

Diabetes **and** Coronary Artery Disease

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Coronary artery disease (CAD) remains the main cause of mortality in most parts of the world. Diabetes Mellitus is common in the Arab world and elsewhere. The association of diabetes and CAD has been long recognized and well studied. The aim of this brief review is to highlight some important aspects in the pathophysiology and medical treatment for CAD in diabetic patients. The prevalence of the classical risk factors of CAD in the general population is amplified in diabetes. Diabetics are also frequently hypertensive, dyslipidemic and obese. Angiographic studies have shown that Diabetics have more diffuse, multivessel (CAD), smaller reference vessels, less developed coronary collateral circulation and more frequent left main disease (1-4). Silent myocardial ischemia and infarction is not infrequent in diabetics and carry an adverse prognosis due to late diagnosis and management. Accelerated atherosclerosis is a common finding in diabetics and could be due to multiple factors: endothelial dysfunction, prothrombotic state, hyperglycemia, dyslipidemia, and insulin resistance. Diabetics have a worse prognosis after myocardial infarction (MI), more complications and failure rates after coronary revascularization procedures. Diabetes is now recognized as CAD-equivalent disease since newly diagnosed diabetics have a similar risk of developing MI to those non-diabetics who already had their first MI.

Hyperglycemia

Hyperglycemia increases the risk of cardiovascular disease. Even in the non-diabetic range of glycemia, increased glucose is associated with increased risk of cardiovascular complications (5). Hyperglycemia is associated with increased oxidative stress (6), enhanced leukocyte endothelial interaction (7), glycosylation of lipoproteins, apolipoproteins, and clotting factors. All these factors contribute to the development of atherosclerosis/atherothrombosis

Diabetic Dyslipidemia

Lipoprotein abnormalities are common in patients with insulin resistance and type 2 diabetes leading to increased risk

of CAD. The most commonly observed abnormalities is an increase in plasma triglycerides due to an increase in the concentrations of very low density and intermediate density lipoproteins (VLDL, IDL). A decrease in the concentrations of high density lipoproteins (HDL) cholesterol, and abnormalities in the composition and sometimes the concentrations of low density lipoproteins (LDL), with the most common pattern being an increase in the concentrations of the easily oxidizable, more atherogenic small dense LDL(8-11). The dominant mechanism responsible for these abnormalities is an increase in hepatic VLDL synthesis reductions in HDL synthesis, increased HDL catabolism and reductions in the activity of the enzyme lipoprotein lipase.

Increased plasma concentrations of triglyceride-rich lipoproteins is more risky for atherosclerosis in patients with type 2 diabetes than in non-diabetic patients, concurrent hyperglycemia leads to glycation of lipoproteins which may render them more atherogenic. Severe hypertriglyceridemia has commonly been seen in patients with type 2 diabetes who concurrently have an underlying genetic disorder of lipoprotein metabolism (familial combined hyperlipidemia or familial hypertriglyceridemia).

Insulin Resistance

Syndrome X (Metabolic Syndrome or Insulin Resistance Syndrome) is the term coined to describe a combination of hyperinsulinemia and cardiovascular risk factors of CAD like abnormal lipid profile, glucose intolerance, hypertension and upper-body obesity. Several other metabolic abnormalities have been associated with this syndrome,

Insulin causes endothelial dysfunction in humans

including presence of microalbuminuria, abnormalities in fibrinolysis and coagulation, and reduced vasodilatory response to acetyl choline(12,13). There is still controversy about the mechanisms by which the insulin resistance syndrome appears to induce, or at least, enhance atherogenesis. This syndrome may be related to common cardiovascular risk factors or may directly be accelerated by hyperinsulinemia (14-16). one hypothesis is that insulin resistance and the compensatory hyperinsulinemia might be the primary events causing hypertension, leading subsequently to increase the risk of CAD. Moreover, recent data suggest that impaired microvascular function may be a central

mechanism linking insulin sensitivity to increased blood pressure, and therefore to macrovascular disease in insulin resistance states.

