Cardiovascular Morbidity and Mortality in Diabetes Mellitus, Cardiovascular Risk Factors and Treatment

1. Djurayeva Zilola Aramovna
2. Davronov Ma`murjon
3. Mamarakhimov Ramazon
4. Erkinov Javokhir

Abstract: One of the dangerous complications of diabetes is heart failure. It is possible to understand how serious this complication is considering that the death rate from diseases of the cardiovascular system is currently the 1st in the world.

Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in PAD, CHF, CAD, MI, and sudden death (risk increase from one-to fivefold) in DM. The American Heart Association has designated DM as a major risk factor for cardiovascular disease (same category as smoking, hypertension, and hyperlipidemia). Type 2 diabetes patients without a prior MI have a similar risk for coronary artery–related events as nondiabetic individuals who have had a prior MI. Because of the extremely high prevalence of underlying cardiovascular disease in individuals with diabetes (especially in type 2 DM), evidence of atherosclerotic vascular disease (e.g., cardiac stress test) should be sought in an individual with diabetes who has symptoms suggestive of cardiac ischemia, peripheral or carotid arterial disease, a resting electrocardiogram indicative of prior infarction, plans to initiate an exercise program, proteinuria, or two other cardiac risk factors (ADA recommendations). Whether and how to screen asymptomatic individuals with diabetes for CAD is controversial. The absence of chest pain (“silent ischemia”) is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individuals undergoing major surgical procedures. The prognosis for individuals with diabetes who have CAD or MI is worse than for nondiabetics. CAD is more likely to involve multiple vessels in individuals with DM.

The increase in cardiovascular morbidity and mortality appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors. For example, after controlling for all known cardiovascular risk factors, type 2 DM increases the cardiovascular death rate twofold in men and
fourfold in women. Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hyper-tension, obesity, reduced physical activity, and cigarette smoking. Additional risk factors more prevalent in the diabetic population include microalbuminuria, macroalbuminuria, an elevation of serum creatinine, and abnormal platelet function. Insulin resistance, as reflected by elevated serum insulin levels, is associated with an increased risk of cardiovascular complications in individuals with and without DM. Individuals with insulin resistance and type 2 DM have elevated levels of plasminogen activator inhibitors (especially PAI-1) and fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favoring the development of thrombosis. Diabetes is also associated with endothelial, vascular smooth-muscle, and platelet dysfunction.

Evidence that improved glycemic control reduces cardiovascular complications in DM is inconclusive. In the DCCT, the number of cardiovascular events in patients with type 1 diabetes did not differ between the standard and intensively treated groups during the trial but was reduced at follow-up 17 years later. An improvement in the lipid profile of individuals in the intensive group (lower total and LDL cholesterol, lower triglycerides) during intensive diabetes management was noted. Trials to examine whether improved glycemic control reduces cardiovascular events in type 2 diabetes are underway. Concerns about the atherogenic potential of insulin remain, since in nondiabetic individuals, higher serum insulin levels (indicative of insulin resistance) are associated with a greater risk of cardiovascular morbidity and mortality. In the UKPDS, improved glycemic control did not conclusively reduce cardiovascular mortality. Importantly, treatment with insulin and the sulfonylureas did not appear to increase the risk of cardiovascular disease in individuals with type 2 DM, refuting prior claims about the atherogenic potential of these agents.

In addition to CAD, cerebrovascular disease is increased in individuals with DM (threefold increase in stroke). Individuals with DM have an increased incidence of CHF. The etiology of this abnormality is probably multifactorial and includes factors such as myocardial ischemia from atherosclerosis, hypertension, and myocardial cell dysfunction secondary to chronic hyperglycemia.

**Cardiovascular Risk Factors**

**Dyslipidemia**

Individuals with DM may have several forms of dyslipidemia. Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be assessed aggressively and treated as part of comprehensive diabetes care (Fig. 19-12). The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels. DM itself does not increase levels of LDL, but the small dense LDL particles found in type 2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation.

