The Impact of Diabetes Mellitus on the Progression of Coronary Artery Disease: Clinical Outcomes, Pathophysiology, and Potential Targets for Therapies

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INTRODUCTION

Diabetes mellitus currently affects 17 million Americans and is associated with a significant increase in cardiovascular morbidity and mortality. Atherosclerosis accounts for approximately 80% of all diabetic-related deaths. Approximately 75% of the atherosclerotic deaths are secondary to cardiovascular disease while 25% are related to cerebrovascular and peripheral vascular disease[1]. The World Health Organization[2] estimates that there will be an increase in the number of adults with diabetes from 135 million to 300 million by the year 2025. Specifically, the United States will have an increase from 17 million adults to 22 million adults by the year 2025, in part secondary to an increase in the prevalence of obesity. Due to an increase in the prevalence of diabetes, we will be encountering a similar increase in cardiovascular disease.

Although advances have occurred in medical therapy, percutanous coronary revascularization and surgical coronary revascularization, diabetics continue to have a disproportionate increase in cardiovascular morbidity and mortality. This includes diabetics without clinical cardiovascular disease as well as diabetics with either acute coronary syndromes or ST segment elevation myocardial infarctions.

Today, I would like to discuss how cardiovascular disease differs with respect to clinical outcomes, markers of inflammation and alterations in the endogenous fibrinolytic system in diabetics and how novel treatment strategies might improve their cardiovascular prognosis.

CLINICAL TRIALS ESTABLISHING INCREASED MORBIDITY AND MORTALITY

In 1979, the Framingham study[3]demonstrated an increase in cardiovascular disease in diabetics with a relative risk of 2.1 for men and 2.0 for women. More recently, Hafner et. al. published the myocardial infarction rates and mortality rates of both diabetic and nondiabetic subjects stratified by the presence/absence of prior myocardial infarctions[4]. He demonstrated that diabetics without antecedent myocardial infarctions have a similar risk of a new myocardial infarction as nondiabetic patients with an antecedent myocardial infarction (20% vs 19%). Furthermore, diabetics with an antecedent myocardial infarction have a two fold increase in the risk of a subsequent myocardial infarction compared to nondiabetics with an antecedent myocardial infarction (45% vs 19%). This increase in myocardial infarction rates for diabetics translates into an increase in mortality rate at 7 years (42% vs 16% for antecedent MI, 15% vs 2% without antecedent MI).

Seven Year Incidence of Cardiovascular Events in Diabetics and Nondiabetics		
	Diabetic (MI Rate/ Mortality Rate)	Nondiabetic (MI Rate/ Mortality Rate)
Prior MI	45% / 42%	19% / 16%
No Prior MI	20% / 15%	4% / 4%

In addition to the increased morbidity and mortality secondary to myocardial infarction, diabetics admitted with acute coronary syndromes are also at increased risk. The OASIS

(Organization to Assess Strategies for Ischemic Syndromes) Registry analyzed the two-year prognosis of diabetic and nondiabetic patients hospitalized with unstable angina or a non-ST segment elevation myocardial infarction[5]. Of the 8013 patients, 1718 (21%) had diabetes mellitus. Diabetes proved to be an independent predictor of increased mortality (RR 1.57) and increased rates of congestive heart failure, stroke and recurrent myocardial infarctions. In addition, the negative prognostic influence of diabetes resulting in increased mortality was greater for women than men (RR 1.98). The OASIS registry confirmed the Hafner data that diabetic patients without cardiovascular disease have similar cardiovascular event rates and mortality rates as nondiabetics with clinically established vascular disease.

OASIS TWO YEAR MORTALITY RATE		
	DIABETES MELLITUS	NO DIABETES MELLITUS
PREVIOUS CVD	20%	13%
NO PIOR CVD	13%	7%

A comparison of the diabetic and nondiabetic groups reveals similar rates of aspirin use, lower rates of beta-blocker administration (59% vs 65%) and higher rates of ace-inhibitor administration. Both groups had similar rates of angiography (50% vs 52%) and percutaneous revascularization (18%) while diabetics had higher rates of surgical revascularization (23% vs 20%) due to higher rates of multivessel coronary artery disease. The excess morbidity including recurrent myocardial infarction and congestive heart failure and the increase in mortality are not due to a lack of administration of traditional anti-ischemic medical therapy and/or coronary revascularization.

