Diabetes Mellitus and Cardiovascular Disease

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Abstract

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes mellitus. Patients with diabetes mellitus have a 2 to 4 time’s higher risk of cardiovascular disease and up to a 3 times increase in mortality than non diabetics. The accelerated rate of atherosclerosis seen in diabetes mellitus predisposes patients to coronary artery disease and to higher rates of myocardial infarction and death. This review article discusses cardiovascular disease in diabetics and the management of these patients.

Introduction

The prevalence of diabetes mellitus is rising at an alarming rate. In the United States, 23.6 million people, or 7.8% of the population, have diabetes mellitus, with 1.6 million new cases diagnosed annually [1]. Over 200 million people are affected worldwide with diabetes mellitus [2]. Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes mellitus. Despite a marked decline in cardiovascular disease related deaths over the past several decades, a smaller reduction has occurred in diabetics compared to non diabetics [3]. Diabetes mellitus remains a key risk factor for cardiovascular disease and is widely recognized as a coronary artery disease risk equivalent [4]. It is associated with a 2 to 4 times higher risk of cardiovascular disease, as well as an increased risk of mortality by up to 3 times [5,6].

Epidemiology

Epidemiological studies of diabetes mellitus have shown that gender, age, and ethnic background are important factors when considering the development of diabetes mellitus and its complications. Given similar levels of fasting glucose and proteinuria, women with diabetes mellitus at diagnosis tend to be older and more likely hypertensive. Among those diagnosed at younger ages, women are more likely than men to be obese [7]. Compared to the non-diabetic population, the overall mortality from acute myocardial infarction in the diabetic population was 4 times higher among men and 7 times higher among women [8]. Despite a similar rate of myocardial infarction and chronic heart disease, the rate of transmural coronary angioplasty and coronary bypass grafting was doubled in diabetic male patients [9].

According to the National Diabetes Information Clearinghouse (NDIC), after adjusting for population age differences, 2004-2006 national survey data for people aged 20 years or older indicate that 6.6% of whites, 7.5% of Asians, 10.4% of Hispanics, and 11.8% of African-Americans had diagnosed diabetes mellitus [10]. Interestingly, a study by McWilliams et al. [11] showed Medicare coverage after age 65 years is associated with reductions in racial, ethnic, and socioeconomic differences in patients with cardiovascular disease and diabetes [11].

The clinical and economic burden of diabetes mellitus and its sequelae are immense. According to the American Diabetes Association (ADA), the actual national burden of diabetes mellitus is estimated to exceed $174 billion; excluding indirect costs such as disability, work loss, and premature mortality [12]. These costs are primarily due to the macro vascular and micro vascular complications of diabetes mellitus. In addition to heart disease (68%) and stroke (16%) being the biggest contributors to diabetes-related deaths, other complications include hypertension, retinopathy, end-stage renal disease, neuropathy, peripheral vascular disease, electrolyte imbalance, immune suppression, erectile dysfunction, and complications of pregnancy [13].

Patients with diabetes mellitus continue to remain at a higher risk of all-cause and cardiovascular disease mortality than those without diabetes. Diabetics are more likely to have coronary artery disease, which is more often multi vessel, and to have episodes of silent myocardial ischemia. Traditional coronary heart disease risk factors such as hypertension, dyslipidemia, and obesity cluster in patients with diabetes mellitus, but this clustering does not account for all of the increased risk in these patients [14]. Research has shown a number of diabetes-specific risk factors contributing to the acceleration of atherosclerosis and increased morbidity and mortality of coronary artery disease. For example, the coronary arteries of patients with diabetes mellitus exhibit a larger content of lipid-rich, inflamed atheromas, with macrophage infiltration, and subsequent thrombosis that is more vulnerable to rupture than plaque found in patients without diabetes [15].

Pathogenesis

Diabetes mellitus promotes the accumulation of foam cells in the sub endothelial space by increasing the production of leukocyte adhesion molecules and pro inflammatory mediators [16]. This augmented vascular inflammatory reaction may result from overexpression of receptor for advanced glycation end products, which correlates linearly with hemoglobin A1c levels. Receptors for advanced glycation end products enhance matrix metalloproteinase activity that can destabilize plaques [17].

Endothelial dysfunction has been documented in diabetic patients who have normal coronary arteries and no other risk factors for coronary disease. The presence of insulin resistance alone may be associated with coronary endothelial dysfunction. In a prospective, open-label
treatment study of 50 insulin-resistant and 22 insulin-sensitive subjects without glucose intolerance or traditional risk factors for or evidence of coronary artery disease, endothelium-dependent coronary vasomotor function is abnormal (as assessed by myocadial blood flow response to a cold pressor test) in the insulin-resistant compared to the insulin-sensitive group. After 3 months of thiazolidinedione therapy in the insulin-resistant subjects, insulin sensitivity improved, fasting plasma insulin levels decreased, and myocardial blood flow responses to cold pressor test normalized [18].

