The 6th Annual World Congress on the Insulin Resistance Syndrome

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This is the second of a series of articles based on presentations at the 6th Annual World Congress on the Insulin Resistance Syndrome held 25–27 September 2008 in Los Angeles, California.

Gary Lewis (Toronto, Canada) discussed the effect of prolonged free fatty acid (FFA) elevation on pancreatic β-cell function. FFAs are essential for maintenance of basal insulin secretion, and acute FFA elevation increases glucose-stimulated insulin secretion, but prolonged FFA elevation consistently impairs glucose-stimulated insulin secretion (GSIS) in vitro. There is no consensus regarding in vivo effects in part because of FFA-induced insulin resistance, so that lack of change in insulin levels may actually indicate failure of compensatory increase in insulin secretion. Lewis described studies of this with graded glucose infusion. After doubling FFA levels with heparin plus lipid infusion, comparing acute with prolonged FFA elevation, insulin secretion did not change, but there was reduction in insulin sensitivity (1). Given the hyperbolic relationship between insulin sensitivity and insulin secretion, the product of the two, termed the disposition index, is a more important measure (2). With use of this measure, GSIS increases by ∼50% with the acute increase in FFA levels, countering FFA-induced reduction in insulin sensitivity, so that the disposition index is unchanged, whereas with prolonged FFA elevation, β-cell compensation is not shown—a phenomenon particularly observed in obese nondiabetic subjects (3,4). Elevated glucose has additive effects to FFA in reducing GSIS in obese subjects (5). Monounsaturated (MUFA), polyunsaturated (PUFA), and saturated (SFA) fats appear to differentially affect GSIS. Longer FFA chain length and degree of saturation are associated with

greater insulin resistance. In a study comparing olive (78% MUFA), safflower (78% PUFA), and palm (50% SFA) oils, ingested over 24 h, insulin sensitivity was particularly decreased by SFA, leading to a greater reduction in the disposition index (6), although all three oil emulsions similarly reduced β-cell function.

Lewis reviewed evidence that oxidative stress inhibits β-cell function (7). He discussed results of a study showing that orally administered taurine, an effective aldehyde scavenger, improved the FFA-induced impairment in insulin sensitivity and β-cell function, although oral N-acetyl-L-cysteine, a precursor in the formation of the free radical and aldehyde scavenger glutathione, did not improve insulin sensitivity or the disposition index (8); in an animal model, both of these antioxidants were effective in increasing insulin secretion (9). FFA may increase inflammatory markers in muscle, and there is evidence that the anti-inflammatory drug salsalate improves glycemia in obese nondiabetic adults (10), although others have reported that aspirin impairs insulin sensitivity in healthy and in type 2 diabetic subjects (11); Lewis's group has found evidence that salicylate reduces insulin sensitivity and lowers the disposition index.

Ralph DeFronzo (San Antonio, TX) discussed the question of whether there is a role of hyperglycemia in macrovascular atherosclerotic disease. Certainly, there is a strong relationship between glycemia and microvascular complications of diabetes, but the UKPDS (UK Prospective Diabetes Study) showed 14 and 12% decrease in risk of myocardial infarction and stroke per 1% reduction in A1C, considerably less than the effect of glycemia with microvascular outcomes (12). Optimizing glycemia in the ADVANCE (Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation),

ACCORD (Action to Control Cardiovascular Risk in Diabetes), and VADT (Veterans Affairs Diabetes Trial), moreover, failed, according to DeFronzo, to improve macrovascular outcomes, although this is somewhat controversial. Is glycemia, DeFronzo asked, not a major risk factor for cardiovascular disease (CVD)? Was the wrong patient population studied: patients with advanced disease and long-standing diabetes? Was the wrong drug used: insulin? DeFronzo suggested that aggressive insulin treatment exacerbates insulin resistance, is associated with weight gain, activates inflammatory and atherogenic pathways, increases VLDL, lowers HDL, increases LDL transport in vascular smooth muscle cells, and, perhaps, promotes atherogenesis. He further pointed out that the sample size of the studies was inadequate, given the exemplary CVD risk factor treatment in the three studies, with annual 2.3 and 2.2% incidences in the ACCORD and ADVANCE studies. In a population with a 1.5% annual CVD rate, to demonstrate a 25% reduction in CVD, 3-, 5-, and 10-year studies will require ∼28,000, 14,700, and 6,800 patients; in fact, it is likely that populations with recent-onset diabetes will have event rates below 1% and that optimal glycemic treatment will only reduce CVD by ∼15%, so that even larger numbers of patients will need to be followed to demonstrate macrovascular benefit.

