Chapter 10

Diabetes and Coronary Artery Disease – Pathophysiologic Insights and Therapeutic Implications

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http://dx.doi.org/10.5772/61875

Abstract

Cardiovascular disease is the leading cause of morbidity and mortality among people with diabetes worldwide, accounting for 60% of all deaths in diabetics. Despite advances in our pathophysiologic understanding of diabetic co-morbidities and measures to help counter these, diabetics still remain at increased risk for cardiovascular disease complicating our overall approach to management. Diabetics, in particularly type 2, are often fraught with additional risk factors contributing to their overall propensity for developing cardiovascular disease. These include, but are not limited to, obesity, dyslipidemia, poor glycemic control, lack of physical activity, and hypertension. In response to this, research driven guidelines focusing on primary prevention have continued to arise with new clinical targets and goals substantially changing our approach with the diabetic population. It is important to note early on, type 1 diabetics carry a higher risk of cardiovascular disease for which the pathophysiology is only recently being elucidated. The underlying relationship between cardiovascular events and risk factors is, however, not well understood. For this reason, management approaches to risk reduction have been extrapolated from experience in type 2 diabetes mellitus. The purpose of this chapter is to present the conclusions of current literature pertaining to blood pressure and blood glucose control, cholesterol management, aspirin therapy, and lifestyle modification. We present a synthesis of the new guidelines, and clinical targets, including preventative measures for subclinical cardiovascular disease for the contemporary management of patients with diabetes mellitus.

Keywords: Diabetes, atherosclerosis, coronary artery disease, glycemic control, antidiabetic medications

1. Introduction

1.1. Diabetes and cardiovascular risk: Scope of the problem

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in the diabetic population which is rapidly expanding around the globe and is increasing due to the rising epidemic of obesity and increasing sedentary lifestyle along with poor dietary habits.[1] The cardiovascular events associated with type 2 diabetes and the high incidence of other macrovascular complications, such as strokes and amputations, are major causes of illnesses and a large economic burden. Heart disease and strokes account for over 2/3 of mortality in the diabetic population who are 2–4 times more likely to have atherosclerotic heart disease compared to non-diabetic individuals. In fact, diabetes itself is considered a cardiovascular risk equivalent and the diabetic population is less likely to survive when they develop CVD, compared to their non-diabetic counterparts. While the additional risk diabetes confers cannot be completely eliminated, large benefit is seen when multiple risk factors and associated comorbid conditions are addressed globally in this patient population and addressed specifically with respect to treatment targets and goals.

1.2. Risk factors for cardiovascular disease in diabetes

Risk factors for increased CVD among people with diabetes include traditional ones such as insulin resistance, hypertension, dyslipidemia, central obesity, and cigarette smoking. Non-traditional risk factors include microalbuminuria, increased inflammation, oxidative stress, hyperuricemia, hypercoagulable states, endothelial dysfunction, decrease nitric oxide function, increase vascular reactivity and permeability, increased glycated end products, as well as stimulation of the renin angiotensin aldosterone (RAAS) system.

Modifiable Risk Factors	**Non-modifiable Risk Factors**
Overweight/obesity	Family history of diabetes or premature coronary disease
Sedentary lifestyle	Latino/Hispanic, Non-Hispanic black, Asian American, Native American, or Pacific Islander ethnicity
Hypertension	History of gestational diabetes
Elevated LDL-C and/or triglycerides and/or low HDL-C	History of infant delivery birth weight "/>9 pounds
Psychiatric illness	Polycystic ovarian syndrome
IGT, IFG	Age
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance	
Adapted from Diabetes Care Volume 38, Supplement 1, January 2015 [2]	