Changes in vascular function may also contribute to the poorer outcomes in diabetes mellitus. Increased levels of endothelin-1 stimulate vasoconstriction, induce vascular smooth muscle hypertrophy, and activate the renin-angiotensin system. At the same time, reduced prostacyclin and nitric oxide activity enhances platelet aggregation and adhesiveness, which leads to endothelial dysfunction [19,20]. In addition to the atherosclerotic and vascular effects, the hematologic system is also adversely affected. Diabetes mellitus promotes platelet activation by increasing platelet-surface expression of glycoprotein Ib, which mediates binding to the glycoprotein Ib/IIa receptor and to the von Willebrand factor [21]. It also increases coagulation activity by stimulating production of pro coaguants such as tissue factor and by reducing levels of anticoagulants such as protein C and antithrombin III [22]. Also, patients with diabetes have increased levels of plasminogen activator inhibitor type 1 in plasma and in atheromas [23]. Elevated tissue plasminogen activator inhibitor type 1 could decrease fibrinolysis, increase thrombus formation, and accelerate plaque formation [24]. Therefore, agents directing at inhibiting platelet aggregation, such as aspirin, clopidogrel, and glycoprotein Ib/IIa blockers, are indispensable in reducing the incidence of thrombotic events [25].

Clinical Outcomes

Myocardial infarction

Myocardial infarction rates are increased among diabetics of all ages. In a study by DeLuca et al. [26], the prevalence of unrecognized myocardial infarction and silent myocardial ischemia detected by a treadmill exercise sestamibi stress test was increased in patients with diabetes mellitus. In patients without a history of myocardial infarction, myocardial infarction was diagnosed by a treadmill exercise sestamibi stress test in 40 of 217 patients (18%) with diabetes mellitus and in 16 of 224 patients (7%) without diabetes mellitus. In patients without a history of angina pectoris, silent myocardial ischemia was diagnosed in 62 of 189 patients (33%) with diabetes mellitus and in 35 of 191 patients (15%) without diabetes mellitus [26].

A Finnish population-based study by Haffner et al. [27] showed that, among 1,373 non diabetic subjects and 1,059 diabetic subjects, 7-year incidence rates of myocardial infarction in non diabetic subjects with and without prior myocardial infarction at baseline were 18.8% and 3.5%, respectively, whereas for diabetic subjects were 45% and 20.2%, respectively [27]. This study showed that diabetics who have not had a myocardial infarction have as high a risk of myocardial infarction as non diabetics with previous myocardial infarction.

In a study of 274 elderly diabetics and 386 elderly non dabetics without glucose intolerance or traditional risk factors for or evidence of coronary artery disease, endothelium-dependent coronary vasomotor function is abnormal (as assessed by myocadial blood flow response to a cold pressor test) in the insulin-resistant compared to the insulin-sensitive group. After 3 months of thiazolidinedione therapy in the insulin-resistant subjects, insulin sensitivity improved, fasting plasma insulin levels decreased, and myocardial blood flow responses to cold pressor test normalized [18].

Following an acute myocardial infarction, diabetics carry worse short- and long-term outcomes. In a study based on the FINMONICA myocardial infarction registry, a part of the Finnish contribution to the WHO MONICA Project (World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease), diabetics and non diabetic patients with their first myocardial infarction were followed to determine their overall 1-year mortality, and out-of-hospital mortality during the years 1988-1992. This study showed that the 1-year mortality rate was 44.2% in diabetic men and 32.6% in non diabetic men (a significant 38% increase in diabetic men) and 36.9% in diabetic women and 20.2% in non diabetic women (a significant 86% increase in diabetic women). The out-of-hospital mortality rate was 28.3% in diabetic men and 22.4% in non diabetic men (a 25% significant increase in diabetic men) and 10.4% in diabetic women and 11.0% in non diabetic women (an insignificant difference). The high mortality rate of diabetic patients after their first myocardial infarction and the high proportion of out-of-hospital deaths in this group indicate that vigorous primary and secondary preventive measures should become an integral part of their medical care [29].