Almost all treatment studies of diabetic dyslipidemia have been performed in individuals with type 2 DM because of the greater frequency of dyslipidemia in this form of diabetes. Interventional studies have shown that the beneficial effects of LDL reduction are similar in the diabetic and nondiabetic populations. Large prospective trials of primary and secondary intervention for CHD have included some individuals with type 2 DM, and subset analyses have consistently found that reductions in LDL reduce cardiovascular events and morbidity in individuals with DM. Most clinical trials used HMG CoA reductase inhibitors, although gemfibrozil is also beneficial. No prospective studies have addressed similar questions in individuals with type 1 DM. Since the frequency of cardiovascular disease is low in children and young adults with diabetes, assessment of cardiovascular risk should be incorporated into the guidelines discussed below.

Based on the guidelines provided by the ADA and the American Heart Association, priorities in the treatment of hyperlipidemia are (1) lower the LDL cholesterol, (2) raise the HDL cholesterol, and (3) decrease the triglycerides. A treatment strategy depends on the pattern of lipoprotein abnormalities
Initial therapy for all forms of dyslipidemia should include dietary changes, as well as the same lifestyle modifications recommended in the nondiabetic population (smoking cessation, blood pressure control, weight loss, increased physical activity). The dietary recommendations for individuals with DM are similar to those advocated by the National Cholesterol Education Program and include increased monounsaturated fat and carbohydrates and reduced saturated fats and cholesterol. Though viewed as important, the response to dietary alterations is often modest (<10% reduction in the LDL). Improvement in glycemic control will lower triglycerides and have a modest beneficial effect by raising HDL. HMG CoA reductase inhibitors are the agents of choice for lowering the LDL. According to guidelines of the ADA and the American Heart Association, the target lipid values in diabetic individuals (age >40 years) without cardiovascular disease should be LDL <2.6 mmol/L (100 mg/dL); HDL >1.1 mmol/L (40 mg/dL) in men and >1.38 mmol/L (50 mg/dL) in women; and triglycerides <1.7 mmol/L (150 mg/dL). The rationale for these goals is that the risk of CHD is similar to that in patients without diabetes who have had a prior MI. In patients >40 years, the ADA recommends addition of statin, regardless of the LDL, to reduce LDL by 30–40%.

If the patient is known to have cardiovascular disease, the ADA recommends an LDL goal of <1.8 mmol/L (70 mg/dL) as an “option” [in keeping with evidence that such a goal is beneficial in nondiabetic individuals with CAD (Chap. 21)]. Fibrates have some efficacy and should be considered when the HDL is low in the setting of a mild elevation of the LDL. Combination therapy with an HMG CoA reductase inhibitor and a fibrate or another lipid-lowering agent (ezetimibe, niacin) may be needed to reach LDL or HDL goals, but statin/fibrate combinations increase the possibility of side effects such as myositis. Nicotinic acid effectively raises HDL and can be used in patients with diabetes, but high doses (>2 g/d) may worsen glycemic control and increase insulin resistance. Bile acid–binding resins should not be used if hypertriglyceridemia is present. Pharmacologic therapy of dyslipidemia to achieve a LDL <2.6 mmol/L (100 mg/dL) should be considered in diabetic individuals <40 years of age without cardiovascular disease if the individual also has other risk factors.

Hypertension

Hypertension can accelerate other complications of DM, particularly cardiovascular disease and nephropathy. In targeting the goal of BP <130/80, therapy should first emphasize lifestyle modifications such as weight loss, exercise, stress management, and sodium restriction. Realizing that more than one agent is usually required to reach a blood pressure goal, the ADA recommends that all patients with diabetes and hypertension be treated with an ACE inhibitor or an ARB. Subsequently, agents that reduce cardiovascular risk (beta blockers, thiazide diuretics, and calcium channel blockers) should be incorporated into the regimen. While ACE inhibitors and ARBs are likely equivalent in most patients with diabetes and renal disease, the ADA recommends (1) in patients with type 1 diabetes, hypertension, and micro- or macroalbuminuria, an ACE inhibitor slowed progression of nephropathy; (2) in patients with type 2 diabetes, hypertension, and microalbuminuria, an ACE inhibitor or an ARB slowed the progression to macroalbuminuria; and (3) in patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency, an ARB slowed the decline in GFR. Additional points of emphasis include:

1. ACE inhibitors are either glucose- and lipid-neutral or glucose- and lipid-beneficial and thus positively impact the cardiovascular risk profile. Calcium channel blockers, central adrenergic antagonists, and vasodilators are lipid- and glucose-neutral.

2. Beta blockers and thiazide diuretics can increase insulin resistance and negatively impact the lipid profile; beta blockers may slightly increase the risk of developing type 2 DM. Although often questioned because of the potential masking of hypoglycemic symptoms, beta blockers are safe in most patients with diabetes and reduce cardiovascular events.
3. Sympathetic inhibitors and α-adrenergic blockers may worsen orthostatic hypotension in the diabetic individual with autonomic neuropathy.

4. Equivalent reduction in blood pressure by different classes of agents may not translate into equivalent protection from cardiovascular and renal endpoints. Thiazides, beta blockers, ACE inhibitors, and ARBs positively impact cardiovascular endpoints (MI or stroke).

5. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem), rather than dihydropyridine agents (amlodipine and nifedipine), are preferred in diabetics.

6. A blood pressure goal of <125/75 is suggested for individuals with macroalbuminuria, hypertension, and diabetes.

7. Serum potassium and renal function should be monitored.

Because of the high prevalence of atherosclerotic disease in individuals with DM, the possibility of renovascular hypertension should be considered when the blood pressure is not readily controlled.

*Treatment*

In general, the treatment of coronary disease is not different in the diabetic individual. Revascularization procedures for CAD, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), may be less efficacious in the diabetic individual. Initial success rates of PCI in diabetic individuals are similar to those in the nondiabetic population, but diabetic patients have higher rates of restenosis and lower long-term patency and survival rates in older studies. More recently, the use of drug-diabetic patients, and whether there is a difference in efficacy of PCI in diabetic individuals is not clear. Although CABG may be preferred over PCI in diabetic individuals with multivessel CAD or recent Q-wave MI, PCI is preferred in patients with single-vessel CAD or two-vessel disease (no involvement of left anterior descending).

The ADA has emphasized the importance of glycemic control and aggressive cardiovascular risk modification in all individuals with DM. Past trepidation about using beta blockers in individuals who have diabetes should not pre- vent use of these agents since they clearly benefit diabetic patients after MI. ACE inhibitors (or ARBs) may also be particularly beneficial and should be considered in individuals with type 2 DM and other risk factors (smoking, dyslipidemia, history of cardiovascular disease, microalbuminuria). Patients with atypical chest pain or an abnormal resting ECG should be screened for CHD. Screening of asymptomatic individuals with diabetes is controversial.

Antiplatelet therapy reduces cardiovascular events in individuals with DM who have CAD. Current recommendations by the ADA include the use of aspirin for secondary prevention of coronary events. Although data demonstrating efficacy in primary prevention of coronary events in DM are lacking, antiplatelet therapy should be strongly considered, especially in diabetic individuals >30 years of age with other coronary risk factors such as hypertension, smoking, family history, or dyslipidemia. The aspirin dose (75–162 mg) is the same as that in nondiabetic individuals. Aspirin therapy does not have detrimental effects on renal function or hypertension, nor does it influence the course of diabetic retinopathy.

**Conclusion**

In conclusion, it can be said that diabetes mellitus leads to serious changes and complications in the cardiovascular system, these complications are especially evident in older patients, and the treatment is accordingly more difficult.

For this reason, patients over 40 years of age, those with diabetes in their relatives, and overweight patients should be screened for diabetes annually.
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