Insulin causes endothelial dysfunction in humans (17). Hyperinsulinemia of insulin-resistant states was found to abolish endothelium-dependent vasodilation in large conduit arteries, probably by increasing oxidant stress. This data may provide the pathophysiological basis to the epidemiological link between hyperinsulinemia/insulin-resistance and atherosclerosis in humans.

Endothelial Dysfunction in Diabetes

Endothelial dysfunction occurs commonly in diabetes mellitus and contributes to the initiation also progression of atherosclerosis as well as to the occurrence of clinical events. In diabetes, there is enhanced leukocyte adhesion to the vascular endothelium possibly explained by the fact that hyperglycemia stimulates the expression of adhesion molecules molecule-1 (VCAM-1) and E-selectin (18). There is also impairment of endothelium-dependent vasodilation and reduced coronary flow reserve which may be related to hyperglycemia with increased generation of oxygen free-radicals that inactivate endothelium-derived relaxing factor (EDRF) (19); The production of prostacyclin (PGI₂), an endothelial vasodilator which also inhibits platelets adhesion and aggregation, is also reduced (20). Production of endothelin-1, a potent vasoconstrictor and mitogen for smooth muscle proliferation, is significantly increased in hyperinsulinemic patients with type2DM (21).

Diabetes as a Prothrombotic State

Diabetes mellitus and its associated metabolic abnormalities are characterized by alterations in the coagulation and fibrinolytic systems that combine to produce a prothrombotic state. These

alterations include increased platelet activity, increased levels of several coagulation components, and impaired fibrinolysis. This enhanced thrombogenicity among diabetics plays an important role in accelerated atherogenesis and restenosis.

Altered platelet function is involved in the increased thrombogenic potential in diabetics. Diabetic platelets are larger and have a greater number of GP IIb/IIIa receptors (22). Platelets aggregation and adhesion are increased in response to shear stress and platelets agonists (23,24). There is a higher plasma level of platelets that release products such as b thrombomodulin, platelet factor-4, and thromboxane B₂. In addition, there is an enhanced activity of arachidonic acid metabolism with increased thromboxane A₂ (TXA₂) formation.

There is elevated activity of procoagulants with increased levels of fibrinogen, von Willebrand factor activity, and thrombin activity together with a decrease concentration of the antithrombotic factors with decreased activity of antithrombin III and decreased sulfation of endogenous heparin. Fibrinopeptide A, a marker of thrombin activity is also elevated in diabetics. Moreover, there is decrease in the factors attenuating fibrinolysis: plasminogen activator inhibitor type I (PAI-1) and a₂- antiplasmin. These various abnormalities may contribute to heightened susceptibility to the higher risk of adverse outcomes and the thrombotic complications in diabetics (24).

Management of cardiovascular risk factors

Control of Hyperglycemia

The Diabetes Control and Complications Trial (DCCT)(25) clearly demonstrated that tight glycemic control reduces the chronic microvascular complications among diabetic patients. There was a non-significant trend toward reduction of CV events in diabetics with intensive therapy versus conventional therapy. The United King-

dom Prospective Diabetes Study (UKPDS)(26) demonstrated that intensive glycemic control by either insulin or sulphonylureas significantly reduced (by 25%) the risk of microvascular complications in type 2 diabetic patients. The trend toward a reduction in CV events did not reach statistical signifi-

cance. However, epidemiological analysis of the UKPDS cohort showed a significant benefit of glycosylated haemoglobin (HbA1c) reduction: a 14% reduction in all cause mortality and MI for every 1% reduction in HbA1c.