Table 1. Modifiable and non-modifiable risk factors associated with type 2 diabetes mellitus and cardiovascular disease

http://dx.doi.org/10.5772/61875

1.3. Hypertension

Hypertension is the most common comorbid disease associated with diabetes. It has been found to increase the risk of nephropathy, retinopathy, left ventricular hypertrophy, and cardiovascular events.[3] Prevention of these vascular complications is a worldwide priority as the prevalence of diabetics by 2030 is estimated to be approximately 350 million.[4] As a result, blood pressure (BP) management is arguably one of the more critical aspects of the care of the patient with diabetes. The current 2015 American Diabetes Association (ADA) recommendations are for all diabetics to achieve a systolic blood pressure (SBP) of <140 and a diastolic blood pressure (DBP) of <90. This has been revised to reflect the most recent high-quality evidence that exists to support a goal of DBP, 90 mmHg. Although, it has been traditionally recommended that diabetics achieve a blood pressure of less of 130/80, there is insufficient evidence to justify the benefit of this value.[5] While hypertension therapy is not the main focus of this chapter, it is important to realize that lifestyle therapy for hypertension should be offered to all patients as a reasonable first intervention; this includes weight loss, increased physical activity, and a Dietary Approaches to Stop Hypertension (DASH)–style diet. If despite this the patient is unable to achieve the goal BP pharmacological therapy should comprise a regimen that includes either an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor inhibitor (ARB)–either of which are effective in preventing the development or progression of microalbuminuria which reduces the incidence of new or worsening nephropathy.[6]

2. Hyperglycemia and cardiovascular risk

Hyperglycemia, even in the non-diabetic range such as impaired fasting glucose and/or impaired glucose tolerance (collectively classified as pre-diabetes) is associated with increased risk of coronary artery disease. This has been shown in several trials and also evidence exists that glycemic control is associated with decreased coronary artery disease. For example, the landmark United Kingdom Diabetes Perspective Study (UKPDS) showed a graded risk reduction in myocardial infarction among the diabetic population with 14% decreased risk for every 1% decrease in A1C. Glucose control is important and associated with decreased microvascular complications such as diabetic nephropathy, retinopathy, as well as neuropathy, with about 30% risk reduction with each 1% decrease in A1C, as evidenced from large trials in type 1 DM such as Diabetes Complication (DCCT) in type 1 diabetes and from UKPDS study in type 2 diabetes in patient with new onset/early onset diabetes.[7]

Long term follow up of these cohorts also provided evidence of decreased macrovascular disease such as in the Epidemiology of Diabetes Interventions and Complications (EDIC), a follow up of the DCCT trial where intensive blood glucose control reduced risk of any CVD event by 42% and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular causes by 57%.[8] However, tight glycemic control has been shown to be associated with increased mortality among high-risk population. In the large randomized controlled trial, ACCORD (Action to Control Cardiovascular Risk in Diabetes), tight control of blood glucose to a hemoglobin A1C of 6.4%, compared to 7.5% in the control group, was associated with a

22% increased mortality leading to premature termination of the study protocol. Furthermore, there was increased risk of hypoglycemia requiring assistance and an average of 10 kg weight gain in the period of 3.5 years of follow up. This study, as well as others, triggered a Position Statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) calling for an individualized patient approach with less stringent glycemic control for patients with established vascular complications, as well as those with longer diabetes duration and increased risk of hypoglycemia such as those with CKD and the elderly with long standing diabetes and neuropathy.

2.1. Cardiovascular disease in the high-risk diabetic sub-population

Diabetes disproportionately affects minority populations such as blacks, Hispanics, Native Americans, and South Asians. In these populations, the prevalence of diabetes is much higher compared to Whites and they are disproportionately affected by diabetes complications including chronic kidney disease, strokes, and coronary artery disease.

Premenopausal women with diabetes lose the estrogen protective effects that are partially mediated through nitric oxide and women with diabetes have worse outcomes compared to men when presented with acute coronary syndrome. Despite advances in the diagnosis and treatment of acute coronary syndrome, and through improved medical therapies such as revascularization, improved survival among men and women without diabetes as well as men with diabetes has been observed, but evidence suggests worse prognosis for women with diabetes remains.

2.2. Screening for cardiovascular disease

Screening of asymptomatic patients with high CVD risk is not recommended, as there have been no trials that demonstrate improved outcomes even in the setting of angiographically defined coronary disease. One of the largest trials to address this concern was the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. DIAD randomized 1,123 subjects into two categories: those who would and would not be screened with stress myocardial perfusion imaging (MPI). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac events were lower than expected and equivalent in screened versus unscreened patients.[9] Furthermore, trials including the COURAGE and BARI 2D have shown no difference between revascularization and optimal medical therapy in patients who are effected by stable coronary disease supporting a less invasive approach to management. [10,11] The favorable cardiac outcomes among asymptomatic diabetics can likely be attributed to guideline-driven management of cardiac risk factors. Therefore, the current standard of care for type 2 diabetes should focus on the reduction of cardiovascular risk factors with avoidance of indiscriminate screening.

