

18 The Dual Epidemic of Diabetes and Heart Disease

Abstract: The epidemic of Diabetes is growing at an unprecedented rate. According to the World Health Organization, at least 171 million people worldwide have diabetes and this figure is likely to be more than double by 2030. WHO predicts that developing countries will bear the brunt of this epidemic in the 21st century, with 80% of all new cases of diabetes is expected to appear in the developing countries by 2020. Among developing countries, the highest increase in prevalence will be in China followed by India. However, the greatest increase in numbers will be seen in India, where the number of diabetics will rise from 19 million in 1995 to 57 million in 2025, heading the list of countries with the greatest numbers of diabetics. India is thus destined to become the “diabetes capital of the world”. The global increase in diabetes occurs because of population ageing and growth, and because of increasing trends towards obesity, unhealthy diet and sedentary lifestyle.

Diabetes has been rated as an equivalent of coronary heart disease (CHD), hence there is a proportionate increase in the number of cases of coronary artery disease (CAD) world over. Apart from CAD, diabetes also increases the risk of cardiomyopathy and heart failure, thereby contributing to mortality and morbidity. Every 10 seconds a person dies from diabetes-related causes, mainly from cardiovascular disease. This dual epidemic of heart disease and diabetes has serious social and economic consequences. In 2007, the world is estimated to spend at least US\$ 232 billion to treat and prevent diabetes and its complications. In industrialized countries, about 25% of medical expenditures are used for treating diabetics elevated blood sugar; 25% for treating long-term complications, largely cardiovascular disease, and 50% is consumed by the additional general medical care that is associated with diabetes.

Estimated combined cost of diabetes, heart disease and stroke over the next 10 years: (WHO)

- \$555.7 billion is lost as national income in China
- \$303.2 billion in the Russian Federation
- \$333.6 billion in India
- \$49.2 billion in Brazil
- \$2.5 billion even in like Tanzania

With such disastrous social and economic consequences, it is fair enough to say that the dual epidemic of diabetes and heart disease poses one of the biggest challenges to modern medicine today.

DIABETES AND HEART: THE RELATIONSHIP?

Approximately 80% of all deaths and over 75% of all hospitalizations in people with diabetes are due to cardiovascular disease, primarily CAD. Several studies have demonstrated that diabetics have a CAD risk that is two to three times higher in diabetics and particularly higher in women with diabetes. In the Multiple Risk Factor Intervention Trial, the age-adjusted incidence of CAD was 4 times greater in people with diabetes than in those without diabetes.

Heart Failure and Cardiomyopathy

Congestive heart failure is twice as prevalent in diabetic men and five times as common in diabetic women when compared to their non diabetic counterparts mainly due to the high prevalence of CAD and hypertension among diabetics. Diabetic cardiomyopathy is another distinct entity that results in diastolic dysfunction in the absence of any co-existing CAD¹. It occurs as a consequence of hyperglycemia although hypertension alongwith several other factors are also contributory. Diabetes is also the leading cause of idiopathic dilated cardiomyopathy.

Idiopathic dilated cardiomyopathy mainly presents as systolic dysfunction in the absence of ischemia, alcohol, myocarditis or any other risk factor for cardiomyopathy.

Cardiac Autonomic Neuropathy

Cardiac autonomic neuropathy is one of the long-term complications of diabetes. It occurs more often in the patients with peripheral autonomic dysfunction and is a leading cause of sudden cardiac death and silent MI in diabetics.

Diabetes and Coronary Artery Disease

Is CAD Different in Diabetics?

The epidemiology, presentation and the prognosis of CAD is altered by the presence of co-existing diabetes. CAD in diabetics has the following characteristics:

- Diabetics are 2 to 4 times more prone to develop CAD when compared to non-diabetics.
- In people with diabetes, CAD occurs at a younger age and women are affected as often as men.
- The disease tends to be more severe and extensive, with more common involvement of the LAD artery.²
- Silent ischemia atypical symptoms are common among patients with diabetes and CAD. In the Framingham heart study up to 32-42 % of the diabetics with MI had atypical symptoms when compared to 6-15 % among non-diabetics.³ Silent ischemia may be due to the coexistence of autonomic neuropathy in diabetics, however, recent studies have shown that silent ischemia may occur in the absence of autonomic neuropathy, the exact reason being unknown.
- Diabetics with CAD have higher morbidity and mortality and hence a worse outcome ⁴. Table 1 shows the case fatality rates in diabetics vs. non diabetics.

Table 1: Risk of Fatal CAD in Diabetic vs. Non-Diabetic White Adults*

Population	Age year	Years follow-up	Sex	Number		Adjusted risk ratio	
				Diabetic	Non-diabetic	Duration	Multiple
Alameda	>40	9	M	51	1648	–	1.5
Country, CA			F	70	1982	3.5	3.1
Chicago, IL	35-64	9	M	377	10843	4.0	3.8
			F	170	7860	5.9	4.7
NHANES I	40-77	9	M	189	3151	2.3	2.4
			F	218	3823	2.8	2.6
Rancho	40-79	14	M	207	893	1.8	3.3
Bernardo, CA			F	127	1224	3.3	3.3
Nurses Health Study	30-55	8	M	1483	114694	6.9	–
New Haven, CT.	>65	6	M	156	994	–	1.6
			F	230	1388	–	4.5