Diabetes mellitus also has a profound influence on the clinical outcome of patients presenting with acute ST segment elevation myocardial infarctions treated with thrombolytic therapy or primary angioplasty. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries study (GUSTO) included 41,021 patients who were randomized to receive t-PA, streptokinase or both [6-7]. Of these patients, 5,944 were diabetics. Compared to the nondiabetics, diabetic patients were older, more often women, presented later and more often experienced an anterior myocardial infarction[6]. Congestive heart failure, shock, atrioventricular conduction block and atrial fibrillation more often complicated their hospital course. Both groups had similarly sized infarctions and similar rates of coronary revascularization. Despite similar infarct size and treatment, the presence of diabetes was an independent risk factor for 30-day mortality and 1 year mortality (14.5% vs 8.3%).

The GUSTO –1 angiographic substudy[8] included 2431 patients and has provided useful insights regarding the excess mortality secondary to diabetes mellitus. The excess mortality is not secondary to a blunted response to thrombolytic therapy. Diabetics and

nondiabetic patients had similar 90-minute angiographic patency rates (70% vs 67 %) and similar rates of normal flow (TIMI 3 flow). Several differences were noted. Specifically, diabetics had smaller coronary vessels, more often had multivessel coronary artery disease (54% vs 41%), less often had hyperkinesia in the noninfarct zone and had increased rates of reocclusion of the infarct related artery at one week (9.2% vs 5.0%). Clinical outcomes in diabetics following percutaneous revascularization were strikingly different with an increase in mortality rate following both rescue angioplasty (22% vs 9%) and elective angioplasty (8% vs 2%). There was no difference in mortality in the diabetic patients treated with coronary artery bypass graft surgery (8% vs 5%). Following an adjustment of clinical and angiographic variables, diabetes remained a strong predictor of increased mortality at 30 days (RR 2.0).

The Gusto IIb substudy[9] is the largest randomized trial of thrombolytic therapy versus primary angioplasty in patients with ST-segment elevation myocardial infarctions. Of the 1138 patients enrolled, 177 were diabetic. Compared with nondiabetics, diabetics more often had multivessel coronary artery disease (43% vs 32%) and more often had an occluded infarct related artery (71% vs 62%). Of the patients undergoing angioplasty, procedural success rates were similar in diabetics and nondiabetics (70% vs 72%). Compared with thrombolysis, primary angioplasty in diabetics resulted in a decrease in reinfarction (6% vs 2%) and recurrent ischemia (9% vs 3 %) without decreasing 30-day mortality (8% vs 6%). In fact, the early one-week rates of cardiogenic shock (10% vs 6%) and mortality (9% vs 5%) trended higher in diabetic patients treated with angioplasty compared to thrombolysis. Thus, primary PTCA in diabetics does offer advantages, mainly a decrease in recurrent ischemia, but with a troubling trend towards an increase in cardiogenic shock and excess mortality. The

recent incorporation of glycoprotein 2b/3a inhibitors and coronary stenting may improve clinical outcomes in the setting of acute myocardial infarctions.

