Review Article

Cardiovascular Disease In Diabetes – Prevention & Management

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Abstract

Among individuals with diabetes, cardiovascular disease (CVD) is the leading cause of morbidity and mortality. Adults with diabetes have a two- to fourfold higher risk of CVD compared with those without diabetes. Diabetes is also accompanied by a significantly increased prevalence of hypertension and dyslipidemia. The intent of this article is to clarify and reinforce the importance of identifying and treating a core set of risk factors (hypertension, dyslipidemia, obesity and tobacco use). Moreover, since recent evidence suggests that risk assessment and adherence to guidelines remain woefully suboptimal, we call for a renewed effort to prevent and treat these conditions.

Key Words : Cardiovascular disease, Diabetes, Prevention, Risk assessment, Risk management, Revascularisation.

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in people with diabetes mellitus[1,2]. Aggressive control of hypertension and lowering cholesterol levels with statins reduce the risk of cardiovascular events, and there is conclusive evidence that improving glycaemic control significantly reduces the risk of developing diabetic microvascular complications (retinopathy, nephropathy, and neuropathy)[3,4,5]. But there is little evidence that specifically targeting glycaemic control can reduce the frequency of cardiovascular endpoints.

With the exception of glucose management, prevention of CVD follows the same general principles as for people without diabetes. A multifactorial approach to treatment and achieving low BP levels and low LDL and total cholesterol concentrations is particularly important, many of the treatment targets are tougher for patients with diabetes. The typical patient with type 2 diabetes has multiple cardiovascular risk factors, each of which should be treated in accordance with existing guidelines.

A high priority must be given to modification of the major risk factors for CVD in patients with diabetes. Increasing evidence indicates that controlling CVD risk factors will reduce onset of CVD and its complications in patients with diabetes. In the clinical management of patients with diabetes, attention must be given both to major risk factors (cigarette smoking, hypertension, elevated LDL cholesterol and diabetic dyslipidemia, and hyperglycemia) and to underlying risk factors (overweight/obesity, physical inactivity, and adverse nutrition)

Pathogenesis of Atherosclerosis in Diabetes

The pathogenesis of atherosclerosis in diabetes is complex and multifactorial. Five general areas of mechanism were defined. Metabolic factors, excessive oxidation/glucoxidation, endothelial dysfunction, inflammation, prothrombotic state. Overall, a better understanding of the pathophysiological mechanisms of atherosclerosis may provide a better understanding of the process in general.

Glucose control

The UKPDS evaluated the effect of improved metabolic control on the risk of developing CVD.[1,2] The study demonstrated a 16% risk reduction for myocardial infarction that was not statistically significantly (P 0.052) associated with the 0.9% difference in HbA1c that was obtained between the intensive and conventional treatment groups. In overweight patients treated with metformin, a significant reduction in risk of myocardial infarctions was seen(P , 0.01).

Three recent trails were conducted to see if cardiovascular events could be reduced further with lower target HbA1c levels.[3,4,5] In the ACCORD study, 10,000 patients with type 2 diabetes and either a history of CVD or additional cardiovascular risk factors were randomized to intensive therapy, with a target HbA1c,6.0% or standard glycaemic control target HbA1c 7.0–7.9%, The trial was stopped prematurely at 3.5 years due to a significantly increased total mortality in the intensive treatment group: 257 vs. 203 (p = 0.04) for deaths due to any cause and 135 vs. There were

significantly more cases of hypoglycaemia requiring assistance in the intensive group, who also experienced significantly more weight gain. The reason for the poorer outcome in the intensive group is not clear, but may be associated with hypoglycaemia.

The Action in Diabetes and Vascular Disease Trial (ADVANCE) randomized .11 000 patients with type 2 diabetes to either standard or intensive glucose control.[3] Intensive control significantly reduced the total number of major macrovascular events (death from cardiovascular causes, non-fatal myocardial infarction, nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), but only the reduction in microvascular events was statistically significant. Weight gain and hypoglycaemia were less frequent than in the ACCORD study.

Recent meta-analysis examined trials of intensive vs. conventional glycaemic control,Showed a significant reduction in CHD and CVD events, but no reduction in cardiovascular mortality or total mortality.

Blood Pressure management

Epidemiological analyses and randomized clinical trials have demonstrated the impact of elevated blood pressure as a risk factor for both microvascular and macrovascular disease in diabetes. Blood pressure management is the most critical aspect of the care of the patient with diabetes.

The Hypertension Optimal Treatment trial[6] randomized patients with diastolic blood pressure of 100 to 115 mm Hg to diastolic blood pressure targets of ≤ 90, ≤85, and ≤80 mm Hg. It demonstrated a significant decline in the rate of major cardiovascular events with lower diastolic blood pressure targets. In the group randomized to a diastolic target of ≤80 mm Hg, the risk of major cardiovascular events was halved compared with the group with a target of ≤90 mm Hg.[6] For patients with diabetes, it generally is agreed that the appropriate diastolic blood pressure target is ≤ 80 mm Hg.