* *RSSDI Textbook of Diabetes Second Edition, 2008, Chapter 60.*

Epidemiology of CAD in Type 1 Diabetes

The long term follow up of patients with type 1 DM has demonstrated that the first indications of clinically manifested CAD appears late in the third or fourth decade of life, regardless of whether diabetes developed early in childhood or in late adolescence. The CAD risk increases rapidly

after the age of 40. By 55 years of age, 35% of diabetic men and women are likely to die from a coronary event.⁵

The Wisconsin Study and the Health Study are two large prospective studies of CAD in diabetes, which separately reported CAD incidence in persons with Type 1 diabetes, and Type 2 diabetes. Wisconsin study showed that CAD relative risk estimates in men with Type 1 diabetes or Type 2 diabetes were 9.1 and 2.4 respectively while in women, the same were 13.5 and 2.2.⁶ Among the nurses, the age adjusted relative risks of CAD for diabetic vs. non-diabetic women were 12.2 for Type 1 diabetes compared to Type 2 diabetes.⁷ The reports of these studies clearly indicated that Type 1 diabetics have a higher relative risk of CAD. According to Barret-Connor, et al the higher relative risks associated with Type 1 diabetes may reflect the greater duration of diabetes, more severe metabolic disturbances and the relatively low CAD rates among persons without diabetes.

The Role of Nephropathy

It has been reported that kidney involvement even in the earliest stages increases the risk of CAD. The patients with Type 1 DM followed from the onset of micro-albuminuria developed CAD eight times more frequently than patients without micro-albuminuria. Micro-albuminuria therefore, is not only an indicator of renal disease but is also a strong risk factor for CAD. Krolewski reported that the risk of development of CAD in patients with persistent proteinuria was 15 times higher as compared to those without proteinuria.⁷ Similarly, a long term follow up study conducted at Steno Memorial hospital (Denmark) showed that patients with persistent proteinuria had a 37 fold increase in mortality from CAD relative to the general population.⁸ The risk for the development of diabetic nephropathy is only partially determined by glycemic control and is highly influenced by genetic susceptibility.

Epidemiology of CAD in Type 2 Diabetes

The Strong Heart Study conducted in 13 American Indian communities in Arizona, Oklahoma and Dakotas, showed two to three fold increase in prevalence of CAD in diabetic than in non-diabetic subjects in all the groups and both the sexes.⁹ Similarly, three studies in Finland also revealed that the rate of MI was two to four times higher in diabetics when compared to non-diabetics.

Epidemiological Variations According to Age, Sex and Duration of Diabetes

The incidence and prevalence of CAD in DM varies according to age, sex, race, and duration of DM and the presence of the risk factors. In Framingham study, the average annual incidence of cardiovascular disease per 1000 persons at risk was calculated in three age groups i.e. 45-54 years, 55-64 years and 65-74 years. Both in males and females the highest relative risk for CAD in diabetics was in the younger age group of 45-54 years.¹⁰ The overall prevalence of CAD in male diabetics was two fold higher than non-diabetic whereas it was three fold higher in the female diabetics than non-diabetics. The effect of duration of DM on the development of CAD was assessed in a 24-year follow up study of patients at Joslin Center. The cause of death was CAD in 38% of men and in 39% of women. The increasing risk of CAD with duration of diabetes reflects the combined effect of aging and hyperglycemia.

Nephropathy and CAD

In Type 2 diabetes, the diabetic nephropathy in all the three stages namely microalbuminuria, macroalbuminuria and end stage renal disease (ESRD) serves as a fertile soil in the occurrence of ischemic heart disease (IHD) and cardiomyopathy. Macroalbuminuria usually heralds the development of both microvascular (retinopathy) and macrovascular diseases. Recent data

suggests that micro albuminuria is a surrogate marker not only for glomerular injury but also for diffusely increased endothelial permissibility, which correlates with cardiovascular morbidity and mortality.¹¹

Several mechanisms are implicated in the development of atherosclerotic process in the presence of diabetic nephropathy. The onset of microalbuminuria is associated with the development of hypertension and with numerous prothrombotic and atherogenic changes, including raised triglycerides, low HDL cholesterol and increased circulating levels of factor VII, PAI-1 and fibrinogen. These changes may possibly contribute to the increased risk of CAD in the setting of nephropathy.

Gender Difference in the Epidemiology of Diabetes and CAD: The Effect of Diabetes on CAD in Women

In the general population women are considered to be at a much lower risk of CAD mortality than men. Lee et al carried out a meta-analysis of seven prospective cohort studies and reported the impact of the risk of CAD in diabetic men and women.¹² The analysis suggests that the relative risk of CAD death from diabetes is higher among women when compared to that of men (relative risk for women is 2.5 vs 1.85 for men). In Framingham study, the overall prevalence of CAD in male diabetics is two fold higher than non-diabetics whereas it is three fold higher in the female diabetics than non-diabetics. Hu, et al examined mortality from all causes and from CAD among 121046 women aged 30-55 years with Type 2 diabetes in the Nurses Health Study who were followed up for 2 years.¹³ Compared with women with no diabetes or CAD at baseline, age adjusted relative risks of fatal CAD was 8.7 for women with a history of diabetes and no CAD at baseline, 10.6 for women with a history of CAD and no diabetes at baseline and 25.8 for women with both conditions at baseline. Thus diabetes seems to negate the protective effect provided by estrogen in women rendering them more susceptible to CAD.

Average annual incidence of cardiovascular disease per 1000 persons at risk (Adopted from Framingham study) Table 2.