Insulin resistance includes obesity, diabetes, hypertension, dyslipidemia, increased plasminogen activator inhibitor-1 (PAI-1), endothelial dysfunction, hyperinsulinemia, and atherosclerosis and is likely to account for the residual risk after optimal blood pressure, lipid, antiplatelet, and glycemia treatment. Normal-weight diabetic patients have insulin resistance similar to that of obese nondiabetic patients, with the major defect in the ability of tissues to take up glucose and store it as glycogen (13), with similar insulin resistance in patients with hypertension and with hypertriglyceridemia and in those with coronary artery disease. Prospective epidemiological studies show a relationship between insulin resistance and CVD. In the San Antonio Heart Study, the most insulin-resistant quintile

of 2,569 nondiabetic individuals followed for 8 years had a 2.5-fold increase in CVD, with remaining 2-fold increase after adjustment for age, sex, blood pressure, LDL and HDL cholesterol, triglycerides, cigarette use, exercise, and waist circumference (14). DeFronzo suggested that "the unexplained risk [in CVD after risk factor adjustment (15)] is in fact insulin resistance."

The molecular etiology of insulin resistance involves abnormality of insulin receptor signal transduction (16), the pathway leading to GLUT4 activation also responsible for generating nitric oxide (NO), involving serine rather than tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), whereas the mitogen-activated protein kinase pathway remains insulin sensitive, leading to atherogenesis and inflammation. In a study of lean offspring of two diabetic parents, the metabolic pathway was underactive while the mitogenic pathway of insulin signaling was overactive (17). The offspring, DeFronzo said, "are not only sitting in a sea of [cardiovascular] risk factors, they have the molecular defect that is driving atherogenesis."

Lipotoxicity involves increased plasma FFA, increased tissue fat content, altered fat distribution, and/or increased adipocytokine release, with elevation of FFA alone able, in a dose-responsive fashion, to increase hepatic glucose production while decreasing muscle glucose uptake (18), which DeFronzo termed "the two major core defects." In contrast, FFA lowering with acipimox reduces FFA during a euglycemic insulin clamp and improves insulin signaling (19).

DeFronzo suggested that FFA is "the neglected lipid" in atherosclerosis, increasing nuclear factor-κB (NF-κB)–cells and reducing the inhibitor of κB (IκB) because increased fatty acyl-CoA activates IkB kinase, causing it to dissociate from NF-κB, with IκB kinase also serine phosphorylating IRS-1. Dissociated NF-κB enters the nucleus, activating production of inflammatory cytokines and growth factors that lead to inflammation and atherosclerosis. Physical exercise increases the reassociation of IκB with NF-κB (20). Cultured human myocytes show increased NF-κB activity when incubated with the fatty acid palmitate, associated with production of cytokines. Toll-like receptor (TLR) 4 is a plasma membrane receptor that plays an important role in the innate immune system, which is activated by circulating FFA, setting in mo-

tion a series of phosphorylation reactions leading to IκB phosphorylation. TLR4 mRNA and protein are increased in muscle of insulin-resistant individuals, while IκB content is decreased and TLR4 correlates with insulin resistance as measured by the homeostasis model assessment (HOMA). Thiazolidinediones reverse lipotoxicity, reducing plasma FFA, normalizing fat distribution, and improving insulin sensitivity (21). In nonalcoholic steatohepatitis, the thiazolidinedione pioglitazone reduced liver fat, lowered alanine transaminase, and improved histological findings of inflammation, ballooning necrosis, steatosis, and fibrosis (22). Pioglitazone also improved coronary (23) and carotid (24) atherosclerosis in diabetic patients.

