Third Annual World Congress on the Insulin Resistance Syndrome

Atherothrombotic disease

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Diabetes and vascular disease

At a symposium cosponsored by the International Society of Diabetes and Vascular Disease (www.dvdres.com), Peter Grant (Leeds, U.K.) discussed the role of insulin signaling pathways in acute coronary syndrome (ACS), pointing out that type 2 diabetes is characterized by fasting hyperglycemia, usually with obesity, accompanied by a clustering of CVD risk factors, with 80% of persons with type 2 diabetes dying of premature vascular disease. In persons with diabetes, glycemic abnormality is superimposed on the abnormalities of the insulin resistance sydrome, so that similar considerations apply to the larger group of persons with insulin resistance. Indeed, we may underestimate the importance of glycemic abnormality in cardiovascular disease (CVD), with recent studies suggesting that some 40% of persons with myocardial infarction have diabetes, with an additional 40% having impaired glucose tolerance (1). The cardiovascular manifestations of insulin resistance sydrome constitute a series of inflammatory atherothrombotic processes, with atherectomy specimen analysis showing more thrombus, more macrophage infiltration, and a greater area of lipid-rich atheroma in persons with diabetes (2). Furthermore, type 2 diabetes alters fibrin structure, coagulation, and platelets in a prothrombotic direction (3).

It is not apparent why insulin resistance should be linked to atherosclerosis. The thrifty genotype hypothesis suggests that there is a survival advantage to insulin resistance during periods of feast alternating with famine (4), but that chronic exposure to high nutrient intake converts the organism to the phenotype of insulin resistance sydrome and diabetes, with energy preferentially stored in the liver and in fat and with the clustering of risk markers we have come to identify with insulin resistance. The common-soil hypothesis suggests that diabetes and CVD are the same condition, underpinned by common genetic and environmental influences (5).

Grant continued that inflammation and thrombosis are related processes that must have primary protective function, that the adipocyte response to fat loading also must be interpreted as a physiological response, and that to understand the inflammatory atherothrombotic insulin resistance syndrome, we must unravel its derivation as a set of normal responses to an abnormal setting, perhaps with abnormal cyclical responses underpinning the link between diabetes and CVD (6). The organism exhibits a variety of cycles, ranging from the cell cycle to circannual rhythms, the menstrual cycle, and diurnal variation. A set of circadian oscillators exists to keep life functions synchronized with the external environment. Light acts at the suprachiasmatic nucleus to increase levels of melatonin, regulating the hypothalamic "clock," which generates protein signals feeding back to create rhythmic behaviors and metabolic changes. Rhythmic mRNA expression of clock genes and adipokines can also be demonstrated in mouse visceral adipose tissue, with adiponectin and resistin responses both attenuated in obese mice. Grant showed an animal model in which pioglitazone improved hepatic rhythmicity. Thus, light, as well as other stimuli such as ambient temperature, acts via the suprachiasmatic nucleus to send signals to adipocytes, the endothelium, liver, fibroblasts, cardiac myocytes, and multiple other tissues, regulating reproductive, metabolic, and behavioral aspects of life.

An interesting model of insulin resistance that also demonstrates the importance of cycles is the hibernating animal. Such animals eat during the summer, gaining weight, becoming hyperinsulinemic and insulin resistant, with increased free fatty acid levels and increased inflammatory response. Adipocyte-derived cytokines lead to what is termed endothelial cell dysfunction, but during hibernation, these factors are reversed over a several-week period, while in humans with insulin resistance sydrome, there is progressively worsening insulin resistance at the heart of a "broken relationship to the environment," leading to ever-growing fat mass. Grant termed melatonin the "forgotten hormone," regulating the clock systems, activating the adipocyte phosphatidylinositol 3-kinase (PI3K) pathway, increasing insulin sensitivity, and improving glucose metabolism in humans. Interestingly, pinealectonized animals develop type 2 diabetes, and mice with mutations in circadian clock genes develop insulin resistance (7). In the Leeds family study of 537 persons from 89 families, three common polymorphisms have been found in the clock gene, all associated with the insulin resistance sydrome. Persons whose cyclic patterns are disrupted may have adverse health outcomes, with shift working associated with 1.6- and 3-fold increased CVD rates in men and women, respectively. We are meant, Grant concluded, to expe-