Table 2: Annual incidence of CVD Framingham study

Age	Men		Women	
	Diabetics	Non-diabetics	Diabetics	Non-diabetics
45-54	31.7	12.3	24.8	4.3
55-64	48.1	25.1	37.9	12.6
65-74	57.1	28.4	40.4	22.4
Total	39.1	19.1	27.2	10.2

CAD in Indians

Indians have a higher risk of developing CAD, by 20 times higher than Japanese, 6 times higher than Chinese, and 4 times more than Americans.

CAD in Indians has the following peculiarities:

- Commonly manifests at an earlier age, usually a decade earlier (around 45-50 years); 3 to 25% are less than 40 years of age.
- Indians in 30-39 years have 10 times greater risk of AMI than Caucasians of same age.

- Indians with CAD have more extensive triple vessel disease (54% against 21%) than western world; commonly manifests with AMI without prior Angina. Analysis of coronary risk factors often fails to explain marked differences in CAD rates among different ethnic groups.
- The prevalence of CAD in India is higher despite lower prevalence of smoking (3% against 27%), hypertension (14% against 19 %), elevated cholesterol (.240 mg/dl) (17% against 23%), and obesity (31% against 3%) and higher prevalence of spiritual faith and vegetarianism. As per Framingham's study, 30-35% Indians with CAD lack traditional risk factors except for DM (8% against 1% in the West).
- Combination of abdominal obesity, impaired glucose tolerance, hyperinsulinaemia, raised triglyceride, decreased HDL, hypertension known as Syndrome X constitutes a potential risk for CAD among Indians.

Table 3: Prevalence of CAD in diabetes in India*

Author	Year	Place	Prevalence of CAD (%)	
			Male	Female
ICMR	1984-87	Multicentric	8.1	4.7
A Ramachandran	1998	Chennai	3.9	10.3
V Mohan	2001	Chennai		21.40
PODIS	2001	Multicentric		4.50
Gupta P B	2001	Surat		19
Phatak S R	2002	Ahmedabad	20.2	26.1
Agrawal R P	2004	Bikaner, W.India	19.2,	>40 years

Table 4: Prevalence of CAD in migrant diabetic Indians*

State	Country	Sample size (age cut off in yrs)	Year	Prevalence of CAD (%)
London	UK	1421 (40-69)	1993	17
Illinois	USA	1688 (>=20)	1996	10

* RSSDI Textbook of Diabetes Second Edition, 2008, Chapter 60.

CAD in Immigrant Indians

In the course of time, people of Indian origin have migrated to different countries of the world and they share the common genetic predisposition to higher prevalence of CAD. Autopsy reports of Indians and those done in Singapore in 1959 revealed that Indians have seven times higher prevalence of CAD than Chinese males.¹⁴ Several other studies from Singapore, Uganda, South Africa, and Fiji, have also indicated that in Indians the prevalence of CAD was three times higher as compared to respective relative native populations. In the Southall Study the prevalence of CAD was 4% in India-born men as compared to 2.3% in Europeans. Amongst the first generation immigrant Indian physicians in USA it was found that CAD was 3 times more in Indian men (mean age 46.4 years) as compared to the men in Framingham Offspring Study.¹⁵ Thus it can be concluded that the prevalence of CAD among immigrant Indians is about 3 times higher than in indigenous population. Further the mortality due to CAD is quite high among Indian immigrants in all age group particularly in young persons.

CAD and Pre Diabetes^{17,18}

Clinically evident Type 2 diabetes is a well-established cause of CAD and its increased mortality. Many studies have shown that even the subclinical stages of glucose intolerance (comprising of undiagnosed diabetes and IGT) increased the risk of CAD and related mortality. Saydah et al conducted a prospective study to compare the all cause mortality among individuals with diagnosed type 2 diabetes, undiagnosed diabetes and IGT with individuals having NGT in the general US population.¹⁶ They found that in comparison to those with NGT the multivariate adjusted relative risk (RR) of all cause mortality was greatest for adults with diagnosed diabetes (RR-2.11), followed by those with undiagnosed diabetes (RR-1.77) and those with IGT (RR-1.42). A similar pattern of risk was observed for CAD mortality. Further, Haffner et al examined the risk factors in confirmed pre-diabetic individuals and showed that the risk for CAD starts from the stage of IGT itself i.e., even before overt diabetes sets in. He concluded that the clock for CAD starts ticking before the onset of clinical diabetes.¹⁷ Similar results were shown in south Indian population in CUPS study by Mohan and co-workers in Chennai.

Impact of Diabetes on CAD Mortality

A Finnish study by Haffner in 1998 compared the risk of myocardial infarction (MI) over a 7-year period among non-diabetic and diabetic subjects.¹⁸ The patients with DM and no prior MI had a 20.2% incidence of MI during the 7-year follow-up, similar to that of non-diabetic subjects with prior MI (18.8%). It also compared the probability of death from CAD in diabetics vs non-diabetic subjects and showed that the probability of mortality due to CAD is similar in diabetic subjects without prior MI as in non-diabetic subjects with prior MI. Similarly, in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry, diabetic patients without prior cardiovascular disease had the same event rates for all outcomes, as did non-diabetic patients with prior cardiovascular disease. These Adult Treatment Panel III of the National Cholesterol Education Program to establish and emphasize that diabetes is equivalent to CAD requiring aggressive therapy and this was based on the observations from Framingham and other studies.

Pathogenesis of CAD

Hyperglycemia, insulin resistance, central obesity, dyslipidemia, hypertension and altered coagulation profile are the key pathogenic mechanisms for the development of CAD in diabetes. Two of these factors seem to contribute significantly for the increase in cardiovascular disease among diabetics. One, the effects of hyperglycemia per se on cardiovascular disease, and the other the metabolic syndrome, which is a common determinant for both the conditions.