It has been reported that following PTCA, diabetic patients with optimal

glycemic control (HbA1c < 7%) have rates of MACE indistinguishable from non-diabetics (27). Diabetics with sub-optimal control (HbA1c > 7%) are at higher risk. A promising group of agents for treatment of type 2 diabetes includes the thiazolidenediones. These agents lower glucose levels by reducing insulin

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resistance. Troglitazone is the first drug in this class to be approved for clinical use. This agent is approved for use in combination with insulin therapy to improve glycemic control. Recently, the administration of troglitazone was shown to reduce neointimal tissue proliferation after stent implantation in patients with type 2 DM (28).

Lipid Management

Aggressive lipid management is an essential component of therapy in all diabetics. Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol, and lowering triglycerides has been shown to reduce macrovascular disease and mortality in patients with type 2 DM. The objective should be to lower LDL cholesterol to less than 100mg/dL- and may be lower. In three secondary prevention trials using HMG-CoA reductase inhibitors, patients with DM achieved significant reduction in coronary and cerebrovascular events. The Scandinavian Simvastatin Survival Study (4S) (29) included 204 diabetics out of a total of 4444 subjects. It demonstrated that diabetic patients with hypercholesterolemia, normal triglycerides and established CAD, lowering LDL-cholesterol levels with simvastatin was associated with a marked reduction of major CAD and related to atheroscle-

rotic events. Five-year mortality was decreased by 43% in diabetic versus 29% in nondiabetic patients. Similar outcomes were reported by the Cholesterol And Recurrent Events (CARE) trial(30), including 586 diabetic patients, evaluating the benefits of pravastatin in patients with average cholesterol levels after MI. There was a greater benefit of pravastatin in diabetics than in non-diabetics, with greater relative risk reduction of CAD major events and as for revascularization procedures during a five-year follow-up. Finally! In the Long term, Intervention with Pravastatin in Ischemic Disease (LIPID)trial(31) pravastatin therapy also showed a 19 %, albeit not statistically significant, reduction of the composite end point of CAD related death and MI during a 6.1-year follow-up in a subgroup of diabetics with a history of MI or unstable angina with a broad range of initial cholesterol levels.

The prevention of clinical events related to plaque instability may be the major benefit of lipid-lowering therapy in patients undergoing PCI.

Control of Hypertension

Recent studies have shown that adequate blood pressure control markedly reduced major cardiovascular events related to macrovascular complications

(32). The guidelines for the treatment of hypertension Joint the National Committee of Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommended a level of 130/80 mm Hg for diabetic patients.

Aggressive risk factor modification in diabetics cannot be over emphasized. Cessation of cigarette smoking, physical activity and optimization of body weight

An aggressive, global approach to control risk factors in diabetics remains the mainstay of therapy

are important life style changes. Aspirin, beta-blockers, and angiotensin-converting-enzyme inhibitors are cornerstones of therapy in all diabetic patients unless clearly contraindicated (33).

An aggressive, global approach to control risk factors in diabetics remains the mainstay of therapy. Revascularization strategies of coronary artery disease in diabetics have received great attention in recent years. This topic will be addressed in future reviews.

The cardiovascular **impact** of **cigarette** smoking in diabetic **patients**

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Cardiovascular disease (CVD) is a major global health issue worldwide and is the leading cause of death worldwide (7.4 million/year) accounting for 13.7% of all deaths. The increasing incidence of CVD in developing countries, including the Arab World, is attributed to several factors including high prevalence of cigarette smoking and diabetes mellitus, increase in life expectancy, urbanization, industrialization, and economic transition, change in lifestyle habits such as physical inactivity and unhealthy diet (1).

Diabetes and smoking as risk factors for CVD

Diabetes mellitus type 1 and type 2 are powerful and independent risk factors for CVD, stroke, and peripheral arterial disease (2). For each single patient diagnosed as diabetic after the age of 20 who dies from renal disease, nine others die from CVD and two other from stroke (3). Diabetes predisposes to atherosclerotic CVD because of the associated platelet and endothelial dysfunction, coagulation and fibrinolysis abnormalities, and atherogenic dyslipidemias (4,5). Approximately half the diabetics have one or more variants of these dyslipidemia, including (a) low levels of high-density lipoprotein cholesterol (HDL-C), (b) high levels of total cholesterol, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), and (c) alterations in the composition and concentration of B, E and Lp(a) apolipoproteins (3). A 13-year follow-up of diabetics at the Mayo Clinic demonstrated that age, smoking, fasting blood sugar, and serum TG level were

strong predictors of CVD in diabetics (6).