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Abbreviations: ACEI, ACE inhibitor; ACS, acute coronary syndrome; ADMA, asymmetric dimethylarginine; apo, apolipoprotein; CHF, congestive heart failure; COX, cyclooxygenase; CRP, C-reactive protein; CVD, cardiovascular disease; IL, interleukin; MMP, matrix metalloproteinase; NF, nerve factor; NOS, NO synthase; PAI, plasminogen activator inhibitor; PCI, percutaneous intervention; PGE, prostaglandin E; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator–activated receptor; RAGE, receptor for advanced glycation end products; SSPG, steady-state plasma glucose; tPA, tissue plasminogen activator; TZD, thiazolidinedione; VTE, venous thromboembolism; vWF, von Willenbrand factor; WBC, white blood cell.

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rience short-term periods of weight gain that are seasonal and beneficial, with our "abnormal relationship with our environment" leading us to ignore the adaptations for which certain basic genes have been developed.

Paul Martin (Geneva, Switzerland) discussed the evidence base of acute management of ACS in diabetic patients. During the ACS, there is acute reduction in coronary blood flow in the setting of thrombosis superimposed on atherosclerosis. The activation of multiple hemostatic mechanisms suggests the potential for multiple approaches to prevention and reversal of pathological thrombosis, including aspirin, clopidogrel, heparin, glycoprotein IIb/IIIa inhibitors, thrombolysis, and percutaneous intervention (PCI); the approach of PCI/thrombolysis versus medical management is determined by clinical findings, such as troponin levels and angiographic findings. The objective of ACS management is the restoration of blood flow, myocardial salvage, and maintenance of left ventricular function. Studies comparing PCI with thrombolysis suggest that diabetic patients with ACS have better outcome with angioplasty (8,9). Martin pointed out that fibrinolysis leads to increased thrombin release, potentially further activating platelet aggregation and contributing to undesirable outcome. Further studies of ACS without electrocardiographic ST elevation suggest that invasive approaches are optimal. Persons with diabetes have twice the early mortality in ACS, more periprocedural complications, a higher rate of early reinfarction after PCI, and a higher restenosis rate, despite similar procedural outcome, with greater risk for early and late congestive heart failure (CHF) after myocardial infarction and longer intensive care unit and hospital stays. This leads to the question of whether coronary artery bypass grafting is better for persons with diabetes (10). With drug-eluting stents, restenosis rates have decreased dramatically, suggesting that surgery and PCI may now have comparable outcome. PCI may, however, have prothrombotic effects, leading to tissue factor and adhesion molecule generation. PCI with IIb/IIIa inhibitor treatment is recommended for single-vessel disease, but American College of Cardiology/American Heart Association guidelines currently recommend that coronary artery bypass grafting using an internal mammary artery graft is preferred over PCI in diabetic persons with multivessel disease.

The National Registry of Myocardial Infarction involves 1.4 million persons. Registry patients with diabetes tended to use less aspirin, β-blockers, heparin, and IIb/IIIa inhibitors and more ACE inhibitors (ACEIs). Similarly, in the CRUSADE registry of 36000 persons, those with diabetes were less likely to have appropriate treatment and more likely to have had myocardial infarction, CHF, and death. Adherence to guidelines appeared to improve mortality in this study, with each 10% increase in guideline adherence associated with an 11% decrease in mortality. A number of new biomarkers are being developed, with C-reactive protein (CRP), basic natriutretic peptide, placental growth factor, ischemia-modified albumin, fatty acid–binding protein, and soluble CD40 ligand appearing potentially useful in addition to the electrocardiogram and quantitative troponin. The ideal cardiac biomarker will be specific and sensitive when used early in myocardial infarction, will have therapeutic implications if positive, and should be precise, reliable, and cost-effective. In a study of the use of multiple markers, a combination of troponin I, CRP, and brain natriuretic peptide allowed improved prediction (11). Martin concluded by reminding the audience of the important new understanding of the use of primary angioplasty and drug-eluting stents for ST elevation myocardial infarction, as well as of aspirin, low–molecular weight heparin, β-blockers, ACEIs, clopidogrel, IIb/IIIa, and insulin-glucose infusion with subsequent targeting of HbA_{1c} (A1C) to a goal $<7\%$ (12,13).