Coronary revascularization

Patients with diabetes mellitus have increased morbidity and mortality after coronary revascularization. A study by Elezi et al. [30] analyzed a consecutive series of 715 patients with diabetes and 2,839 patients without diabetes after successful stent placement. At 1-year follow-up, event-free survival was significantly lower in diabetic than in non diabetic patients (73.1% versus 78.5%). Survival free of myocardial infarction was also significantly reduced in the diabetic group (89.9% versus 94.4% in nondiabetics). The incidence of both restenosis (37.5% versus 28.3%) and stent vessel occlusion (5.3% versus 3.4%) was significantly higher in diabetic patients. Diabetes mellitus was identified as an independent risk factor for adverse clinical events and restenosis and lower rates of event-free survival than nondiabetic patients. Diabetes mellitus confers a higher incidence of death, recurrent myocardial infarction, restenosis, and repeat revascularization rates [30].

Multiple subgroup analyses of major trials, such as the SIRollim US-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) trial [31], the German Multicenter Investigation on the Effectiveness of Sirolimus-Eluting Stents in Diabetic Patients (SCORPIUS) trial [32], the DIABETES and sirolimus Eluting Stent (DIABETES) trial [33], and the Paclitaxel-Eluting Stent (TAXUS) trials [34] have shown better outcomes in diabetic patients with drug-eluting stents compared to bare-metal stents. Significantly lower rates of target lesion revascularization were noted with sirolimus-eluting stents in the SIRIUS trial (7% versus 22% at 9 months), in the SCORPIUS trial (5.3% versus 21.1% at 1 year), in the DIABETES trial (7.7% versus 35.0% at 2 years), and with paclitaxel-elongating stents in the TAXUS trials (12.4% versus 24.7% at 4 years).

Similarly, death and adverse nonfatal outcomes after coronary artery bypass graft surgery are higher in patients with diabetes mellitus. In multiple large observational studies, diabetic patients had higher mortality rates at 30 days (5% versus 2.5%) and at 5 to 10 years (22% versus 12% and 50% versus 29%, respectively) [35,36]. However despite a worse long-term prognosis after coronary artery bypass grafting in patients with diabetes mellitus, the outcomes are still better than with medical therapy or percutaneous coronary intervention in selected subgroups [37].
For patients with diabetes mellitus or multi vessel coronary artery disease, several trials have demonstrated long-term benefits of coronary artery bypass grafting over percutaneous coronary intervention. In the Bypass Angioplasty Revascularization Investigation (BARI) trial, 1,829 symptomatic patients with multi vessel coronary artery disease were randomly assigned to initial treatment with percutaneous coronary intervention or coronary artery bypass grafting and followed up for an average of 10.4 years. At 10.4 years, the percutaneous coronary intervention group had significantly higher subsequent revascularization rates than the coronary artery bypass grafting group (76.8% vs. 20.3%), and in the subgroup with treated diabetes, the coronary artery bypass grafting group had a significantly higher survival than the percutaneous coronary intervention assigned group (57.8% vs. 45.5%). The study concluded that among patients with treated diabetes mellitus, coronary artery bypass grafting conferred long-term survival benefit which persisted at 10-years [38].

Similarly, the synergy between PCI with Taxus drug-eluting stent and cardiac surgery (SYNTAX) trial, which randomized 1,800 patients with severe coronary artery disease to either bypass surgery or drug-eluting stents, showed that the use of coronary artery bypass grafting, as compared with percutaneous coronary intervention, resulted in lower rates of the combined end points of the major adverse cardiac or cerebrovascular events at 1 year [39]. In addition, in a meta-analysis of 10 studies involving 7,812 patients who had undergone either percutaneous coronary intervention or coronary artery bypass grafting, there was a significant 30% reduction in total mortality among patients with diabetes mellitus who had undergone coronary artery bypass grafting [40].

Recently, the results of the BARI 2D trial replicated the principal findings of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial that an initial strategy of percutaneous coronary intervention provided no incremental clinical benefit over intensive medical therapy in patients with diabetes mellitus and coronary artery disease. In this study, 2,368 patients with type 2 diabetes mellitus and stable ischemic heart disease (≥50% stenosis of at least 1 major epicardial coronary artery associated with a positive stress test or ≥70% stenosis and classic angina pectoris) were randomly assigned to either initial revascularization (either coronary artery bypass grafting or percutaneous coronary intervention based on the cardiologist's selection) within 4 weeks versus intensive medical therapy. The mode of revascularization was left to the investigator's discretion. At 5 years, the primary end points of the rates of survival or freedom from major cardiovascular event (death, myocardial infarction, or stroke) did not differ significantly between the revascularization group and the medical-therapy group (88.3% versus 87.8% and 72.2 versus 77.7%, respectively) [41].

However, in a sub-group analysis, the rate of major cardiovascular events was significantly lower in the coronary artery bypass grafting group (22.4% versus 30.5%), predominantly attributable to a reduction in non-fatal myocardial infarction. The trial reinforced prior scientific evidence supporting the benefits of coronary artery bypass grafting, with the goal to reduce long-term events such as myocardial infarction, over percutaneous coronary intervention in patients with diabetes mellitus or multi vessel coronary artery disease.