Similarly, cigarette smoking is a major independent risk factor for CVD in men and women. The Framingham study showed that the risk of sudden cardiac death has increased in smoking by 2-3 folds in each decade of life between the 4th and 6th decades of life (7). Among diabetics, the risk of cardiovascular events has increased by a factor of at least two in diabetics who smoke, and

Passive smoking exposure in nonsmokers may also increase the risk of CVD

this risk declines after smoking cessation (8).

The vascular adverse effects of smoking is mediated by its adverse effect on the endothelial cells, epicardial and

microvascular coronary blood flow, platelet aggregation, mediators release and serum lipoproteins (9-11). Passive smoking exposure in nonsmokers may also increase the risk of CVD (12).

Synergism between smoking and diabetes: serum lipids and coronary lesions

Synergism between multiple CVD risk factors is well established, such as the influence of the coexistence of diabetes, smoking, hypercholesterolemia, low levels of HDL-C, arterial hypertension and left ventricular hypertrophy in the estimated 10 year risk of coronary heart disease. This risk rises gradually from <10% in the absence of any risk factor to approximately 55% in the presence of all six risk factors (13). Likewise, smoking multiplies the effect of other coronary risk factors and poses a synergistic effect on CAD mortality and morbidity (14). Moreover, diabetics with albuminuria are more likely to be smokers (15).

Specific cardiovascular adverse effects of the synergism of smoking and diabetics include a higher absolute risk of CVD due to smoking in diabetics than in non-diabetics (3), worse lipid profile and worse coronary lesions in acute myocardial infarctions (AMI) victims.

In a study of lipid profile in 2000 consecutive individuals in Jordan, (mean age of the group was 52 years [range 17-88], 71% were men, 30% diabetics and 24% smokers). Diabetic smokers, compared to non-diabetic smokers and non-diabetic nonsmokers respectively, had lower serum HDL-C (34 mg/dl vs 36 mg/dl and 41 mg/dl, $p<0.0001$), and higher TG (205 mg/dl vs 176 mg/dl and 168 mg/dl, $p=0.0013$) (16). Low HDL-C and high TG serum levels are well known risk factors for CVD.

The impact of the coexistence of diabetes and smoking on the severity of CAD was studied in 470 patients (mean age was 53.5 years [range 23-77]) presenting with AMI (ST-segment elevation 84%, and non ST-segment elevation 16%) who underwent coronary angiography during the index admission (17).

The severity and extent of CAD in the whole group, and severity of occlusion in the infarct-related artery (IRA) in the ST elevation MI patients were assessed in diabetic smokers (Group 1, 16%) compared with non-diabetic smokers and nonsmoker diabetics (Group 2, 64%) and non-diabetic nonsmokers (Group 3, 20%). Patients In Group 1 tended to have a totally occluded IRA more than Groups 2 and 3 (52.1%* vs 48.6% vs 38.9%* respectively, * $p=0.33$), and significantly less likely to have non-obstructive or normal IRA (2.8%* vs 8.4% vs 13.9%*, * $p=0.03$). Multivessel CAD was more common among Group 1 (58%) than amongst the rest (43%), $p=0.16$, and non-diabetic smokers (34%), $p=0.025$. There was less incidence of normal or non-obstructive CAD in Group 1 than the rest (1.3% vs 8.9%, $p=0.03$), and also non-diabetic smokers (1.3% vs 9%, $p=0.033$). Compared with non-diabetic nonsmokers, diabetics who do not smoke had higher incidence of multivessel CAD (69% vs 38%, $p=0.021$) and lower incidence of normal or non-obstructive CAD (3.3% vs 14.4%, $p=0.02$).