In a substudy of the UKPDS, patients with hypertension were randomized to intensive (mean BP 144/82 mmHg) or less intensive antihypertensive therapy.[7] There was a marked and significant 44% risk reduction for stroke and a non-significant 21% risk reduction for myocardial infarction associated with a 10 mmHg reduction in SBP and a 5 mmHg reduction in DBP.

In the ADVANCE BP study, lowering BP to a mean of 135/75 mmHg further reduced the risk of cardiovascular events and total mortality.[8]

In diabetic patients, antihypertensive treatment should be initiated when the BP is ≥140/80 mmHg. The SBP goal traditionally recommended in diabetes (i.e. ,130 mmHg) is based on epidemiological evidence, and not on evidence from randomized trials.

Regardless of the initial therapy, most patients will require multiple-drug therapy for hypertension in the setting of diabetes. Thiazide diuretics, β-blockers, ACE inhibitors, ARBs, and calcium channel blockers are beneficial in reducing CVD incidence in patients with diabetes. Current guidelines suggest that ACE inhibitors are the drugs of choice in the initial management of hypertension in people with diabetes or kidney disease.A low-dose thiazide diuretic generally should be one of the first 2 drugs used for management of hypertension in these patients.

Dyslipidaemia

In patients with type 2 diabetes mellitus, triglycerides are often elevated, HDL-C is generally decreased, and LDL-C may be elevated, borderline, or normal. LDL particles are small and dense, carrying less cholesterol per particle. Thus, the LDL-C concentration may be misleading: There will be more LDL particles for any cholesterol concentration if the LDL particles are small and dense. Additionally, these small, dense LDL particles may be more atherogenic than would be suspected by their concentration[9] .

Earlier and intensive prevention using lipid-lowering drugs irrespective of basal LDL cholesterol and aiming at lower lipid level goals, particularly in patients with type 2 diabetes, is needed. For patients with type 2 diabetes who have overt CVD or CKD and have one or more other CVD risk factors, the optimal level of LDL cholesterol should be 70 mg/dL.

However, it has to be stressed that in patients with type 2 diabetes, LDL cholesterol often remains within the normal range or is just moderately elevated, while one of the major CVD risk factors in these patients is diabetic dyslipidaemia characterized by hypertriglyceridaemia and low HDL cholesterol. Combination therapy of LDL-lowering drugs (eg, statins) with fibrates or niacin may be necessary to achieve lipid targets.

Antithrombotic therapy

The role of aspirin in primary prevention remains unproven. In the HOT study, 75 mg of aspirin further reduced the risk of major cardiovascular events in well-controlled hypertensive patients with diabetes, but non-fatal major bleeds were significantly more common among patients receiving aspirin.[6]

A recent meta-analysis of six RCTs found no statistically significant reduction in the risk of major cardiovascular events or all-cause mortality when aspirin was compared with placebo or no aspirin in people with diabetes and no pre-existing CVD.[10]

Microalbuminuria and multifactorial intervention

Microalbuminuria (urinary albumin excretion from 30 to 300 mg/ 24 h) predicts the development of overt diabetic nephropathy in patients with type 1 or type 2

diabetes, while the presence of overt proteinuria (300 mg/24 h) generally indicates established renal parenchymal damage. In both diabetic and non-diabetic hypertensive patients, microalbuminuria—even below the currently used threshold values—predicts cardiovascular events, and a continuous relationship between cardiovascular as well as noncardiovascular mortality and urinary protein/creatinine ratios has been reported in several studies.

An intensified multifactorial intervention including glucose management, statins,ACE inhibitors, other antihypertensive agents, aspirin, and lifestyle interventions (smoking cessation, increased physical activity, and diet) demonstrated a significant reduction in the incidence of microvascular complications after 4 years and a significant 53% risk reduction in macrovascular complications after 8 years[10].After a further 5 years of observational follow-up this was associated with a significant reduction in cardiovascular mortality[11]. Thus in high-risk patients polypharmacological multifactorial intervention is needed to obtain the maximum risk reduction.

Lifestyle Management

Lifestyle measures such as medical nutrition therapy and aerobic exercise have been demonstrated to modify lipids and reduce blood pressure and are integral to the management of glycemia and weight control[12,13] .Numerous epidemiological analyses suggest that nutrition and physical activity are predictors of age-specific mortality and cardiovascular event rates. To date, short-term studies of medical nutrition therapy,[12] physical activity, and comprehensive lifestyle approaches have been shown to improve the control of risk factors and intermediate markers of CVD risk.

Weight

Weight reduction in obese persons will reduce all of the CVD risk factors associated with type 2 diabetes mellitus and will improve hyperglycemia. Moderate weight loss (eg, 7% to 10% of body weight in 1 year) is often attainable, whereas efforts to achieve ideal body weight in short periods of time usually fail. Even if no weight reduction can be achieved, weight maintenance is certainly preferable to weight gain. Diets low in carbohydrate may be associated with greater weight loss in the short term but have not been demonstrated to result in greater weight loss after 1 year than diets with more balanced proportions of fats and carbohydrates.[14]

To improve glycemic control and reduce the risk of CVD at least 150 minutes of moderate-intensity aerobic physical activity per week or at least 90 minutes of vigorous aerobic exercise per week is recommended. Thus, patients with diabetes should be encouraged to perform 30 to 60 minutes of moderate-intensity aerobic activity such as brisk walking on most (preferably all) days of the week, supplemented by an increase in daily lifestyle activities (eg, walking breaks during the workday, gardening, and household work).