**Congestive heart failure**

Diabetes mellitus is also a strong and independent risk factor for congestive heart failure [42]. Risk factors for development of heart failure include age (5% increase per 1 year increase in age), male gender (40% increase), diabetes mellitus (60% increase), hypertension (2.5 times increase), and coronary artery disease 4.0 times increase) [43]. Older persons with diabetes mellitus, mean age 81 years, had a 1.3 times higher chance of developing congestive heart failure than those without diabetes mellitus [44].

In a substudy of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, patients with new-onset diabetes mellitus had a significantly 49% higher event rate of new-onset atrial fibrillation compared with patients without diabetes mellitus. Diabetics also had more persistent atrial fibrillation (87% significant increase). Patients with new-onset diabetes mellitus and atrial fibrillation had a 3.56 times significant increase in heart failure compared with patients with new-onset diabetes without atrial fibrillation [45].

Not only are diabetic patients at higher risk for congestive heart failure, but those who develop congestive heart failure have a worse prognosis than non diabetics with congestive heart failure. Poor glycemic control increases the risk of developing heart failure in patients with diabetes mellitus. The importance of glycemic control was illustrated in a report from Kaiser Permanente that evaluated 48,858 diabetic patients ≥19 years of age and no heart failure who were followed for a mean of 2.2 years. Each 1% increase in hemoglobin A1c was associated with a significant 8% increase in heart failure, and a hemoglobin A1c ≥10 increased the risk of heart failure by 1.56 times compared to a hemoglobin A1c <7 [46]. In addition, Barzilay et al. [47] showed in a study of 5,201 patients that the higher the fasting blood glucose, the higher the incidence of heart failure at 5-8 year follow-up (41% increase in heart failure for each increase in fasting blood glucose of 61 mg/dl) [47].

In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) trial looking at 48,612 patients from 259 hospitals, of which 42% of patients had diabetes mellitus, there was no difference in in-hospital mortality observed between diabetics and nondiabetics, but heart failure patients with diabetes mellitus experienced a significantly longer length of stay (5.9 days versus 5.5 days for nondiabetic patients). In the 5,791 patients in the follow-up cohort, 2,464 patients with diabetes mellitus had a similar post-discharge mortality but significantly increased all-cause re-hospitalization (31.5% versus 28.2% for nondiabetic patients). This study revealed a high prevalence of diabetes mellitus in patients hospitalized with heart failure. Heart failure patients with diabetes mellitus had a similar short-term mortality compared with patients without diabetes but had a higher risk of re-hospitalization [48].

A study by Halon et al. [49] looked at the development of heart failure and its prognostic implications in 363 diabetic patients, of which 193 underwent percutaneous transluminal coronary angioplasties and 170 coronary artery bypass operations, over 13-year follow-up. The cumulative incidence of hospitalization for heart failure was significantly higher in the diabetic cohort (25% versus 11%), with a rapidly increasing incidence after 5 years. Survival after first hospitalization for heart failure was significantly reduced in diabetics (11 of 20 (55%) versus 25 of 31 (81%) in non diabetics at 3 years), as was survival free of further hospitalization for heart failure (5 of 20 (25%) for diabetics versus 20 of 30 (63%) for nondiabetics) [49].

Long-term 13-year survival (43% versus 78%) and survival free of heart failure (33% versus 71%) were significantly decreased in diabetics, especially in those with reduced left ventricular function at baseline (17% versus 42%). Multivariate analysis showed diabetes mellitus to be the strongest independent predictor of decreased survival.
Diabetes mellitus and ischemic heart disease interact to accelerate the progression of myocardial dysfunction. According to the Studies of Left Ventricular Dysfunction (SOLVD) Prevention and Treatment trials, which enrolled 6,791 patients, including 1,310 with diabetes, patients with diabetes were 1.6 times significantly more likely to be admitted for heart failure and had higher rates at one year of all-cause mortality (32% versus 22%), cardiovascular mortality (28% versus 19%) and mortality related to pump failure (11% versus 6%) [50]. A study by Gustafsson et al. [51] showed that, among 5,491 patients hospitalized with heart failure, diabetes mellitus significantly increased mortality in men by 40% and in women by 70% [51]. For those with left ventricular dysfunction, diabetes mellitus significantly increased mortality in patients with ischemic cardiomyopathy by 37% [52].