H. Bryan Brewer (Washington, DC) gave an update on the role of HDL cholesterol in insulin resistance and CVD. He extended DeFronzo's discussion of residual CVD risk by pointing out that with maximal clinical LDL cholesterol reduction there is still an unmet clinical need "to add to the statins" even with LDL cholesterol <70 mg/dl (25). The lipoprotein profile of the at-risk person is the atherogenic dyslipidemia of increased triglyceride and dense LDL and decreased HDL cholesterol levels associated with elevated blood pressure, abnormalities of glycemia, hypercoagulability, and all the components of metabolic syndrome. There is controversy about the diagnostic criteria, but clearly HDL cholesterol is a significant component of the state, although there is insufficient evidence to support HDL cholesterol lowering. HDL cholesterol certainly is a risk factor for CVD in the Framingham (26) and PROCAM (PROspective CArdiovascular Münster) (27) studies. For each 1-mg increase in HDL cholesterol, CVD risk decreases 3%. Low HDL cholesterol is highly prevalent, seen in 30% of nondiabetic and 45% of diabetic patients (28).

There are a number of mechanisms by which HDL may decrease atherosclerosis. HDL acts to mediate reverse cholesterol transport. Cholesterol derived from LDL is modified and binds to scavenger receptor SR-B1 in tissues, particularly the vasculature, activating macrophage ATP-binding cassette, subfamily A (ABCA1) and ABCG1 receptors, leading macrophage cholesterol to be taken up by lipid-poor apolipoprotein A1 after binding with the ABCA1 transporter. Lecithin-cholesterol acyltransferase (LCAT) leads to formation of pre–β-HDL, comprising

5% of circulating HDL. Further action of LCAT leads to formation of α-HDL, comprising 95% of circulating HDL, which binds to the SR-B1 receptor and ABCG1 transporter, then delivering cholesterol to LDL via cholesteryl ester transfer protein (CETP). LDL cholesterol can return to the liver or can be delivered to tissues, or direct uptake of α-HDL to the liver can occur via SR-B1. HDL may also exhibit anti-inflammatory (29) and antioxidant effects, the latter by blocking oxidized-LDL formation and taking up oxidized fatty acids. HDL can also decrease adhesion molecules, can increase NO synthase, can act to transport other molecules, can increase endothelial stem cells, may have role in binding endotoxin and acting as an anti-infectious agent, and may have antithrombotic effects.

Although animal models suggest that HDL has antiatherosclerotic effects (30), clinical studies showing benefit from increasing HDL are limited. Niacin reduced events in the coronary drug project (31), and niacin appears to improve the effect of statins (32,33). Infusion of A-1 Milano improved atherosclerosis, as measured by intravascular ultrasound (34). "The challenge," Brewer said, "has been to develop a good HDL-raising drug." Statins raise HDL cholesterol level by 6–14%, fibrates by 15%, and niacin by 20–30% but with poor tolerability; although CETP inhibitors double HDL, "we'll have to find out if they are safe and effective," with adverse outcome seen with such an agent in a recent large clinical trial (35).

Ronald Krauss (Oakland, CA) discussed nutritional and genomic regulation of atherogenic dyslipidemia and focused on small dense LDL particles. LDL consists of four distinct subsets, classes 3 and 4, smaller particles with greater arterial proteoglycans binding, greater oxidative susceptibility, greater endothelial transport, and reduced LDL receptor binding; medium size class 2 particles, the most abundant species in plasma of healthy individuals; and large LDL class 1 particles that carry the largest cholesterol mass but do not have adverse arterial effects, explaining the relatively weak correlation of LDL with CVD. Apolipoprotein B and, even more, particle number may be better measures than LDL cholesterol per se. The identification of LDL subpopulations is aided by plasma triglyceride levels, with two clusters of subjects, those with peak LDL diameter >260 and those with LDL peak <260 A, the latter having higher triglyceride levels.

VLDL secreted by the liver is acted upon by lipoprotein lipase, forming LDL. High triglyceride levels are associated with large VLDL production, forming remnant particles that are slowly acted on by lipoprotein and hepatic lipase to produce small LDL. HDL interacts with small LDL via CETP.