Hyperglycemia as a Risk Factor

According to the reports of EUROASPIRE I Trial, apart from smoking, diabetes is the single most important risk factor for the development of CAD. In the EUROASPIRE II Study, 29% of all coronary patients had known diabetes and another 23% had impaired glucose tolerance. Several other studies revealed an association between 2 hours plasma glucose (PG) and CAD in the general population. The most convincing evidence for a relation between abnormal glucose tolerance and an increased CAD risk has been provided by the DECODE Study, jointly analysing data from more than 10 prospective European cohort studies including more than 22 000 subjects. Death rates from all-causes, CVD, and CAD were higher in diabetic subjects diagnosed by 2-hour PG than in those not meeting this criterion. Significantly, increased mortality was also observed in subjects with IGT, whereas there was no difference in mortality between subjects with impaired and normal fasting glucose. Thus postprandial hyperglycemia seems to be directly linked with cardiovascular disease and its mortality. Post-prandial (post-load) glucose provides better information about the future risk for CVD than fasting glucose, and elevated post-prandial glucose also predicts the cardiovascular risks in subjects with normal fasting glucose levels.

Hyperglycemia Induced Oxidative Stress and Endothelial Dysfunction (Fig. 1)

Several lines of evidence support the concept that hyperglycemia decreases endothelium-derived nitric oxide (NO) availability and affects vascular function mainly through the overproduction of reactive oxygen species (ROS). The mitochondrial electron transport chain is probably one of the first targets of high glucose, with a direct net increase in superoxide formation. A further increase in superoxide production is driven by a vicious circle involving ROS-induced activation of protein kinase C (PKC) and vice versa. PKC activation induces an upregulation of inducible COX-2 and eNOS expression as well as a selective increase of thromboxane production and reduced NO release. Hence, activation of the PKC pathway represents a proximal node in the intracellular signaling leading to hyperglycemia-induced oxidative stress and endothelial dysfunction.¹⁹

AGE and RAGE in Cardiac Disease

Mitochondrial production of superoxide increases intracellular formation of advanced glycation end-products (AGEs), which adversely affects the endothelial function by increasing ROS production and inflammatory cytokines from vascular cells, thereby enhancing endothelial expression of various adhesion molecules implicated in atherogenesis. Moreover, activation of the receptor for AGEs (RAGE) increases intracellular superoxide anion production and seems to represent a key step in atherosclerotic lesion development.²⁰

Role of Insulin Resistance

Insulin resistance is a typical characteristic of type 2 diabetes. Insulin stimulates NO production from endothelial cells by increasing the activity of NOS via activation of phosphatidylinositol-3 kinase (PI-3K) and Akt kinase. Thus, in healthy subjects, insulin increases endothelium dependent (NO-mediated) vasodilatation. On the contrary, endothelium-dependent vasodilatation is reduced in insulin resistant subjects.²⁰

Role of Diabetic Dyslipidemia

Classically, DM induces elevation in triglyceride and LDL, and decline in HDL plasma levels. These changes clearly affect the natural history of the atherosclerotic disease, and render patients with diabetes more prone to develop CAD. Recent evidence confers to diabetes-related enhanced FFA liberation, a crucial role in producing the well-described changes in lipid profile. Excess circulating levels of FFA results from both enhanced release from adipose tissue and reduced uptake by skeletal muscle. The liver responds to FFA excess by increasing VLDL production and cholesteryl ester synthesis. The accumulation of triglyceride-rich lipoproteins, depends also on their reduced clearance by lipoprotein lipase, triggers hyper-triglyceridemia and lowers HDL levels by promoting exchanges from HDL to VLDL via cholesteryl ester transfer protein. HDLs are not only reduced in quantity, but also impaired in function. Moreover, increase VLDL production and abnormal cholesterol and triglyceride transfer between VLDL and LDL enhances plasma levels of small and dense proatherogenic LDLs, which are more prone to thrombosis and coagulation.

Platelet function is crucial in determining the natural history of atherosclerosis and consequences of plaque rupture. The intracellular platelet glucose concentration mirrors the extracellular environment and is associated with increased superoxide anion formation, PKC activity, and decreased platelet-derived NO. Moreover, diabetic patients show increased expression of glycoprotein Ib and IIb/IIIa, which enhances both platelet-von Willebrand factor and platelet-fibrin interaction. Hyperglycemia further affects platelet function by impairing calcium homeostasis, and thereby altering platelet conformation, secretion, aggregation, and thromboxane formation. Moreover, blood coagulability is enhanced in diabetic patients. Plasma

coagulation factors (e.g. factor VII and thrombin), lesion-based coagulants (e.g. tissue factor), plasminogen activator inhibitor-1 (PAI-1) (a fibrinolysis inhibitor) are increased, and endogenous anticoagulants (e.g. thrombomodulin and protein C) are decreased. Thus, a propensity for platelet activation and aggregation, coupled with a tendency for coagulation, amplify the risk that plaque rupture results in thrombotic occlusion of arteries.²⁰

The Cardiometabolic Approach (Fig. 2)

Diabetes and cardiovascular diseases (CVD) often appear as the two sides of a coin: on one side, DM has been rated as an equivalent of CHD, and conversely, many patients with established CHD suffer from diabetes or its pre-states. Thus, it is high time that diabetologists and cardiologists join forces together to improve the quality management in diagnosis and care of diabetes.¹⁹

Screening for Diabetes in Patients with CAD

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. However, screening the general population for the disease is not cost effective and unnecessary. Only individuals at high risk should be screened for diabetes and pre-diabetes. All people with CAD should be screened for diabetes.