Echo cardiographic evaluation of cardiac performance in diabetic patients with heart failure has demonstrated a prolonged pre-ejection period and a shortened ejection time, both of which correlate with reduced resting left ventricular ejection fraction and diminished systolic function. A study by Zarich et al. [53] showed the ratio of peak early to peak late atrial filling velocity was significantly decreased in diabetic compared with control subjects (1.24 versus 1.66). Atrial filling velocity was significantly increased in diabetic patients (74.3 versus 60.3 cm/s), whereas early filling velocity was reduced by a borderline significant degree (88.8 versus 98.5 cm/s). The atrial contribution to stroke volume as assessed by area under the late diastolic filling envelope compared to total diastolic area was also significantly increased in diabetic compared with control subjects (35% versus 27%) [53].

Diabetic patients also have a lower left ventricular ejection fraction in response to exercise, suggestive of a reduction in cardiac reserve. In a study by Mildenberger et al. [54] both groups of patients (with and without diabetes) had a similar rest and exercise heart rate and blood pressure, and both achieved similar workloads. The control group without diabetes mellitus had an ejection fraction at rest of 65.4% and a peak exercise ejection fraction of 77.1%. The diabetic group had a mean ejection fraction at rest of 63.7%, similar to that of the control group, but a peak exercise ejection fraction of 67.7%, significantly lower than that of the control group [54]. The diabetic patients varied widely in ejection fraction response to exercise, ranging from an increase of 25% to a decrease of 21% [53]. This subclinical left ventricular dysfunction may be explained by a defective blunted recruitment of myocardial contractility or an impairment of cardiac sympathetic innervation [55].

Even in the absence of left ventricular dysfunction, abnormal diastolic function has been noted in 27-69% of asymptomatic diabetic patients [56]. Impaired diastolic compliance and maintenance of the systolic function is usually the initial cardiac manifestation in the progression of diabetic cardiomyopathy [57]. Failure of diastolic relaxation of the left ventricle leads to impaired filling and reduced cardiac reserve on exercise. In a sex-specific linear regression analysis of 1,986 men, mean age 48 years, and 2,529 women, mean age 50 years, from the original Framingham Study cohort and the Framingham Offspring Study, diabetics had significantly higher heart rates than non diabetics (67.9 versus 64.0 beats/minute in men, and 73.1 versus 68.3 beats/minute in women). Diabetic women had significantly increased left ventricular wall thickness, relative wall thickness, left ventricular end-diastolic dimension, and left ventricular mass corrected for height [58]. Diabetes mellitus, especially with worse glycemic control, is independently associated with abnormal left ventricular relaxation. The severity of abnormal left ventricular relaxation is similar to the well-known impaired relaxation associated with hypertension. The combination of diabetes and hypertension has more severe abnormal left ventricular relaxation than groups with either condition alone [59].

A variety of factors may contribute to left ventricular dysfunction in diabetic patients, one of which may be autonomic neuropathy [60]. Under normal circumstances, sympathetic stimulation improves left ventricular contraction and increases left ventricular relaxation rates by facilitating calcium uptake into the sarcoplasmic reticulum. Autopsy studies of diabetic patients have shown that myocardial catecholamine stores are depleted which could impair both systolic and diastolic function [61].

In addition, cardiac autonomic neuropathy is portrayed by a significant reduction in heart rate variability and an alteration in the parasympathetic/sympathetic balance leading to parasympathetic reduction and sympathetic overactivity. Resting tachycardia reduces the time of ventricular filling, and over time, may predispose to arrhythmias and left ventricular dysfunction [62]. In a study by Rathmann et al. [63] patients with diabetes and mild cardiac autonomic neuropathy have been shown to have distal left ventricular sympathetic denervation, whereas those with severe cardiac autonomic neuropathy have a pattern of distal sympathetic denervation associated with proximal ventricular islands of hyperinnervation. These areas of denervation and hyperinnervation may cause unstable regions of electrical, vascular, or autonomic heterogeneity conducive to diabetic cardiomyopathy [63].

Decreased insulin availability or responsiveness in diabetes can impair the transport of glucose across the cell membrane. In perfused hearts from diabetic mice, the rate of glycolysis and glucose oxidation was impaired due to reduced content of insulin-sensitive glucose (GLUT4) transporters, whereas palmitate oxidation was increased. These changes were associated with increases of ceramide content, a mediator of apoptosis, and inducible nitric oxide synthase expression. Nitric oxide was found to inhibit creatine kinase and impair contractile reserve in rat hearts [64].

Since ischemic myocardium depends upon anaerobic metabolism of glucose, increased glucose uptake and metabolism are necessary for maintenance of myocardial function [65]. Diminished insulin activity in diabetic hearts limit glucose availability, which results in a shift toward fatty acid metabolism. These changes increase myocardial oxygen utilization, generate reactive oxygen species, accumulate toxic products of fatty acid metabolism, impair calcium handling, and upregulate the renin-angiotensin system [66].