LDL subclass phenotype is 40–75% determined by heredity; however, age, male sex, adiposity, insulin resistance, and diet are important additional factors. The prevalence of small LDL is linearly related to BMI (36); adiposity increases FFA and cytokines, increasing the hepatic triglyceride pool size, driving production of larger VLDL particles. A low-fat, high-carbohydrate (CHO) diet can induce expression of the phenotype B small LDL particle size (37), driven by large VLDL particles secreted as increased dietary CHO raises triglyceride levels (38). Kraus noted that individuals with the genetic tendency to small, dense LDL particles also have an increased LDL response to dietary fat. Kraus therefore addressed the questions of whether lowering dietary CHO would reverse phenotype B, whether weight loss reversed phenotype B independent of dietary composition, and whether CHO limitation and/or weight loss would attenuate the lipoprotein response to SFA intake.

In the NuGAT (Nutritional Genomics of Adipose Tissue) study of 178 healthy men with BMI 26–35 kg/m^2, the basal diet was 54% CHO and 16% protein and the moderate CHO diet was 39% CHO, 29% protein, and 29% fat, followed by a reduction to 26% CHO, increasing to 45% fat, with either more SFAs or MUFAs. After a 3-week stabilization, calories were reduced to induce weight loss. CHO limitation reduced expression of phenotype B, with weight loss additionally improving the atherogenic dyslipidemia, particularly with high CHO diets (39). Reducing dietary CHO from 54 to 26% markedly improved phenotype B and triglyceride levels, with the amount of SFA not having great influence on the lipid pattern, with both weight loss and CHO restriction reducing triglyceride levels. LDL cholesterol reduction was actually greater with more SFA. Adipose tissue biopsy showed that reducing dietary calories and CHO decreased fatty acid desaturase and diacylglycerol O-acyltransferase 2 gene expression, correlating with triglyceride response (40). Interestingly, dietary factors of this sort decrease eicosanoids, which may have effects on inflammation and endogenous cannabinoid levels.

Gunther Boden (Philadelphia, PA) discussed the role of matrix metaloproteinases (MMPs) in insulin resistance and their relationship to the question of whether insulin resistance per se can cause atherosclerosis. In hyperinsulinemic rats, the active forms of MMP-2, -9, and -14 increase, particularly with lipid and heparin infusion to raise FFA levels (41). Tissue inhibitors of MMP increase to some extent, but the ratio of MMP to tissue inhibitors is increased during euglycemic hyperinsulinemia, particularly with concomitant elevation in FFA levels (42). Tissue factor (TF) is present in the adventitia of blood vessels and atherosclerotic plaques, leading to an increase in coagulation with vessel wall injury. It is now recognized that TF is also present on monocytes and microparticles and that circulating TF is thrombogenic. TF-procoagulant activity (PCA) may be stimulated by hyperglycemia and/or hyperinsulinemia. TF-PCA increased minimally with hyperglycemia alone in nondiabetic individuals, to a greater extent with hyperinsulinemia alone, and was particularly increased by the combination of hyperglycemia and hyperinsulinemia. Boden showed analysis of monocyte TF-PCA revealing increases in both mRNA and protein. There is evidence of generation of thrombin and platelet activation by TF-PCA suggesting this to be an important pathogenic process contributing to hypercoagulable state of insulin resistance (43). Boden pointed out that somatostatin increases TF-PCA but abolishes the effects of hyperglycemia and hyperinsulinemia on TF and thrombin activation, so use of somatostatin to characterize insulin sensitivity is invalid in these studies (44).

Type 2 diabetes is associated with marked elevation in TF-PCA, which does not improve after glucose levels are normalized for 24 h (45), and Boden pointed out that in type 1 diabetic patients hyperglycemia increases TF-PCA to a lesser degree than it does in type 2 diabetic patients, suggesting that hyperglycemia is not itself the direct initiator of the hypercoagulable state, but rather should be seen as a potentiator, acting then as a factor enhancing the CVD risk of insulin resistance. Equally, Boden suggested that there may be adverse effects of "massive doses of insulin" in treatment of type 2 diabetic patients.