Darren McGuire (Dallas, TX) reviewed the epidemiology of CVD in diabetes, noting that the number of persons with diagnosed diabetes in the U.S. is estimated at 21 million, driven by obesity and visceral adiposity, which may be seen as behavioral and social as well as environmental disorders. "We have become obese and inactive, overconsuming calories," he stated, with the diabetes prevalence approaching 10% of the adult population. Among persons referred for cardiac evaluation and treatment, some 30–50% have diabetes, many of whom have not been diagnosed. Persons with diagnosed and undiagnosed diabetes and, to a lesser extent, those with impaired glucose tolerance have increased mortality risk when compared with those with normal glucose tolerance (14). Lifestyle modification reduces the need for blood pressure and lipid treatment (15). Current guidelines for CVD risk reduction in persons with diabetes suggest that aspirin and ACEIs should be given to all those >40 years of age or with another CVD risk factor; that all persons with diabetes should be treated with a statin, regardless of their baseline LDL cholesterol, when >40 years of age; and that the blood pressure goal should be 130/85 mmHg. Recent studies, however, show that only one-quarter of diabetic persons receive aspirin, only half are at lipid treatment goal, and only one-third are at blood pressure goal (16,17). An interesting new concept is the potential benefit of combined administration of a thiazolidinedione (TZD) with metformin in persons with diabetes and CVD (18). Furthermore, the risk of metformin-associated lactic acidosis may be considerably lower than previously thought, with limited evidence base for recommendations that its use be restricted in persons with mild renal insufficiency, CHF, and liver disease, so that this agent might be appropriate for many persons with these conditions. Similarly, TZD-related peripheral edema may be less of a risk than generally considered, with the suggestion that TZDs increase CHF hospitalization but decrease mortality (19). McGuire noted that peroxisome proliferator–activated receptor (PPAR)γ is expressed in the inner medullary collecting duct, with a mouse model not expressing this gene at this location preventing TZD-induced edema. Spironolactone and the aldosterone receptor antagonist eplerenone may allow optimal treatment of TZD-induced edema, although caution is required in avoiding hyperkalemia. While hydrochlorothiazide is somewhat effective, furosemide is not effective for this condition.

Francesco Cipollone (Chieti, Italy) discussed the vulnerable plaque in insulin resistance and type 2 diabetes, noting that most myocardial infarctions are caused by small nonobstructive lesions. The stable plaque is characterized by a thick fibrous plaque, small lipid core, and little inflammatory infiltrate, with the vulnerable plaque having opposite characteristics of a large macrophage infiltrate, potentially producing proteolytic factors leading to plaque rupture. Beyond the concept of the vulnerable plaque is that of the vulnerable patient. Multiple plaques with the potential to thrombose are typically present in persons who have a myocardial infarction, and 80% of persons with ACS

have at least one additional ruptured plaque, which is clinically asymptomatic (20). In human atherosclerosis specimens obtained during carotid endarterectomy, plaques from persons with diabetes have more pronounced inflammatory infiltrate, as shown by the presence of CD68 (a macrophage marker), CD3 (T-cell), and HLA-DR (activated macrophage) (21). The interstitial collagen content in plaques from patients with diabetes is less than half of that in plaques from nondiabetic persons, while oxidized LDL staining more than doubles in the plaque of the person with diabetes. Similar assessment of plaque from metabolic syndrome patients shows increased CD68 and CD3 staining.