**Treatment**

Besides glycemic control, the goals of treatment of left ventricular dysfunction and heart failure in diabetic patients are the same as those in nondiabetics. Patients need to stop smoking, lose weight if obese, have hypertension treated with the blood pressure reduced to less than 130/80 mm Hg, have dys lipidemia treated with the serum low-density lipoprotein (LDL) cholesterol level reduced to less than 70 mg/dL, and to perform physical activity if the heart failure is mild to moderate [67-70].

In an observational prospective study of 529 older patients, mean age 79 years, with prior myocardial infarction, diabetes mellitus, and a serum LDL cholesterol of 125 mg/dL or higher, 53% of patients were
treated with statins [71]. At 29-month follow-up, compared with no treatment with statins, use of statins significantly decreased coronary artery death or nonfatal myocardial infarction by 37% and stroke by 47%. The lower the serum LDL cholesterol in persons treated with statins, the greater was the reduction in new coronary events [72] and stroke [73].

Beta-adrenergic blocking agents and angiotensin-converting enzyme (ACE) inhibitors are commonly used for their sympathetic activity and influence on the renin-angiotensin system. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, at 10.4-months follow-up of 2,289 pts with a mean left ventricular ejection fraction of 20% and Class IV heart failure treated with diuretics and ACE inhibitors with or without digoxin, carvedilol significantly decreased mortality by 35% (7.1% absolute reduction). This trial supports and reassures the safety and benefit of beta blockers in a subset of patients with more advanced heart failure [74].

Similarly, the Metoprolol CR/XL Randomised Intervention (MERIT-HF) trial showed that, metoprolol controlled release/extended release (CR/XL) once daily in addition to standard therapy significantly lowered mortality in patients with decreased ejection fraction and symptoms of heart failure. A group of 3,991 patients with chronic heart failure in New York Heart Association (NYHA) functional class II–IV and with an ejection fraction of 40% or less, stabilized with optimum standard therapy, was randomly assigned metoprolol CR/XL 12.5 mg (NYHA III-IV) or 25.0 mg once daily (NYHA II) and 2,001 were assigned placebo. The target dose was 200 mg once daily, and doses were up-titrated over 8 weeks. At 1 year follow-up, all-cause mortality was lower in the metoprolol CR/XL group than in the placebo group (7.2%, per patient-year of follow-up versus 11.0% in the placebo group), with a 34% significant reduction in all-cause mortality in patients treated with metoprolol CR/XL [75].

There were 41% significantly fewer sudden deaths and 49% significantly fewer deaths from worsening heart failure in the metoprolol CR/XL group than in the placebo group. All-cause mortality or hospitalization due to worsening heart failure was significantly reduced 30% in diabetics treated with metoprolol CR/XL [76]. In 532 pts, mean age 78 years, with prior myocardial infarction and diabetes mellitus and no contraindications to beta blockers, use of beta blockers caused a 27% significant independent reduction in the incidence of new coronary events [77].

ACE inhibitors or angiotensin receptor blockers are the drugs of choice in treating diabetics with hypertension and chronic renal disease [78]. They facilitate reverse remodeling and slow the progression of left ventricular dysfunction. An overview of 32 randomized trials of ACE inhibitors in 7,105 pts with congestive heart failure showed that ACE inhibitors significantly reduced all-cause mortality by 23% and significantly reduced all-cause mortality or hospitalization for congestive heart failure by 35%. Patients with the lowest ejection fraction appeared to have the greatest benefit.

In the Heart Outcomes Prevention Evaluation (HOPE) study, 3,577 people with diabetes mellitus aged 55 years or older who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or a low ejection fraction, and who were not taking ACE inhibitors, were randomly assigned ramipril 10 mg daily or placebo. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. Overt nephropathy was a main outcome in a substudy; At 4.5 year-follow-up, ramipril significantly lowered the risk of the combined primary outcome by 25%, myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, and total mortality by 24%, revascularization by 17%, and overt nephropathy by 24%. After adjustment for the changes in systolic (2.4 mm Hg) and diastolic (1.0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% [79].

The Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study assessed the role of the angiotensin-II-receptor antagonist losartan in patients with type 2 diabetes and nephropathy. A total of 1,513 patients were enrolled in this randomized, double-blind study comparing losartan (50 to 100 mg once daily) with placebo, both taken in addition to conventional antihypertensive treatment, for a mean of 3.4 years. At the end of the study, losartan reduced the incidence of a doubling of the serum creatinine concentration (significant risk reduction of 25%) and end-stage renal disease (significant risk reduction of 28%) but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction of 32%). The level of proteinuria significantly declined by 35% with losartan [80].