The ADA has laid down the following criteria for screening asymptomatic individuals for diabetes/pre diabetes.²⁶

1. Testing for diabetes should be considered in all individuals at age 45 years and above, particularly in those with a BMI ≥ 25 kg/m², and, if normal, should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight (BMI ≥ 25 kg/m²) and have additional risk factors:
 - Are habitually physically inactive
 - Have a first-degree relative with diabetes
 - Are members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
 - Have delivered a baby weighing >9 lb or have been diagnosed with GDM
 - Are hypertensive (140/90 mmHg)
 - Have an HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)
 - Have polycystic ovarian syndrome (PCOS)
 - On previous testing, had IGT or IFG
 - Have other clinical conditions associated with insulin resistance (e.g., PCOS or *Acanthosis nigricans*)
 - Have a history of CVD.

The Screening Test

The ADA recommends using fasting plasma glucose for screening of diabetes in high risk groups. However, since postprandial glucose is more directly related to CAD, OGTT after a 75 gm glucose load seems to be a better screening test especially in patients with CAD.¹⁹

Preventing Cardiovascular Disease in Diabetics

Increasing evidence indicates that controlling both major CVD risk factors (cigarette smoking, hypertension, elevated LDL-C and hyperglycemia) and underlying risk factors (obesity, physical inactivity, and adverse nutrition) will reduce the onset of CVD in diabetics.

LIFESTYLE MODIFICATIONS²⁰

Medical Nutritional Therapy (MNT)

Individuals who have pre-diabetes or diabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of diabetes MNT. Eating between three and five servings of fruit and vegetables a day and eating less sugar and saturated fats has been recommended.

Physical Activity

To improve glycemic control, assist with weight maintenance, and reduce risk of CVD, at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate) and/or at least 90 min/week of vigorous aerobic exercise (>70% of maximum heart rate) is recommended. The physical activity should be distributed over at least 3 days/week and with no more than two consecutive days without physical activity.

Blood Pressure

Hypertension is up to three times more common in patients with type 2 DM than in non-diabetic subjects and is frequent in patients with type 1 diabetes as well. The UKPDS and the Hypertension Optimal Treatment (HOT) study revealed that an intensive blood pressure-lowering treatment strategy is associated with a lower incidence of cardiovascular complications (57% lower risk when diastolic BP < 80 mm Hg) in patients with diabetes.²²

Chosen as the initial drug, the beneficial effect of diuretics, calcium channel blockers (CCB), beta-blockers (BB) and ACE-inhibitors are well documented. In the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the outcome was similar in subgroups treated with a diuretic, an ACE-inhibitor, or a CCB. Blockade of the renin-angiotensin-aldosterone system seems to be of particular value, especially when treating hypertension in patients with diabetes at particularly high cardiovascular risk. In the Losartan Intervention for Endpoint reduction in hypertension. Study (LIFE), recruiting patients at high risk due to established LV hypertrophy, blood pressure-lowering therapy initiated with the angiotensin receptor blocker (ARB), losartan, was more effective in reducing the primary composite cardiovascular endpoint than the selective β blocker atenolol. In this study, the beneficial effect of losartan was even more apparent in the diabetic subpopulation.

Recommendations

Patients with diabetes should be treated to a systolic blood pressure <130 mm Hg and a diastolic blood pressure < 80 mm Hg.²¹

Patients with hypertension (systolic blood pressure >140 or diastolic blood pressure >90 mm Hg) should receive drug therapy in addition to lifestyle and behavioral therapy. All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor or an ARB. Patients with a systolic blood pressure of 130–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg should be given lifestyle and behavioral therapy alone for a maximum of 3 months and then, if targets are not achieved, in addition, be treated with pharmacological agents that block the renin-angiotensin system.

Dyslipidemia/Lipid Management

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, which contributes to higher rates of CVD. In studies using statins, patients with diabetes achieved

significant reductions in coronary and cerebrovascular events. A post hoc sub group analysis on data from 202 diabetics out of a total of 4444 subjects with previous MI or angina, included in the Scandinavian Simvastatin Survival Study (4S) demonstrated that cholesterol lowering therapy in MI was highly effective in reducing total mortality and cardiovascular events. The Heart Protection Study demonstrated that in individuals with diabetes over the age of 40 years with a total cholesterol >135 mg/dl, LDL reduction of 30% from baseline with the statin simvastatin was associated with an 25% reduction in the first event rate for major coronary artery events independent of baseline LDL, preexisting vascular disease, type or duration of diabetes, or adequacy of glycemic control. Similarly The Collaborative Atorvastatin Diabetes Study (CARDS), compared atorvastatin 10 mg to placebo, in a population of patients with type 2 diabetes (aged 40-75 years) without high cholesterol [baseline LDL 3 (116 mg/dL)], but along with any other risk factors for CVD: hypertension, retinopathy, proteinuria, or cigarette smoking. After a median follow-up of 3.9 years, the risk reduction in first major cardiovascular events was 37%.

Recommendations

In individuals without overt CVD:²¹

- The primary goal is LDL <100 mg/dl .
- For those over the age of 40 years, statin therapy should be started to achieve an LDL reduction of 30-40% regardless of baseline LDL levels.
- For those under the age of 40 years but at an increased risk due to other cardiovascular risk factors who do not achieve lipid goals with lifestyle modifications alone, the addition of pharmacological therapy is appropriate.
- The use of fibrates has been recommended in patients with high triglyceride values but the benefit accruing is debatable.