Mark Kearney (Leeds, U.K.) dis-cussed vascular insulin resistance as a therapeutic target, asking whether insulin resistance causes endothelial dysfunction, whether endothelial insulin resistance specifically causes atherosclerosis, and whether improvement in whole body insulin sensitivity improves vascular function. The arterial wall abnormalities associated with insulin resistance are well characterized, with changes in the endothelial cell phenotype, particularly decreased NO production, preceding the development of atherosclerosis. The endothelium should then be considered a target tissue for insulin action, with NO synthase activation causing antiatherosclerotic effects, whereas defects in endothelial insulin signaling impact NO synthase (46). In human studies, insulin resistance appears to worsen over time, progressively reducing NO bioavailability. Kearney speculated that the residual risk affecting diabetic patients with coronary disease despite statins, β-blockers, and ACE inhibitors, even with excellent blood pressure and lipid levels, may be mediated in part by reduction in endothelial NO, perhaps explaining the reduction in coronary microvascular function, as well as some of the apparent resistance to aspirin (47). Kearney reviewed evidence that NAD(P)H oxidase is upregulated in insulin resistance, with oxidative stress as a mediator of atherosclerosis in insulin resistance.

Burton Sobel (Burlington, VT) suggested that "there is more to this than glycemic control . . . [and] Insulin resistance is a pivotal determinant" of macroangiopathy. He discussed three sites—the blood, the vessel wall, and the heart—in introducing the topic of insulin resistance and heart failure. Every aspect of coronary disease occurs approximately twice as frequently in diabetic patients. Fibrinolysis involves conversion of plasminogen to plasmin to degrade fibrin clots, with understanding of this pathway leading to development of tissue plasminogen activator (tPA) as a therapy for acute thrombosis. PAI-1 is the natural inhibitor of plasmin generation.

The fibrinolytic system is activated in blood from young survivors of myocardial infarction, with increased PAI-1 and decreased tPA activity (48), suggesting predisposition to thrombosis. Plasma PAI-1 antigen and activity have been recognized to be increased in obesity and in diabetes (49). Insulin stimulates PAI-1 formation in vitro and in animal models, and after infusion of glucose and lipid,

PAI-1 levels increase. This predisposes to the increased thrombosis rate in diabetic patients.

The PAI-1 system also is present in the vessel wall, and plasminogen activator is expressed in cells migrating into the vascular wall, activating MMPs—a process inhibited by PAI-1. Vascular wall PAI-1 mRNA and protein increase after insulin infusion (50). In the Bypass Angioplasty Revascularization Investigation (BARI) 1, mortality was greater for diabetic patients undergoing angioplasty compared with coronary artery bypass grafting (CABG) as a result of high rates of restenosis and thrombosis. PAI-1 levels are increased in coronary atheromas from diabetic patients (51). Sobel contrasted the stable plaque, having a vascular smooth muscle cell infiltrate causing flow restriction, with the unstable coronary artery plaque, which is prone to rupture. In mice that do not express apolipoprotein E, with or without PAI-1 overexpression, vulnerable plaques are seen. These plaques evolve with decreased proteolysis secondary to increased PAI-1, decreased vascular smooth muscle migration, and decreased MMP activity.

For a given size myocardial infarction, diabetes is associated with increased risk of subsequent congestive heart failure (CHF). Even without CHF, there is evidence of decreased heart function with diabetes (52). CHF is more common in type 2 diabetic patients (53), and, after revascularization for acute coronary syndrome and after myocardial infarction (54), diabetes is a major determinant of CHF and mortality. In a myocardial infarction model, echocardiographic segmental wall abnormality correlates with creatine kinase levels, with increase in PAI-1 content at the site of the infarct, potentially increasing local fibrosis. PAI-1 is located in the interstitium and perivascular spaces, and insulin resistant animals overexpress PAI-1, in association with increased hydroxyproline, a marker of fibrosis. PAI-1 overexpression in nondiabetic animals decreases heart function. Sobel noted that thiazolidinediones decrease PAI-1 antigen and activity in insulin-resistant states, with their adverse effect in CHF because of renal-mediated fluid retention (55) rather than being caused by adverse effect on cardiac function (56).