2.3. Type I diabetes mellitus

Type I diabetes is a challenging clinical entity. It deserves separate mention as its management has lagged in success when compared to type II diabetes.

http://dx.doi.org/10.5772/61875

Type I diabetes is associated with an increased risk of early death with acute diabetes-related complications responsible for the majority of younger deaths and cardiovascular disease the main cause for older patients.[12,13,14] CVD occurs much earlier in type I diabetics than in the general population—often after 2 decades of disease. This can occur as early as 30 years of age disease rates of >3% per year.[15] Poor glycemic control has correlated to cardiovascular risk (Table 2), however, the success rates of achieving optimal A1c levels is far from ideal. In two national registries, only 13% to 15% of patients with type 1 diabetes met a target A1c level of <7%.[16,13] The difficulty partially lies in dietary/insulin regimen adherence and risks of tight blood sugar control (absolute risk of severe hypoglycemia increasing with tighter control).[6]

Mean HbA1c	Death from any cause	Death from cardiovascular disease
≤ 6.9%	2.36 (95%CI: 1.97–2.83)	2.92 (95%CI: 2.07–4.13)
7.0%–7.8%	2.38 (95%CI: 2.02–2.80)	3.39 (95%CI: 2.49–4.61)
7.9%–8.7%	3.11 (95%CI: 2.66–3.62)	4.44 (95%CI: 3.32–5.96)
8.8%–9.6%	3.65 (95%CI: 3.11–4.30)	5.35 (95%CI: 3.94–7.26)
≥ 9.7%	8.51 (95%CI: 7.24–10.01)	10.46 (95%CI: 7.62–14.37)

Adapted from Lind et al [11].

Table 2. Adjusted hazard ratios for death from any cause and death from cardiovascular disease among individuals with type 1 diabetes vs control according to the glycated hemoglobin

Even when target glycemic control is achieved, the risk of death from cardiovascular causes is more than twice the risk in the general population and poor glycemic control portends a risk ten times higher.[17] The issue is complicated by several components highlighted by the Scottish Registry Linkage Study. Unlike type 2 diabetics, type 1 diabetics generally do not suffer from obesity and hypertension/dyslipidemia rates are not in excess of the general population.[18] At this time, there is no clear explanation for the additional risk. It is postulated that earlier onset and severely altered glucose homeostasis produces a variety of oxidative stressors promoting a milieu of underlying vascular disease. This may be especially true in the preadolescent years where subclinical disease manifests, priming the cardiovascular system for accelerated atherosclerosis despite the best efforts at achieving glycemic control later in life.[19] The term coined, *metabolic memory*, has been used to denote this theoretical process. The phenomenon gained support after a significant trend was noted at the conclusion of the DCCT and follow-up EDIC trial in regards to microvascular complications, e.g. nephropathy, retinopathy. In summary, the DCCT trial ended with a transition of participants to an intensive insulin regimen secondary to successful glycemic control and reduction in microvascular complications with this method. Interestingly, as the same patients were followed, those originally on the standard insulin regimen continued to have higher incidences of microvascular disease when compared to their counterpart. This occurred despite achieving near equivalent A1c levels.[20,21,22] The notion of early vascular stress portending a worse prognosis was also echoed in a recent Cochrane review where findings concluded that tight

control reduced the risk of developing microvascular diabetes complications (the risk for macrovascular complications was less clear secondary to the younger patient population they examined), but the impact became weaker once complications manifested.[23] Furthermore, during the EDIC study, macrovascular relationship became more apparent. Those participants who initially were under the intensive regimen experienced a 42% reduction in CVD events after 17 years. The ongoing EDIC showed these benefits persisted up to 10 years after the end of the DCCT.[7,24,25,26] These findings are promising as more effort is being placed at identifying subjects and initiating treatment earlier. Early therapy stands to eliminate or reduce a large amount of complications; however, longer-term studies are still needed to realize the full potential. It is also still unclear why cardiovascular complications start so early in the disease history when, presumably, only mild hyperglycemia exists.