Antiplatelet Agents

Many trials using antiplatelet agents have shown an 30% decrease in MI and a 20% decrease in stroke in a wide range of patients, including young and middle-aged patients, patients with and without a history of CVD, males and females, and patients with hypertension.

Aspirin therapy (75-162 mg/day) is recommended as a primary/secondary prevention strategy in those with Type 1 or Type 2 diabetes.

Aspirin therapy should be considered in patients between the age of 30 and 40 years, particularly in the presence of other cardiovascular risk factors. Combination therapy using other antiplatelet agents such as clopidogrel in addition to aspirin have also been tried in patients with severe and progressive CVD.²⁶

Smoking Cessation

Cigarette smoking contributes to one in every five deaths in the US and is the most important modifiable cause of premature death. Smoking is also related to the premature development of microvascular complications of diabetes and may have a role in the development of Type 2 diabetes.

Glycemic Control

Tight glucose control significantly decreases the risk of developing both micro and macro vascular complications.

Tight Glucose Control and Microvascular Complications

In Type 2 Diabetes, the UK Prospective Diabetes Study (UKPDS) demonstrated significant reductions in microvascular and neuropathic complications with intensive therapy. Each 1%

reduction in mean HbA1c was associated with, and 25% for microvascular complications²². Similarly the DCCT (Diabetes Control and Complications Trial) in Type 1 diabetics, showed that intensive glycemic control (HbA1c < 7%) had considerably decreased the risk of micro vascular complications. Each 1% reduction in HbA1c in the DCCT study was associated with a 32% risk reduction in the development of retinopathy, 24-27% risk reduction in the development of nephropathy and upto 30 % risk reduction in the development of neuropathy.²⁴

Tight Glucose Control and Macrovascular Complications

The EDIC Study (Epidemiology of Diabetes Interventions and Complications) is a 8 yr follow up study of the patients included in the DCCT trial. It convincingly demonstrated that a randomly assigned intervention (continuous subcutaneous insulin infusion Vs multiple dose insulin injections), aiming at tight glycemic control (mean HbA1c close to 7% over the first 7-10 years), effectively reduced cardiac and other macrovascular disease by 42%. The risk for MI and stroke, as well as the mortality risk from CVD, was reduced by 57%. In Type 2 diabetes, as shown by the UKPDS, each percent decline of HbA1c caused a 14% lower rate of MI and fewer deaths from diabetes or due to any other cause.²⁵ In the Kumamoto Trial, a lower HbA1c (7.0%) resulted in a cardiovascular event rate over less than 10 years than half in the control group.²⁶ This difference did not, however, reach statistical significance due to small absolute numbers. The Steno 2 Study, with its target HbA1c target below 6.5 %, reported a highly significant reduction of macrovascular events over 7.8 years.

Thus tight glycemic control can considerably decrease the risk of both micro and macro vascular complications of diabetes.²⁵ The goal of therapy is to achieve an A1c as close to normal as possible in the absence of hypoglycemia. The recommended goals for glycemic control as per the ADA position statement for diabetes care 2007 included an HbA1c level of < 7%. The European guidelines for cardiovascular disease prevention has lowered the goal to a HbA1c value of <6.5 %. Addressing the impact of more stringent glycemic control on cardiovascular end points is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. This 5-year trial involving > 10,000 subjects is aiming for an A1c of < 6% in the intensive glycemia group and 7.0-7.9% in the control glycemia group. It is targeted for completion in 2010.

Prevention and Management of Diabetes and CVD (European Guidelines)

The main issues in the management of CAD in diabetes include:

- Detection of silent ischemia
- Management of ACS
- Revascularization in diabetics with CAD.

Detection of Silent Ischemia

Diabetics have a high rate of asymptomatic CAD, silent ischemia and unrecognized MI due to co-existing autonomic neuropathy. Recent evidence from the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study suggests that more than 22% of asymptomatic patients with Type 2 diabetes show evidence of ischemia on stress myocardial perfusion scanning. However, routine screening of all asymptomatic diabetics for silent ischemia is not recommended. According to the ADA all type 2 diabetics with baseline ECG abnormalities, atypical chest pain and multiple risk factors should be screened for ischemia using exercise -ECG or stress ECHO or any another appropriate imaging modality.

Indications for Cardiac Testing in Diabetic Patients¹⁹

Testing for CAD is warranted in patients with the following:

- Typical or atypical cardiac symptoms
- Resting ECG suggestive of ischemia
- Peripheral or carotid occlusive disease
- Sedentary lifestyle, age > 35 yrs and plans to begin a vigorous exercise program
- Two or more of the following:
 - Dyslipidemia
 - BP > 140/90 mm Hg
 - Smoking
 - Family history of premature CAD
 - Positive micro/macroalbuminuria test.