The debate over the method of coronary revascularization in patients with multivessel coronary artery disease is greatest in diabetic patients. Retrospective studies including the Mid-American Heart and Duke reports have not revealed any differences in long-term mortality. The BARI Trial launched in 1987 compared the efficacy of CABG and PTCA in multivessel coronary artery disease as an initial revascularization strategy with subsequent 5-year clinical follow-up. The results did not demonstrate a difference in survival for the overall group[10-11]. A post-hoc analysis of diabetic patients, however, raised serious questions due to an increase in mortality for diabetic patients treated with angioplasty. Treated diabetic patients (19% of overall group) treated with hypoglycemic oral agents or insulin that underwent PTCA had a 5-year mortality of 35% compared to 19% for those who underwent CABG[12]. The excess mortality associated with PTCA was secondary to an excess of cardiac deaths (21% vs 6%) over the 5-year follow-up. Interestingly, nontreated diabetic patients had a similar 5-year mortality as nondiabetic patients (7% vs 9%). Furthermore, the BARI Registry demonstrated similar 7-year mortality rates for treated diabetics revascularized by PTCA versus CABG (24% vs 24%)[13]? Why do treated diabetic patients who undergo PTCA for multivessel coronary artery disease fare worse than similar patients treated with surgery in the BARI trial? Why do the BARI registry patients treated with PTCA have similar mortality rates as those treated with CABG? Do patients who undergo PTCA more often experience subsequent myocardial infarctions?

An analysis of both the BARI trial and BARI registry provides insight regarding subsequent rates of myocardial infarction and the protective effects of revascularization on

subsequent mortality[14]. The likelihood of a spontaneous Q wave myocardial infarction occurring during the 5 year follow-up was 4.8% in the total population but increased to 8.0% for the diabetic patients. Of the diabetic patients experiencing a Q wave myocardial infarction, the mortality rate was 17% for those treated with CABG versus 80% for those treated with PTCA. The protective effects of CABG on mortality were not as great for the diabetic patients who did not experience a Q wave myocardial infarction (15% vs 22%). Two facts are readily apparent. First, the modality of coronary revascularization does not influence the subsequent incidence of Q wave myocardial infarctions. Second, CABG has a strong protective effect on survival for diabetic patients who experience a Q wave MI with a risk reduction of 0.09. Why? It appears that the difference in mortality is, in part, secondary to a higher "jeopardy score" of myocardium in patients treated with PTCA. The one year jeopardy score (amount of myocardium at risk) for patients treated initially with PTCA was two-fold higher (26% vs 14%). This may translate into an increase in the magnitude of ischemia in the setting of an acute myocardial infarction and result in higher mortality rates. The mortality rates in the BARI registry for diabetic patients treated with PTCA vs CABG appear to be similar because of differences in the extent of baseline atherosclerotic disease (greater disease in those treated with CABG).

These clinical studies including diabetics without known cardiovascular disease and those with established coronary artery disease demonstrate that conventional therapies including aspirin, beta blockers, thrombolytic agents and coronary revascularization are still limited by high subsequent coronary events and death. The fundamental question is why do diabetics fare worse than nondiabetics? I believe the reason is that diabetics experience hyperinsulinemia, insulin resistance, hyperglycemia and chronic inflammation that result in

endothelial cell dysfunction, negative arterial remodeling and impaired endogenous fibrinolysis. The consequence of these metabolic disturbances coupled with impaired fibrinolysis translate into a more aggressive atherosclerotic process. Plaques which contain an increased lipid-rich core with decreased cellular constituents and increased concentrations of macrophages and PAI-1, result in plaque instability, rupture, and an increased probability of acute coronary syndromes, myocardial infarctions, and death.

ALTERATIONS IN ACUTE PHASE REACTANTS AND FIBRINOLYSIS

During the past 5 years, multiple studies[15-18] have demonstrated that markers of inflammation are predictive of individuals at increased risk of cardiovascular events. Stimulants of inflammation can include infection, hypercholesterolemia and diabetes, which stimulate the production of pro-inflammatory cytokines such as IL-1 and TNF-alpha. These cytokines, in turn, stimulate the production of IL-6, which stimulates the hepatic production of C-reactive protein (CRP) and serum amyloid A (SAA). In addition, IL-1 and TNF alpha can stimulate the production of leukocyte adhesion molecules and heat shock proteins. Data obtained from the Physicians' Health Study has demonstrated an increase in the risk of a first myocardial infarction with elevated CRP (RR 2.9). Interestingly, the protective effect of aspirin on decreasing the risk of first myocardial infarction was greatest for individuals with the highest levels of CRP. More recently, CRP, at concentrations observed in high-risk subjects, has been demonstrated to have significant proinflammatory effects in coronary artery endothelial cells. CRP increases the expression of adhesion molecules including intercellular adhesion molecules, vascular cell adhesion molecules and E-selectin, which may