3. Multifactorial therapy: A comprehensive evidence based approach

Over the past two decades, diabetes management has evolved substantially as epidemiologic and therapeutic based research has broadened our understanding of this complex disease. As a general principle, diabetes magnifies many of the indolent cardiovascular risk factors for morbidity and mortality amongst non-diabetic patients. As the population of diabetics increases, there is a growing effort to acknowledge the risks and lessen them to the best of our abilities. This begins with addressing modifiable risk factors for late complications in patients which includes hyperglycemia, hypertension, and dyslipidemia—all of which increase the risk of a poor outcomes.

Intensive treatment of multiple cardiovascular risk factors can have a major impact among patients with diabetes. Reduction in glycosylated hemoglobin values, systolic and diastolic blood pressure, fasting serum cholesterol and triglyceride levels, and urinary albumin excretion rate all have their value in reducing cardiovascular morbidity and mortality. Up until the turn of the century, numerous randomized trials investigated the effect of intensified intervention involving a single risk factor in patients with type 2 diabetes demonstrating benefits in terms of both macrovascular and microvascular complications in kidneys, eyes, and nerves.[27,28,29,30,31] This formed the basis of American Diabetes Association recommendations for many years which were finally bolstered by the landmark publication, Steno-2 study, which investigated a multifactorial, goal directed strategy involving lifestyle modification and pharmacologic management addressing all major metrics. An unrivalled 50% reduction in the risk of macro and micro-vascular events was demonstrated in those who received intensive treatment.[32] Since this study, several further trials have replicated these findings and have shown that the benefit of aggressive lifestyle and multi-drug therapy is effective and should be coupled with timely screening to confer a life-long benefit.[33,34,35]

3.1. Dietary management

Diet is one of the most important behavioral aspects of diabetes treatment, slowing and potentially preventing the rate of developing complications. Basic principles of nutritional

http://dx.doi.org/10.5772/61875

management have evolved over the past decade from a generalized approach to an individualized one in the form of medical nutrition therapy (MNT). This approach takes scientific evidence, individual goals and abilities into consideration to formulate lifestyle changes that can be maintained. It is monitored and guided by a dietician or nutritionist with regular follow up. Goals of MNT that apply to individuals with diabetes include achieving and maintaining (1) blood glucose levels in the normal range or as close to normal as is safely possible, (2) a lipid and lipoprotein profile that reduces the risk for vascular disease, (3) blood pressure levels in the normal range or as close to normal as is safely possible, (4) to prevent, or at least slow, the rate of development of the chronic complications of diabetes by modifying nutrient intake and lifestyle to address individual nutrition needs, taking into account personal and cultural preferences and willingness to change, and (5) the pleasure of eating by only limiting food choices when indicated by scientific evidence.[36] By the mid-90's diet directed research had bolstered this involved form of dietary intervention with promising results. Randomized controlled trials of MNT have reported decreases in HbA1c (A1C) of 1% in type 1 diabetics and 1–2% in type 2 diabetics, depending on the duration of diabetes. After initiation of MNT, improvements were apparent in 3–6 months.[10,37,38]

3.2. Lipid management

Both types of diabetes associated with a substantially increased risk of atherosclerotic vascular disease, identification of treatments for the prevention of major occlusive vascular events is a public-health priority.[39,40,41] The most recent meta-analyses have underscored the importance of lipid management and have changed the medical communities general approach to risk reduction in the diabetic community. There appears to be an approximately linear relationship between the absolute reductions in LDL cholesterol achieved in these trials and the proportional reductions in the incidence of major vascular events.[42,43] The implications of this is far reaching. What used to be a categorical approach with a goal cholesterol level in mind has broadened considerably. In all patients with diabetes over the age of 40 years moderate intensity statin treatment should be considered, in addition to lifestyle therapy (Table 3). If the patient falls under a 'high-risk' category—those with acute coronary syndromes or previous cardiovascular events, LDL cholesterol > 100mg/dL, high blood pressure, currently smoking and/or overweight should have more aggressive therapy with high doses of statins.[44,45] This strategy should be coupled with medical nutritional therapy.