Diabetes and Acute Coronary Syndrome (ACS)

Upto 30 % of patients with acute coronary syndrome have diabetes. When patients with AMI, but without known diabetes, are challenged with an OGTT, upto 65% have an abnormal glucose regulation (either diabetes or impaired glucose tolerance). Patients with previously known diabetes admitted with ACS, have higher in-hospital mortality in MI, than patients without diabetes. The main complications in patients with ACS include recurrent myocardial ischemia, LV dysfunction, symptomatic heart failure, electrical instability (ventricular fibrillation, ventricular tachycardia, atrio-ventricular block, and sudden cardiac death), cardiogenic shock, re-infarction and death.²⁰

MEDICAL MANAGEMENT OF ACS IN DIABETICS

Glycemic Control

Oral hypoglycemic drugs and insulin should be used to achieve tight glycemic control, with target HbA1c of <7 %. Intense insulin based glucose control treatment has the potential to improve platelet function, correct the disturbed lipoprotein pattern, and decrease PAI-1 activity, thereby improving spontaneous. The one-year mortality was reduced by 30% in the insulin glucose intensive treatment group in DIGAMI 1 trial. However, the DIGAMI 11 study , which compared glucose control by insulin infusion with oral hypoglycemics found no significant difference in the two groups. Thus, it is not yet clear whether achieving tight glycemic control by exogenous insulin offers better outcome compared to OHA's in patients with Type 2 diabetes and CAD. One study designed to answer this question is the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial (BARI 2D).

ANTIPLATELET AND ANTICOAGULANT THERAPY

Aspirin

Reducing platelet aggregation by acetylsalicylic acid therapy is a cheap and effective way to reduce mortality and morbidity in patients with CAD, not the least those with ACS. However the Second International Study on Infarct Survival (ISIS 2) found no significant benefit from 160 mg/day of aspirin and recommended that a higher dose may be used especially in diabetics. None the less, aspirin should be given to all patients with ACS.

Clopidogrel

The outcome of the CURE Trial resulted in the recommendation to use clopidogrel (75 mg daily) combined with aspirin (75-100 mg daily) for 9-12 months following an acute coronary event.

Among patients with diabetes and vascular disease, clopidogrel provides better protection from serious events (vascular death, re-infarctions, stroke, or recurrent hospitalization for ischaemia) than aspirin (according to the CAPRIE trial).

Unfractionated Heparin and Low Molecular Weight Heparin (LMW Heparin)

Recent publications suggest that LMW heparins are a better choice in ACS owing to their more predictable and stable anticoagulant effect and lower incidence of heparin induced thrombocytopenia.¹⁹

ANTI-ISCHEMIC MEDICATION, ANTI-INFLAMMATORY THERAPY

β Blockers

Based on accumulated evidence of improved survival, prevention of re-infarction, and sudden cardiac death and reduction or treatment of late ventricular arrhythmias, oral β blockers are, in the absence of contraindications, recommended for all diabetic patients with ACS.

ACE Inhibitors

The addition of an ACE-inhibitor to other effective therapies reduces the risk for cardiovascular events in patients with diabetes and established cardiovascular disease. However, ACE-inhibitors have not been shown to offer any particular advantage in diabetic compared with non-diabetic patients in connection to an MI, except from a report from the GISSI-3 Trial. In a subgroup analysis from this study, early institution of lisinopril reduced mortality in patients with diabetes, however, not in their non-diabetic counterparts.

Co-existing Risk Factors

Treatment of co-existing risk factors like hypertension, hyperlipidemia, obesity and smoking should be an important aspect of ACS treatment in diabetic patients.

Emergency Thrombolysis in ACS

Patients with AMI and diabetes should be considered for thrombolytic therapy on the same grounds as their non-diabetic counterparts²⁰. Although there seems to be no major outcome difference among the various thrombolytic strategies, in GUSTO -1 trial there was improved survival of diabetes receiving accelerated TPA . However, the 30- day and 1-year mortality remains high in diabetics receiving thrombolytics, at least 40% more than in non diabetics.

Comparing Thrombolytic Therapy vs. PCI

There are multiple trials comparing the efficacy of thrombolytic regimens with primary PCI in patients presenting with ST- elevation AMI and several meta analysis confer that PCI is associated with better clinical outcomes. The recent DANAMI-2 (Danish Acute Myocardial Infarction trial) showed benefit in favour of PCI for patients with AMI, within 3 hours of onset of pain.

Revascularization Strategies for Diabetics with CAD

PCI Vs CABG: Revascularization procedures may be indicated in diabetic patients with stable or unstable coronary syndromes, covering the whole spectrum of IHD from asymptomatic patients to ST-elevation MI, ACS, and resuscitated sudden cardiac death. Patients with diabetes have a higher mortality and morbidity after CABG compared with non-diabetics, but this is also seen in patients undergoing PCI.¹⁹

CABG in diabetic compared with non-diabetic patients results in lower short- and long-term survival and more complications, including increased incidence of mediastinitis and sternal wound infections and delayed healing in general. Bilateral mammary artery grafting may be a risk factor for complications in the presence of diabetes, but internal mammary artery grafts also improve long-term outcome. Likewise, diabetic patients undergoing PCIs have a lower survival than their non-diabetic counterparts. They are at increased risk for adverse short and long-term outcomes, including a higher need for in-hospital CABG, and a higher incidence of instant thrombosis, restenosis, demand of repeat revascularization and MI.¹⁹

The effectiveness of PCI and bypass surgery as a mode of revascularization has been compared in several RCTs, among them the Bypass Angioplasty Revascularization Investigation (BARI), Coronary Angioplasty vs. Bypass Revascularization Investigation (CABRI), Emory Angioplasty vs. Surgery Trial (EAST), and Randomized Intervention Treatment of Angina. In BARI trial, patients with diabetes and multivessel disease demonstrated a less favourable prognosis when treated with PCI instead of CABG. However, in all these studies, balloon angioplasty was applied as a mode of PCI and no coronary stents were used^{19,20}. Stents and the latest DES have been hailed to improve the outcome of PCIs in the diabetic patient. The use of glycoprotein IIb/IIIa inhibitors have further shown to improve the outcome after PCIs.