increase atherosclerosis and decrease plaque stability. Other studies of the Physicians' Health Study have revealed similar increases in the relative risk of a first myocardial infarction with elevated levels of fibrinogen, sICAM, IL-6 and heat shock proteins. Thus, it appears that individuals with evidence of chronic inflammation are at increased risk of cardiovascular morbidity and mortality. I believe diabetics represent individuals with chronic inflammation who are therefore at increased risk of cardiovascular disease.

Recent literature supports the position that chronic inflammation is increased in individuals with impaired glucose tolerance and in diabetics and may result in an increase in altered fibrinolysis, atherosclerosis, congestive heart failure, and cardiovascular death. The ARIC study was a prospective cohort study which evaluated 1676 men with diabetes without known cardiovascular disease [19-20]. Of these subjects, 186 developed cardiovascular disease. The occurrence of cardiovascular disease was associated with tobacco abuse, hypertension, hypercholesterolemia and a low HDL level. In addition, elevated levels of albumin, fibrinogen, von Willebrand factor, factor VIII activity and leukocyte levels all predicted an increase in the risk of developing cardiovascular disease.

The Insulin Resistance Atherosclerosis Study (IRAS) studied the hypothesis that insulin insensitivity may be associated with inflammation in nondiabetics[21]. A 75-g oral glucose tolerance test was administered to 1088 nondiabetic individuals without clinical cardiovascular disease. Inflammatory markers including CRP, fibrinogen, and leukocyte counts were assessed and stratified by glucose tolerance status (normal versus impaired). CRP was independently related to insulin sensitivity and increased in total value with an increase in the number of metabolic disturbances present (hyperlipidemia, obesity, insulin resistance and hypertension). The levels of CRP were higher with increasing degrees of

insulin resistance. This study may provide insight into the why hyperinsulinemia is an independent risk factor for the development of ischemic heart disease. In 1996, Despres et al. demonstrated that a high fasting insulin concentration was an independent predictor of ischemic heart disease in men with an OR of 1.7 [22]. It is postulated that hyperinsulinemia is a marker of insulin resistance which, in turn, increases the risk of diabetes mellitus. Thus, therapies, which improve insulin sensitivity and decrease plasma insulin levels, may decrease progression of cardiovascular disease.

A study performed by Pickup et al. in 1997 investigated the association of acute-phase reactants and interleukin-6 with metabolic syndrome X, which includes the following entities: hypertriglyceridemia, low serum HDL-cholesterol, hypertension, obesity and accelerated atherosclerosis[23]. Three groups of patients were studied: group 1 noninsulin diabetics with ≥ 4 features of metabolic syndrome, group 2 noninsulin diabetics with ≤ 1 feature of metabolic syndrome, group 3 healthy non-diabetics. A graded increase in markers of acute inflammation was noted. Compared to nondiabetics, diabetics with ≤ 1 feature of metabolic syndrome had intermediate levels of serum sialic acid, alpha1 glycoprotein and interleukin 6. A further increase in these markers were noted in the group 1 patients with 4 or more features of syndrome X. In addition, group 1 also had increases in both serum amyloid A, c-reactive protein and cortisol levels. These chronic abnormalities may result in an increased propensity for atherosclerosis, acute coronary syndromes and increased rates of restenosis following percutaneous revascularization.

In addition to markers of chronic inflammation, diabetics consistently demonstrate multiple abnormalities of the fibrinolytic system including platelet activation and impaired

fibrinolysis[24-25] which may increase thrombotic events and explain the increased rates of myocardial infarction and increased rates of reocclusion following thrombolysis in diabetics.