In terms of diuretics use, mild congestive heart failure may be treated with a thiazide diuretic. However, thiazide diuretics are ineffective when the estimated glomerular filtration rate is <30 ml/min. For moderate or severe heart failure, patients should be treated with a loop diuretic. Metolazone may be needed in addition to loop diuretic for those with severe congestive heart failure or renal insufficiency.

When severe heart failure persists with diuretics, ACE inhibitors or angiotensin receptor blockers, and beta blockers, one can add an aldosterone antagonist [70]. Digoxin may be used in the presence of an abnormal left ventricular to reduce hospitalization for heart failure if symptoms persist despite optimal medical therapy with a class I indication, but the serum digoxin level must be maintained between 0.5-0.8 ng/ml [70]. Isosorbide dinitrate plus hydralazine may be used if symptoms persist despite optimal medical management in blacks with a class I indication and in other races with a class IIa indication [70]. Calcium channel blockers must be avoided if the left ventricular ejection fraction is abnormal.

In addition to optimal pharmacologic therapy, a study by Ghali et al. [81] showed that diabetics with advanced heart failure had substantial benefits from device therapy. Over 600 patients treated with cardiac resynchronization therapy had a 33% significant reduction in mortality and a 48% significant reduction in mortality or hospitalization for heart failure [81].

In addition to modifying cardiovascular risk factors such as obesity, dyslipidemia, hypertension, glycemic control, smoking, and sedentary lifestyle, the current standard of care for type-2 diabetes includes pharmacologic therapies that aim to restore normoglycemia. Sulfonfonylureas were among the first widely used oral hypoglycemic agents. Initially, it was thought that sulfonfonylureas confer an increase risk of cardiovascular mortality and coronary artery disease in patients taking this agent [82]. Sulfonfonylureas are insulin secretagogues, triggering insulin release by direct action on the K+–ATP channel of the pancreatic β cells. K+–ATP channels also exist in the myocardium and blocking them with sulfonfonylureas contributed to ischemic injury in diabetic patients [83]. Because there are data showing an increased incidence of coronary events and of mortality in diabetics with coronary artery disease treated with sulfonfonylureas [84-86], these drugs should be avoided if possible in diabetic patients with coronary artery disease.
Thiazolidinediones are widely used oral hypoglycemic agents which decrease glucose levels in type-2 diabetic patients by increasing the insulin sensitivity of target tissues and also by inducing a wide variety of nonglycemic effects mediated through activation of the peroxisome proliferator-activated receptor (PPAR)-γ nuclear receptor that may benefit the cardiovascular system [87,88]. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, 5,238 patients with diabetes mellitus who had evidence of macrovascular disease were randomized to oral pioglitazone titrated from 15 mg to 45 mg daily or to placebo to be taken in addition to their glucose-lowering drugs and other medications [89].

The primary endpoint was the composite of all-cause mortality, nonfatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. At 34.5 month follow-up, pioglitazone insignificantly reduced the primary endpoint by 10% [89].

In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, 5,269 adults aged 30 years or older with impaired fasting glucose or impaired glucose tolerance or both and no previous cardiovascular disease were randomized to rosiglitazone 8 mg daily or placebo and followed for a median of 3 years. The primary outcome was a composite of incident diabetes mellitus or death. At follow-up, 11.6% of persons given rosiglitazone and 26.0% of persons given placebo developed the composite primary outcome (a significant 60% reduction by rosiglitazone). Normoglycemia was significantly increased 71% by rosiglitazone (50.5% versus 30.3% by placebo). Cardiovascular event rates were similar in both groups, except for rosiglitazone significantly increasing heart failure (0.5% versus 0.1% in the placebo group) [90].

In both PROactive and DREAM, nonfatal congestive heart failure was significantly more common in patients treated with thiazolidinediones presumably because of reversible fluid retention rather than loss of myocardial function. Glitazones may precipitate heart failure in patients with poor left ventricular function and can worsen heart failure [91]. None of the thiazolidinediones are recommended for use in patients with NYHA Class III or IV heart failure.

Among the oral hypoglycemic agents, metformin is the most popular to use due to its favorable profile. Metformin lowers blood glucose both by increasing insulin sensitivity and by decreasing hepatic gluconeogenesis. While it improves glycemic control, this drug does not induce hypoglycemia. Metformin causes weight loss and a modest reduction in serum LDL cholesterol and triglyceride levels (92). Lactic acidosis is a rare but potentially life-threatening complication of metformin use and is seen more commonly in patients with renal insufficiency or with tissue hypoperfusion and hypoxemia [93]. Because patients with heart failure are at higher risk for hypoperfusion or hypoxemia, the use of metformin is contraindicated in those patients who require pharmacologic treatment of heart failure.