Newer stents with improved design and especially new bare metal stents with thin struts have also been successful in decreasing the incidence of restenosis. The best revascularization strategy in patients with diabetes is still being evaluated. The FREEDOM (Future Revascularization Evaluating Patients with Diabetes Mellitus: Optimal management of multivessel disease) study is a prospective multicenter trial comparing DES with CABG in diabetic patients. Also, the ARTS 2 trial is comparing patients with multivessel disease undergoing PCI with DES (sirolimus) versus CABG.

Heart Failure and Cardiomyopathy

Diabetes mellitus (DM) is a common comorbid condition of heart failure (HF), and the prevalence of HF among diabetic patients is 2 to 3 times that of age-matched controls. Studies have reported that upto 40% of patients who get admitted for HF have co-existing diabetes. Moreover, patients with HF and diabetes have a poor outcome with increased morbidity and mortality. CAD and hypertension predominantly contribute to the increased incidence of HF in diabetes. Diabetes is also the leading cause of idiopathic diabetic cardiomyopathy, a condition characterized by systolic dysfunction occurring in the absence of ischemia or any other risk factor for cardiomyopathy. Diabetic cardiomyopathy is another distinct entity with unique pathogenesis. It causes diffuse myocardial fibrosis and hypertrophy and presents echocardiographically as diastolic dysfunction in asymptomatic diabetics.

Diabetic Cardiomyopathy Pathogenesis

Metabolic perturbations in the myocardial cell are the most probable causes for myocardial dysfunction in patients with diabetes. The dominant pathway for myocardial energy production is beta-oxidation of FFAs, but the myocardium is also to a lesser extent dependent on glucose oxidation. When the heart is subjected to ischemic stress or exposed to sustained enhancement of intraventricular pressure, its ATP production changes towards a more dominant glucose oxidation. In diabetes, glucose for energy production is, however, substantially lower, accounting for only about 10% of the myocardial energy production. The shift to a more pronounced beta-oxidation of FFA causes therefore a higher oxygen utilization than under normal circumstances.¹⁹ Thus, in diabetes and heart failure, the heart is exposed to increased concentrations of FFAs, released via stress influenced by an increased sympathetic tone as well as through insulin resistance and insulin deficiency-enhancing lipolysis. It has been proposed that prolonged intracellular accumulation of FFA and its metabolites may cause myocardial dysfunction.

Diabetic cardiomyopathy has also been attributed to abnormality in calcium homeostasis in the myocardium. This impairment occurs in sarcolemmal Na(+)-Ca²⁺ exchanger activity which limits the ability of the diabetic heart to extrude calcium, contributing to an elevation in Ca²⁺ intracellularly. Also promoting the accumulation of calcium by the diabetic cell is a decrease in Na⁺, K⁺ ATPase activity, which is known to increase Ca²⁺ secondary to a rise in Na⁺. The increase in intracellular calcium has been proposed to cause myocardial dysfunction.¹

Treatment

There are very few, if any, clinical trials on HF treatment specifically addressing the diabetic patients. Information on treatment efficacy of various drugs is, therefore, based on diabetic subgroups included in various HF trials. Traditional treatment of HF in diabetic patients is mainly based on diuretics, ACE-inhibitors, and BBs, as outlined in other guidelines. Moreover, it is assumed that meticulous metabolic control should be beneficial in heart failure patients with diabetes.

There is currently no general established effective treatment for left ventricular diastolic dysfunction associated with diabetic cardiomyopathy. However, an investigational agent (ALT - 711) that breaks collagen cross links in the myocardium is showing some promise.²⁰

Glycemic Control in Heart Failure

The role of anti-diabetic agents in managing diabetes in patients with HF is uncertain and considerable controversy exists about their overall effect on outcomes in people with comorbid diabetes and HF. However, adequate control could be achieved especially with insulin and OHA and preferably avoid Thiazolidinediones.

Cardiac Autonomic Neuropathy

Autonomic neuropathy is a serious and common complication of diabetes. It has been estimated that about 20% of asymptomatic diabetic patients have abnormal cardiovascular autonomic function. The risk for cardiovascular

autonomic neuropathy depends on the duration of diabetes and the degree of glycemic control. It is caused by injury to the autonomic nerve fibers that innervate the heart and blood vessels. The hypothesis concerning the etiology of cardiovascular autonomic neuropathy include metabolic insult to nerve fibers, neurovascular insufficiency, neurohormonal growth factor deficiency, and autoimmune damage. Main consequences are dysfunctional heart rate control, abnormal vascular dynamics, and cardiac denervation, which become clinically overt as exercise intolerance, orthostatic hypotension, intraoperative cardiovascular lability, and silent myocardial ischemia. Postural hypotension is common in diabetics with autonomic neuropathy, particularly following bed rest or in patients taking anti hypertensives. The increased risk of sudden cardiac death in diabetic patients with autonomic neuropathy may be in part related to the high incidence of QT prolongation, which in turn may cause malignant ventricular arrhythmias.

To conclude, diabetes and heart disease are like two sides of the same coin. While diabetes considerably increases the risk of heart disease, many people with heart disease suffer from diabetes or its preceding states (pre diabetes). Moreover, the two conditions also share the same predisposing factors like increasing age, obesity, sedentary life style and unhealthy eating habits. The two conditions being so closely linked should be treated with a more unified cardio-diabetic approach to ensure that both diabetes and heart disease are optimally treated. This cardiometabolic approach will go a long way in decreasing the morbidity and mortality associated with the two conditions and thereby decreasing the impact of the dual epidemic.

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