Ronald Witteles (Stanford, CA) discussed the evidence of cardiomyopathy in insulin resistance. Insulin resistance is associated with hypertension and diabetes,

both potential causes of heart failure, and heart failure causes insulin resistance; however, beyond this, there is evidence that insulin resistance itself can cause heart failure, potentially via inefficient utilization of energy substrates, with inflammation as another possible factor. The heart utilizes an immense amount of ATP, completely turning over its supply every 13 s. Cardiac muscle can utilize FFA, glucose, and lactate, with FFA providing 70% of energy requirements for the normal heart. FFAs generate more energy per molecule of substrate metabolized, but in the ischemic heart, glucose has the advantage of generating more energy per oxygen molecule used. Uncoupling proteins are induced by high FFA, further making this substrate less desirable for the stressed heart. Furthermore, fatty acids stored in the heart may have toxic effects, whereas glucose stored in the heart as glycogen has a membrane-stabilizing effect.

FFA levels correlate strongly with cardiac uncoupling protein levels and inversely with cardiac GLUT4 activity. Lipotoxicity appears to occur with overexpression of myocardial long-chain acyl-CoA. Peroxisome proliferator-activated receptor-α overexpression reduces the ejection fraction (EF), particularly with a diet rich in long-chain fatty acids. In the failing human heart, fatty acid transport protein levels are decreased with insulin resistance. In a positron emission tomography imaging study of patients with nonischemic dilated cardiomyopathy, fatty acid oxidation decreased and glucose oxidation increased. The response to injury, then, is to change from FFA to glucose metabolism. Insulin resistance, however, reduces glucose metabolism, increasing reliance on FFA metabolism, increasing uncoupling protein activity, and reducing the efficiency of energy generation. In the failing heart, glucose metabolism is increased and FFA metabolism decreased, resulting in more efficient energy utilization under circumstances of limited oxygen availability. Decreased glucose and increased FFA metabolism in the insulin-resistant setting promote worse response to injury.

Heart failure is an insulin-resistant state that causes insulin resistance and elevated plasma FFA levels. Glycemic abnormality—presumptive evidence of insulin resistance—is associated with increased prevalence of CHF (57), whereas patients discharged from hospital with CHF have a 60% increase in prevalence of

diabetes (58), and glycemic abnormality is seen in patients with idiopathic dilated cardiomyopathy (59). Glycemic abnormalities appear to antedate the development of heart failure, leading to the concept that insulin resistance is causally related to CHF—a finding demonstrable in individuals without evidence of coronary disease (60). Proinsulin levels are increased when measured 20 years before clinical evidence of heart failure (61); the presence of insulin resistance predicts the development of CHF (62), and patients who have heart failure with greater insulin sensitivity have better survival (63,64). Carvedilol leads to a shift from FFA to glucose metabolism and has benefit in CHF; in a study of subjects treated with this agent, insulin resistance is associated with worse outcome (65). An important question, then, is whether treatment of insulin resistance will either prevent development of CHF or improve its outcome when already present.

These considerations have led to the concept that inhibition of FFA metabolism or improvement in glucose metabolism might be used to treat CHF (66). Trimetazidine is an agent approved in Europe for angina that blocks long-chain 3-ketoacyl-CoA thiolase activity, the last enzyme in fatty acid oxidation. This agent increases EF, particularly in patients with nonischemic CHF (67). In a study of such patients treated with 25 mg trimetazidine twice daily for 3 months, insulin sensitivity (HOMA) and HDL cholesterol levels increased, with a small reduction in β-oxidation of FFA β-oxidation and increase in EF, which decreased in the placebo group. Perhexiline, which blocks carnitine palmitoyltransferase-1, is another agent not approved in the U.S., whose use may be limited by neuropathy; it improved EF and maximal oxygen consumption in individuals with CHF (68). Ranolazine, which is available in the U.S., inhibits slow inactivating sodium/calcium exchange, although prolonging the QT interval, leading to concern about arrhythmia induction. Glucagon-like peptide 1 is another potential treatment, more fully discussed by Fonseca in his assessment of gut peptides (vide supra). Thiazolidinedione treatment causes sodium retention and so must be used with great caution in CHF; however, Witteles described a study in which positron emission tomography of nondiabetic patients receiving rosiglitazone showed improvement in insulin sensitivity in association with increase in myocardial glucose up-

take. He concluded that insulin resistance "is the worst of all worlds in heart failure," with the development of treatment options to shift substrate utilization both feasible and promising (69).