Three trials showed that intensive therapy improves the outcome of micro vascular disease [94-96]. Hyperglycemia is an important risk factor for the development of micro vascular disease in patients with diabetes mellitus. Improving glycemic control improves micro vascular outcomes.

The United Kingdom Prospective Diabetes Study (UKPDS) compared the efficacy of different treatment regimens (diet, sulfonylurea, metformin, and insulin) on glycemic control and the complications of diabetes mellitus. The target fasting blood glucose concentration was ≤108 mg/dL. Patients in the intensive-therapy group received a sulfonylurea or insulin. Metformin was added to the sulfonylurea if the fasting blood glucose concentration was >270 mg/dL, whereas insulin was initiated if the combination of oral agents remained ineffective. The conventional therapy group was treated with diet alone. Drugs were added if there were hyperglycemic symptoms or if the fasting blood glucose concentration was >270 mg/dL. Over 10 years, the average hemoglobin A1c value was 7% in the intensive-therapy group compared with 7.9% in the conventional therapy group (an 11% reduction). Most of the risk reduction in the intensive therapy group was due to a 25% significant risk reduction in micro vascular disease [94].

The Kumamoto study was a randomized controlled trial of 110 patients with type 2 diabetes mellitus randomized to a multiple insulin injection therapy group or a conventional insulin injection therapy group and followed for 10 years. The goal of therapy in the multiple insulin injection therapy groups was to reduce the hemoglobin A1c value below 7%. Compared to the conventional insulin injection therapy group, the multiple insulin injection therapy groups had a significant reduction in the progression of retinopathy by 67%, progression of nephropathy by 66%, albuminuria by 100% and clinical neuropathy by 64%. The multiple insulin injection therapy groups also had a significant prolongation of the period in which the patients were free of complications, including 2.0 years for progression of retinopathy, 1.5 years for progression of nephropathy, and 2.2 years for clinical neuropathy. The multiple insulin injection groups achieved a mean hemoglobin A1c level of 7.1% compared with 9.4% in the control group [95].

Diabetics with micro albuminuria have more severe angiographic coronary artery disease than diabetics without micro albuminuria [96]. The Action in Diabetes and Vascular disease: Preterax and Diamicron-Modified Release Controlled Evaluation (ADVANCE) trial assessed the potential benefits of blood pressure lowering using a fixed low-dose combination of perindopril and indapamide versus placebo and of tighter glucose control, using an intensive glitazide-MR-based glucose control regimen versus a standard guidelines-based regimen separately and together in 11,140 patients with long-standing diabetes mellitus. At 4.3-year follow-up, combination treatment significantly reduced the risk of new or worsening nephropathy by 33%, new onset macro albuminuria by 54% and new onset micro albuminuria by 26%. Combination treatment was associated with an 18% significant reduction in the risk of all-cause death. This study concluded that the effects of routine blood pressure lowering and intensive glucose control were independent of one another and when combined produced additional reductions in clinically relevant outcomes [97].

Target hemoglobin A1c levels in patients with type 2 diabetes mellitus should be tailored to the individual, balancing the improvement in micro vascular complications with the risk of hypoglycemia. Diabetics also have a significant increasing trend of hemoglobin A1c levels over the increasing number of vessels with coronary artery disease [98]. In addition, the higher the hemoglobin A1c levels in diabetics with peripheral arterial disease, the higher the prevalence of severe peripheral arterial disease [99].

A reasonable goal of therapy might be a hemoglobin A1c value of ≤7% for most patients. In order to achieve this hemoglobin A1c goal, a fasting glucose of 70 to 130 mg/dL and a postprandial glucose of <180 mg/dL are usually necessary.

Conclusion

Cardiovascular disease, particularly coronary artery disease, is a
major cause of morbidity and mortality among patients with diabetes mellitus. Compared to non diabetic patients, diabetic patients are more likely to have coronary artery disease, which is often multivessel, and to have episodes of silent myocardial ischemia. As a result of this and other factors, diabetic patients with coronary artery disease have a lower long-term survival rate than non diabetic patients with coronary artery disease. The medical and revascularization management of coronary artery disease are generally similar in patients with and without diabetes mellitus. However, the short-term and long-term results of revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery are often worse in diabetic patients. It is therefore of paramount importance that our healthcare system deliver quality primary and secondary prevention of diabetes mellitus with the goal to reducing its prevalence as well as lessening the progression of its micro vascular and macro vascular complications.

References