3.2.1. Aspirin therapy

In general, patients with or without diabetes, who have known occlusive vascular disease, stand to benefit from long-term antiplatelet therapy with aspirin, reducing the yearly risk of serious vascular events. The benefits of antiplatelet therapy substantially exceed the risk of major bleeding events and it is therefore widely accepted as means of secondary prevention. For primary prevention, however, the balance is less clear with no single trial demonstrating a clear benefit.[46,47] In order to reconcile the uncertainty regarding primary prevention the American Diabetes Association performed a meta-analysis that added data from additional trials performed specifically in patients with diabetes to the data from the subgroups of

Age	Risk factors	Recommended statin dose*	Monitoring with lipid panel
< 40 years	None	None	Annually or as needed to monitor for adherence
	CVD risk factor(s)**	Moderate or high	
	Overt CVD***	High	
40-75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	High	
	Overt CVD	High	
>75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	Moderate or high	
	Overt CVD	High	

* Moderate-Intensity Statin Therapy: Atorvastatin 10-20 mg, Rosuvastatin 5-10 mg, Simvastatin 20-40 mg, Pravastatin 40-80 mg, Lovastatin 40 mg. High-Intensity Statins Therapy: Atorvastatin 80 mg, Rosuvastatin 20-40 mg

**CVD risk factors include LDL cholesterol $100 mg/dL (2.6 mmol/L), high blood pressure,

smoking, and overweight and obesity.

***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

Adapted from Diabetes Care Volume 38, Supplement 1, January 2015 [2]

Table 3. Recommendations for statin treatment in people with diabetes

patients with diabetes from the six trials included in the ATT (Antiplatelet Trialists' Collaboration Collaborative) meta-analysis. They concluded that aspirin appears to produce a modest-sized reduction in MI and stroke in patients with diabetes, but current evidence remains inconclusive. This was partially rectified by recent 14 trial meta-analysis which found a significant net benefit, but the authors still concluded inconclusiveness in regards to diabetic patients.[48,49,50]

In 2010, a position statement of the ADA, the American Heart Association, and the American College of Cardiology Foundation recommended physicians consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). However, aspirin was no longer recommended for those at low CVD risk (women under age 60 years and men under age 50 years with no major CVD risk factors; 10-year CVD risk under 5%) as the low benefit is likely to be outweighed by the risks of significant bleeding.[27]

3.3. Anti-diabetic medications and cardiovascular disease

Several classes of antidiabetic medications are currently available and effectively decreased hyperglycemia; however, concern regarding increased CVD risk was raised with the publication of the famous metanalysis by Nissen et al (2007) and showed rosiglitazone to be associated

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with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. This study eventually, as well as other concerns, led to the withdrawal of the medication from the European Union as well as severe restriction that amounted to effective withdrawal in the United States as well. These findings also prompted the FDA to require cardiovascular safety data prior to approval of new diabetes drugs in the USA. Currently, evidence available regarding cardiovascular safety and even protective effects for metformin either neutral or uncertain effects of others agents due to lack of long-term safety data.

4. Global control of cardiovascular risk in the diabetic population

The estimation and categorization of cardiovascular risk requires close attention to the risks being explored (Table 4). While certain CVD risks are modifiable such as smoking, obesity, hypertension and dyslipidemia, others are non-modifiable such as family history of premature coronary artery disease. Despite evidence for improved CVD outcomes with control of CVD risk factors, data from our group (McFarlane et al., 2002, 2005) conducted at multiple centers in the USA, among various ethnic groups and practice settings, showed largely suboptimal control of glycemia, blood pressure, and cholesterol and also demonstrated gender disparity in the outcomes of diabetic care. For these reasons, a multifactorial targeted and evidence based approach as detailed in this chapter needs to be employed for the appropriate and adequate management of these diabetic patients at risk for cardiovascular disease.

Modifiable Risk Factors	Non-Modifiable Risk Factors
Hypertension	Age
Diabetes	Sex
Dyslipidemia	Race/Ethnicity
Tobacco Use	Family history of premature CAD
Poor dietary habits (high fat, high carbohydrate)	
Sedentary lifestyle	
Obesity (particularly central distribution)	
microalbuminuria	
Increased inflammation	
Stimulation of RAAS	

CAD= Coronary artery disease

RAAS = Renin Angiotensin Aldosterone System

Table 4. Risk Factor Categorization

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