A dynamic equilibrium exists between t-PA, which promotes thrombolysis, and PAI-1, which inhibits thrombolysis. Endothelial cells are thought to be the primary source for both endogenous t-PA and PAI-1. A study by Festa et al. investigated the relationship of insulin and pro-insulin to fibrinogen and PAI-1 in subjects with varying degrees of glucose tolerance (normal glucose tolerance, impaired glucose tolerance, type 2 diabetics)[26]. These investigators were able to demonstrate that PAI-1 was independently related to increased levels of insulin and pro-insulin across all levels of glucose intolerance whereas increased fibrinogen levels were independently related to decreased insulin levels. In addition to altered levels of PAI-1, McGill et al. have demonstrated not only basal abnormalities of the fibrinolytic system in diabetics, but also an attenuated augmentation of fibrinolysis induced by venous occlusion[27]. The degree of attenuation correlated with the severity of hyperinsulinemia. In addition, the increase in PAI-1 activity correlated with increasing levels of C-reactive protein. These abnormalities in the fibrinolytic system did not correlate with fasting glucose levels suggesting that hyperglycemia is not the cause of the impaired fibrinolytic response.

The systemic abnormalities of the fibrinolytic system coupled with elevated markers of chronic inflammation affect the composition of coronary plaques in the diabetic population. Atherectomy specimens obtained from patients with diabetes with acute coronary syndromes were compared to atherectomy specimens from matched, nondiabetic patients[28-29]. Compared to nondiabetic specimens, diabetic atherectomy specimens were characterized by greater lipid rich atheroma, greater thrombus content, and increased macrophage content.

Sobel et al. have also studied atherectomy samples from diabetic patients with symptomatic coronary artery disease[30]. Compared to the nondiabetics, diabetic atherectomy samples had an elevation of PAI-1 and a decrease in uokinase-type plasminogen activator (uPA). These studies are consistent with a clinical situation where alterations of the systemic and vascular fibrinolytic system coupled with plaque components including increased lipid content, macrophage content, and vascular intramural alterations in PAI-1 and uPA act to increase the tendency for plaque rupture with consequent formation of a thrombus. The altered local, intramural concentrations of uPA and PAI-1 are postulated to increase the ratio of plaque core lipid to cellular elements secondary to a decrease in the stimulus for migration of smooth muscle cells and a decrease in the neointimalization of the plaque. These lipid rich, relatively acellular, plaques are prone to rupture and may explain why diabetic patients have an increase in acute coronary syndromes, myocardial infarctions and respond poorly to conventional medical therapy and coronary revascularization.

NEW MEDICAL THERAPIES

Although conventional therapies[30-34] including aspirin, beta-blockers and lipid lowering therapies have reduced rates of myocardial infarction and death in diabetics, this patient group continues to have high rates of subsequent cardiovascular morbidity and mortality. A recent study has confirmed the efficacy of fibrates in diabetics and demonstrated that fenofibrate is able to attenuate the progression of coronary artery disease as assessed by angiography with a strong trend towards a decrease in cardiovascular events[35]. In addition, the MICRO-HOPE substudy demonstrated that diabetics with a prior cardiovascular event or

at least one cardiovascular risk factor had a 22% decrease in myocardial infarctions, a 33% decrease in stroke, a 17% decrease in the need for coronary revascularization and a 37% reduction in cardiovascular death[36]. These changes may be secondary to increases in bradykinin concentrations and decreases in angiotensin II concentrations, which increase vasodilation, coupled with changes in the local relative concentrations of PAI-1 and tPA. In addition, glycoprotein 2b/3a inhibitors have decreased rates of myocardial infarction in diabetics with acute coronary syndromes and decreased clinical restenosis in diabetics undergoing percutaneous stenting. Will new therapies which target insulin resistance, which decrease chronic inflammation, and which alter the abnormalities in the fibrinolytic system further decrease the progression of cardiovascular disease and decrease the rates of acute myocardial infarction?