Martin LeWinter (Burlington, VT) further discussed the interrelationships between insulin resistance, diabetes, and heart failure and pointed out that although type 2 diabetes doubles the risk of CHF in men and more than triples it in women, insulin resistance independently confers a 50% increase in risk, with both factors synergistically interacting with hypertension and coronary disease, and an interaction effect of diabetes with sex on mortality among individuals hospitalized with CHF (70). Metabolic syndrome is associated with CHF in older people, LeWinter stated, with proinflammatory biomarkers such as C-reactive protein and interleukin-6 appearing to explain the increased risk. Not only is diabetes a major independent risk for heart failure, but there is a high incidence of diastolic dysfunction and left ventricular hypertrophy in otherwise healthy, normotensive diabetic patients, with myocardial abnormality invariably found in animal models of diabetes, so that the existence of diabetic cardiomyopathy is currently accepted, recognizing that further risk factors, such as coronary disease and hypertension, usually contribute to the clinical syndrome. Diastolic dysfunction may be associated with normal EF in diabetic patients with CHF (71). Determinants of diastolic dysfunction in diabetes include increased ventricular mass-to-volume ratio and reduced arterial compliance, caused by "stiff vessels," increasing afterload (72). Diastolic dysfunction occurs in asymptomatic normotensive type 2 diabetic patients, and LeWinter reviewed studies of epicardial biopsies performed during CABG from diabetic patients with normal EF and normal wall motion with increased carboxymethyllysine staining in collagen fibrils and increased fibrosis, particularly affecting extracellular matrix. Diabetic patients with normal EF undergoing CABG exhibit decreased cardiac reserve during exercise, a phenomenon particularly occurring in female subjects, potentially caused by abnormalities of calcium cycling and altered myofilament function.

Cardiomyocyte damage in diabetes may be related to effects of FFA, insulin resistance, hyperinsulinemia, endothelial dysfunction, renin-angiotensin-aldosterone system (RAAS) activation,

and hyperglycemia (although this appears to be of lesser importance). All these factors lead to cardiac hypertrophy (activated by inflammatory signaling), apoptosis, oxidative stress, protein kinase C activation, uncoupling of mitochondrial oxidation, and lipotoxicity. Extracellular matrix remodeling occurs in the heart in diabetes, with RAAS activation as a well-recognized signaling system for fibrosis, and second, advanced glycation end products (AGEs) crosslinking adjacent collagen fibers and rendering them resistant to degradation, as well as activating the receptor for AGE, causing cytokine-induced collagen production. Another mediator may be the increase in myocardial triglyceride content associated with insulin resistance (73).

Pharmacological management of diabetic patients with systolic dysfunction that causes CHF includes the standard treatment modalities of β-adrenergic blockers, particularly carvedilol, and RAAS blockers, increasingly recognizing the importance of aldosterone, with spironolactone (74) and eplererinone as useful agents. Diet may be more beneficial than generally recognized, with 16 weeks of a very-low-calorie diet in type 2 diabetic patients associated with reduction in myocardial triglyceride, in left ventricular mass, and in diastolic dysfunction (75). There is no evidence that improved glycemic control is beneficial in CHF; observational studies actually suggest that high A1C is associated with lower mortality (76), and individuals receiving insulin treatment have increased mortality rates (77), recognizing that the inference of causality from such analyses may be somewhat tenuous. Insulin may, however, have anti-inflammatory or energy metabolism benefits, so this area deserves further research. LeWinter pointed out that in 2006 the metformin "black box warning" against use in individuals with heart failure was removed and that an observational study shows reduced mortality in diabetic patients receiving this agent (78), although caution is, of course, required with renal disease. He also addressed the question of whether there may be cardiovascular benefit of thiazolidinediones and pointed out that they improve lipids and blood pressure, can be shown to reduce vascular smooth muscle cell proliferation/migration and to decrease cardiac remodeling, and may have other cardioprotective effects. The occurrence of CHF with thiazolidinedione treatment reflects vascular permeability

and/or renal collecting duct effects superimposing fluid retention on underlying diastolic dysfunction rather than being a direct adverse effect on the myocardium.

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