is recommended for any decline in visual acuity, maculo-pathy, proliferative disease or advanced background changes. Inspection of the feet should be done at each visit and the patient should be educated regarding foot care. The HbA1c-levels should be checked frequently, in conjunction with home glucose profiles, and maintained at below 7% (preferably 6,5%). The lipogram should be done initially and six monthly thereafter, and therapy adjusted to attain goal levels.❐

Please refer to CPD Questionnaire on pg 51

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