Thiazolidenediones are insulin sensitizers, which improve muscle and adipose tissue sensitivity to insulin by acting as a selective agonist for peroxisome proliferator activated receptor-gamma (PPAR-gamma). The activation of PPAR-gamma nuclear receptors modulates the transcription of some insulin responsive genes, which affect glucose and lipid metabolism. These agents have beneficial effects on glucose control. Monotherapy with troglitazone augments glucose-disposal rate by 97%, primarily in skeletal tissue, without decreasing endogenous glucose production and results in a 20% decrease in mean fasting glucose levels. It is clear that thiazolidenediones are beneficial in improving glycemic control and work in a complementary fashion with metformin and/or insulin[37]. Do diabetics have additional benefits from this class of drugs? Several studies suggest the answer to be yes.

Twenty-seven patients with type II diabetes were randomized to receive troglitazone or placebo for 16 weeks. Baseline and 16 week measurements of acute-phase serum proteins

including serum amyloid A, C-reactive protein, complement protein and alpha 1 acid glycoprotein were obtained. Compared to the elevated baseline levels of these acute-phase reactants, therapy with troglitazone, but not placebo, resulted in a decrease in these levels, except for C-reactive protein[38]. These findings are consistent with the ability of thiazolidenediones to decrease in vitro levels of cytokines including TNF alpha and to decrease the production of monocyte inflammatory cytokines [39-43]. These effects could potentially decrease the progression of coronary artery disease and the propensity for plaque rupture. A second study provides further insight into this class of drugs[44]. Individuals with polycystic ovarian syndrome are characterized by an impairment of insulin action and secretion consistent with insulin resistance. In addition, these individuals have an impaired fibrinolytic system characterized by elevated PAI-1 levels. The administration of troglitazone for 12 weeks to these subjects had a marked improvement in glycemic control and increased insulin sensitivity. In addition, troglitazone resulted in a 50% reduction in PAI-1 activity, which correlated with a decrease in insulin levels.

These two studies demonstrate favorable effects of troglitazone in improving insulin sensitivity, in decreasing markers of chronic inflammation, and in improving the fibrinolytic system. Thus, troglitazone may attenuate the progression of coronary artery disease and decrease the propensity to develop acute coronary syndromes and acute ST segment elevation infarcts by favorably influencing macrophage function, by restoring the altered ratio of tPA to PAI-1 and by decreasing the ratio of lipid content to cellular content of plaques. A third study demonstrates that troglitazone serves as a ligand to PPAR-gamma, which may regulate vascular smooth muscle cell migration, expression of matrix metalloproteinases and macrophage activation. Troglitazone activates PPAR-gamma and

inhibits vascular smooth muscle migration from the media to intima (in respone to mitogens or direct injury) in *in vitro* studies[45]. These multiple effects may stabilize plaques and decrease the tendency for plaque erosion, rupture and thrombosis. In addition, troglitazone may attenuate the endothelial dysfunction present in diabetics. Studies of troglitazone in patients with diabetes mellitus with Prinzmetals angina have revealed a decrease in clinical episodes of angina, a reduced needs for nitrates and improved endothelial-dependent brachial artery vasodilation[46].

CONCLUSIONS

Multiple clinical studies have demonstrated the increased incidence of cardiovascular morbidity and mortality in diabetic subjects. Although current cardiovascular therapies are beneficial in diabetics, patients continue to experience excessive morbidity and mortality. In order to improve clinical outcomes in these patients, internists, cardiologists and endocrinologists will need an increased understanding of their respective disciplines and will need to work in concert with hematologists, immunologists, and vascular biologists. Therapies such as glycoprotein 2b/3a inhibitors [47-48] and intensive metabolic control have already yielded clinical improvements with a reduction in myocardial infarction and death in diabetics admitted with acute coronary syndromes[49]. Future therapies which improve insulin sensitivity, which decrease chronic inflammation, which decrease systemic cytokines, and which favorably alter the systemic and vascular intramural ratios of plasminogen activators to plaminogen activator inhibitors will likely decrease progression of atherosclerosis and increase plaque stability. Such therapies will likely decrease the incidence of acute coronary syndromes, myocardial infarctions and death in diabetics.

Time will tell.

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