The study concluded that diabetic smokers who present acute MI are more likely to have an occluded IRA, a higher incidence of multivessel CAD, and less incidence of normal or non-obstructive coronary arteries than in non-diabetic nonsmoker patients, and nonsmoker diabetics.

This data concurs with other angiographic and autopsy studies which demonstrated that diabetics, compared with age- and sex-matched non-diabetics, have more extensive coronary disease, higher frequency of left main coronary artery disease, diffuse lesions, and plaque rupture (18).

Beyond the increased risk of cardiovascular disease of smoking in diabetics, smoking also increases insulin resistance and increases the incidence of albuminuria, diabetic nephropathy, end-stage renal disease, neuropathy and non-proliferative retinopathy.

Glycosylated hemoglobin :	<7%
Blood pressure :	<130/80
LDL-C :	<100 mg/dl
HDL-C :	Men >40 mg/dl Women >50 mg/dl
TG :	<150

Table 1 - Risk factors in diabetics: target levels (American Diabetes Association, reference 25)

Diabetic women who smoke

The Nurses Health Study (NHS) studied several lifestyle factors, use of hormones and medications, and incidence of cardiovascular events as well as cancer in >120,000 US female nurses who were followed up for 20 years. In a subgroup of about 6500 type 2 diabetic women; the relationship between cigarette smoking and the risk of CVD was assessed (19). There was a dose-response relationship between current smoking status and risk of CVD among these women. Compared to nonsmokers, the relative risks (RRs) for CVD were 1.21 for past smokers, 1.66 for current smokers of 1-14 cigarettes per day and 2.68 for current smokers of >15 cigarettes per day. Diabetic women who currently smoke >15 cigarettes per day had RR of 7.7 compared to nonsmoker diabetics. Quitting smoking has been found to decrease this excess risk substantially.

Diabetes, itself is a more powerful risk factor for women than men. Coronary mortality is 3-7 times higher in diabetic women than non-diabetic women, compared with 2-4 times higher in diabetic men compared to non-diabetic men (20).

Quitting smoking

Smoking cessation decreases the risk of MI to almost the level of nonsmokers within 3-5 years after quitting, and also improves survival after MI, and substantially decreases morbidity and mortality after coronary bypass surgery (21). Continuing to smoke after coronary revascularization substantially reverses the beneficial effects gained from the procedure (22,23).

Despite the observation that quitting smoking in diabetics and non-diabetics, especially among patients who have CVD, improves the cardiovascular risk, the rate of quitting smoking is disappointingly low and ranges between 23-75% (22-24).

In a study on 397 smokers who sustained acute coronary event (mean age 55 years, 97% were men) only 22.7% quit after the event and the remaining 77.3% continued to smoke at the end of the follow up period (24). Smoking cessation was significantly higher amongst patients who had coronary revascularization than among those treated medically (32.8% vs. 14.8% respectively,

$p=0.0002$). Although one expects that undergoing a major cardiac surgery would serve as a strong "teachable moment" to quit smoking, the study found that smoking cessation was not dependent on whether the patients had undergone percutaneous or surgical revascularization (31.1% vs. 35.2% respectively, $p=0.57$).

Conclusions

Cardiovascular morbidity and mortality carry a major burden in diabetics. A diabetic who smokes increases the risk of acute cardiovascular event (i.e.

macrovascular complications), as well as microvascular complications. The American Diabetes Association (25) advocates achieving several target levels of risk factor control in diabetics (table 1). Intensive interventions in life style behavior, especially smoking cessation, and medical treatment to control blood pressure, dyslipidemia, and blood glucose levels have been shown to lower the risk by (50%) in:

- ◆ Cardiovascular end points including cardiac death, non-fatal myocardial infarction and stroke, revascularization, and amputations,
- ◆ The microvascular complications including neuropathy and retinopathy (26).

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