Cyclooxygenase (COX)-2 does not appear to play a role in plaque growth, with COX-2 polymorphisms not associated with different size of atherotic lesions (22), but COX-2 overexpression does appear to increase the likelihood of plaque rupture (23). COX-2 may be involved in expression of the receptor for advanced glycation end products (RAGE), with evidence of increased RAGE expression in diabetic plaque (24). RAGE may induce nerve factor (NF)-κB expression, with the p50 and p65 NF-κB subunits more strongly present in diabetic plaque, as well as in COX-2 and matrix metalloproteinase (MMP)-9 and MMP-2, the prostaglandin E (PGE)2-dependent MMPs. Isolated monocytes from diabetic patients show advanced glycation end product–induced expression of COX-2, with both suppressed by antibody to RAGE. Regulation of RAGE in diabetic plaque shows both glucose-dependent and -independent components. Comparing persons treated with 40 mg simvastatin versus diet alone for 4 months before carotid endarterectomy, staining for myeloperoxidase, MMP-2 and -9, RAGE, NF-κB, COX-2, and PGE synthase-1, the enzyme involved in PGE2 synthesis, were markedly decreased by the statin, while collagen staining was increased following simvastatin treatment. Thus, Cipollone suggested that focal intervention to stabilize the ruptured plaque, followed by systemic medical therapy with agents including aspirin, clopidogrel, statins, and ACEIs, will be appropriate, with the additional mechanisms of plaque abnormality suggesting the potential for development of new approaches.

Nikolaus Marx (Ulm, German) discussed the role of C-peptide in diabetes and in atherogenesis, reviewing the importance of monocytes and CD4-positive lymphocytes that differentiate into the activated, mediator-releasing Th1 cells. These steps are increased in persons with type 2 diabetes who exhibit multiple and diffuse angiographic lesions. Given the elevated C-peptide seen in early type 2 diabetes, he asked whether there might be a causal role of this peptide in early atherogenesis. Increased endothelial permeability is seen in early atherosclerosis, and C-peptide but not insulin or proinsulin immunostaining was seen in early atherosclerotic lesions of persons with diabetes but not in nondiabetic persons. The C-peptide colocalized with monocyte/macrophages, although macrophages were only present in 75%, whereas C-peptide was present in 100%, of specimens from persons with diabetes, suggesting C-peptide to be a macrophage chemoattractant, with confirmatory studies suggesting that C-peptide, but not insulin, acts as a chemoattractant for macrophages in vitro to the same degree as macrophage chemoattractant protein 1 (25). Furthermore, studies with CD4-positive lymphocytes show these cell types also colocalize with C-peptide, with evidence that C-peptide acts as chemoattractant for T-cells. C-peptide is not, however, a chemoattractant for neutrophils. C-peptide induces T-cell migration, which is inhibited by pertussis-toxin, suggesting that a G-protein–coupled receptor is involved, and by wortmanin, suggesting a role of PI3K. Furthermore, C-peptide stimulation leads to translocation of PI3K-γ but not class IA PI3K, suggesting a specific isoenzyme to be involved in the effect. Thus, C-peptide appears to phosphorylate a number of steps involved in macrophage motility, perhaps binding to a G-protein–coupled receptor and leading to activation of Rho-GTPase and subsequently to cell adhesion and contraction, with a potential role in the early phases of atherogenesis.