Medical Nutrition Therapy

To achieve reductions in LDL-C, saturated fats should be <7% of energy intake, dietary cholesterol intake should be <200 mg/d, and intake of trans-unsaturated fatty acids should be <1% of energy intake. Total energy intake should be adjusted to achieve body-weight goals.

Total dietary fat intake should be moderated (25% to 35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat. Ample intake of dietary fiber (≥14 g per 1000 calories consumed) may be of benefit.

In both normotensive and hypertensive individuals, a reduction in sodium intake may lower blood pressure. The goal should be to reduce sodium intake to 1200 to 2300 mg/d (50 to 100 mmol/d), equivalent to 3000 to 6000 mg/d of sodium chloride.

Tobacco Use Cessation

All patients with diabetes should be asked about tobacco use status at every visit.Every tobacco user should be advised to quit. The patient can be assisted by counseling and by developing a cessation plan.Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion) should be incorporated as needed.

Management of CAD in diabetes

Screening

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with diabetes. CAD is often asymptomatic in these patients, until the onset of myocardial infarction or sudden cardiac death. Consequently, proper screening and diagnosis of CAD is crucial for the prevention and early treatment of coronary events.

Although it remains controver¬sial to screen asymptomatic patients with diabetes, screening patients with a limited functional status is probably a reasonable approach for people at moderate to high risk of underlying CAD. An exercise TMT can be a safe and effective initial screening test in patients who can exercise and have a normal baseline ECG. Screening should also be con¬sidered in patients with an abnormal ECG tracing suggestive of ischemia or infarction. Coronary arteriography remains the gold standard for identifying obstructive lesions, though it is never used as an initial screening test.

The treatment goals for patients with coronary artery atherosclerosis are to relieve symptoms of CAD and to prevent future cardiac events, such as unstable angina, AMI, and death. The mainstays of pharmacologic therapy of angina include nitrates, beta-blockers, statins, calcium-channel blockers, and ranolazine.The prevention and treatment of atherosclerosis requires control of the known modifiable risk factors for this disease. This includes therapeutic lifestyle changes and

the medical treatment of hypertension, hyperlipidemia, and diabetes mellitus.Typically, patients with CAD are first seen after they present with a cardiac event.

In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, of 2, 248 patients with stable CAD randomized to optimal medical therapy plus percutaneous coronary intervention (PCI) vs. optimal medical therapy alone, 766 patients (34%) had diabetes mellitus, and 1,362 patients (61%) had the metabolic syndrome[15]. At 4.6-year median follow-up, the risk of death or myocardial in infarction in patients with diabetes mellitus and in patients with the metabolic syndrome was similar in patients with and without early PCI.

These data favor optimal medical therapy alone in patients with diabetes mellitus and stable CAD. However, if disabling angina pectoris despite optimal medical therapy occurs coronary revascularization is recomended.

Revascularization therapies for symptomatic or ischemia-producing atherosclerotic lesions include percutaneous approaches and open heart surgery. Long-term mortality is similar after CABG and PCI in most patient subgroups with multivessel coronary artery disease; therefore, the choice of treatment should depend on patient preferences for other outcomes. Exceptions to this are patients with diabetes and those age 65 years or older; CABG is a superior option in these subgroups, because of lower mortality[16].

Conclusion

Intensive management of hyperglycaemia in diabetes reduces the risk of microvascular complications and, to a lesser extent,that of cardiovascular disease.Intensive treatment of hypertension in diabetes reduces the risk of macrovascular and microvascular outcomes and multiple antihypertensive drugs are usually required to reach the target. Increased plasma cholesterol and LDL cholesterol are among the main risk factors for CVD. Hypertriglyceridaemia and low HDL cholesterol are independent CVD risk factors. Statin therapy has a beneficial effect on atherosclerotic CVD outcomes.Lifestyle modification is an important aspect in the management.

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Good, Bad and the Ugly!

Most health-conscious people are aware of the eternal conflict between the "good" cholesterol ((High Density Lipoprotein) and the "bad" cholesterol (Low Density Lipoprotein) for the human heart and if "bad" gains the upper hand, heart may suffer a fatal damage. But that is not the whole story, because we have left out "Mr. Ugly". In a study published in the Journal of the American College of Cardiology, the authors after having examined 73,000 persons, have concluded that it is the "ugly" cholesterol that is truly harmful. It increases the risk of ischaemic heart disease by three times. "Ugly" cholesterol is 'remnant-like particle cholesterol'. Its level in the blood is high when the level of triglyceride (normal fat) is high. The authors hope that pharmaceutical industry will respond by developing new drugs to keep "Mr. Ugly" in check. (Journal of the American College of Cardiology, 2012; DOI:10.1016/j.jacc.2012.08.1026)

- Dr. K. Ramesh Rao