Insulin resistance and CVD

Patrick Vallance (London, U.K.) discussed studies of the relationship between inflammation and CVD. In a mouse model expressing neither apolipoprotein (apo)E (apoE$^{-/-}$) nor endothelial nitric oxide (NO) synthase, atherogenesis is enhanced with the development of aneurisms. There is decreased NO-mediated dilation in hypertension, diabetes, hypercholesterolemia, smoking, and renal disease. Inflammation may underlie some of these relationships. Two distinct time courses of inflammation may be relevant to the atherosclerotic process: *1*) chronic inflammation associated with slow progression and *2*) acute inflammatory processes leading to acute CVD events. Vallance reviewed evidence that acute infections are associated with increased CVD event rates. In a study of patients with bacteremia, 4% had a myocardial infarction within the following month (26). Similarly, as many as 10% of all strokes may be preceded by bacteremia (27), there is a several-week period of increased myocardial infarction and stroke risk following abdominal surgery (28), and a 2-week period of increased myocardial infarction and stroke risk follows respiratory and urinary infections (29). In vivo, endotoxin and proinflammatory cytokines induce endothelial dysfunction (30). In six men before and after administration of typhoid vaccine, which caused an inflammatory response over 8 h with mild leukocytosis, levels of interleukin (IL)-6 and IL-1 receptor antagonist increased, with evidence of decreased endothelial function, as shown by decreased bradykinin response in flow-mediated vasodilation. High-dose aspirin blocked the effect on IL-1 receptor antagonist and on endothelial function. Vallance suggested that CRP is not involved, as the decrease in flow-mediated vasodilation paralleled that in IL-6, during a time period without an increase in CRP (31). In the apoE$^{-/-}$ mouse following γ-herpes virus infection, aortic atherogenesis is markedly increased, but this is blocked by antiviral treatment, suggesting either effects of systemic or local inflammatory response or direct arterial wall infection, with strong correlation between the T-cell response and increased atherosclerosis.

Gerald Reaven (Stanford, CA) reflected on hypertension as a disease of carbohydrate and lipid metabolism. He noted the six- to eightfold variation in insulin sensitivity among persons with normal glucose homeostasis. Approximately one-quarter of this variation may be explained by obesity, measured either with BMI or waist circumference, another one-quarter is related to physical fitness, and ethnic/genetic factors appear to explain approximately half of the variation in insulin sensitivity. Essential hypertension is associated with mild glucose intolerance and marked hyperinsulinemia, with increased steady-state plasma glucose (SSPG). Similar evidence of insulin resistance is seen in normotensive first-degree relatives of hypertensive persons, with

fasting insulin a predictor of risk of hypertension (32,33). Half of newly diagnosed hypertensive persons are insulin resistant, and it is this subset that is associated with the greatest degree of dyslipidemia, particularly in triglyceride elevation, and with the greatest likelihood of CVD. In the Copenhagen male study, hypertensive persons with a normal lipid pattern had no increase in CVD risk, while low HDL cholesterol and high triglyceride levels had additive effects on risk (34). Mononuclear cell binding to endothelium correlates with blood pressure and with the SSPG. A mediator of hypertension may be the endogenous endothelial NO synthase (NOS) inhibitor asymmetric dimethylarginine (ADMA), produced by adipose tissue, with levels associated with the degree of obesity and with a strong correlation between the SSPG and ADMA levels in insulin-resistant versus insulin-sensitive persons with versus without hypertension. ADMA is a CVD risk marker (35). In obesity, ADMA levels are higher only in the insulin-resistant subgroup and decrease in this group with weight loss. Similarly, rosiglitazone decreases ADMA.

Reaven reviewed several additional potential links between insulin resistance and hypertension. Hyperinsulinemia causes increased sympathetic nervous system activity even with insulin resistance, with there being an association between heart rate and the insulin response to a meal and between heart rate and SSPG. Another link may be related to sodium retention, with hypertensive persons who are "salt sensitive" the insulin-resistant subset. The predictor of weight gain on a high-salt diet is the lack of natriuresis and the degree of insulin resistance. Similarly, lower sodium excretion predicts increases in blood pressure. Thus, insulin resistance and associated metabolic abnormalities are increased in hypertension and predicts risk of hypertension, defining the subgroup at greatest CVD risk, with multiple potential mechanisms of causation of these processes.

Coagulation

Peter Grant discussed the link among insulin resistance, inflammation, and thrombosis, reviewing the processes of adhesion and migration of leukocytes involved in the development of the atherosclerotic plaque. Plaque rupture leads to formation of a thrombus with a highly organized fibrin mesh causing arterial occlusion. Persons with diabetes and the metabolic syndrome are at high risk of thrombotic events, and persons with a new event are often found to have either or both conditions. Pathologic examination of atheromas from persons with diabetes show increased lipid area, macrophage infiltration, and thrombosis (36). Similar abnormalities are seen in persons with IGT or hyperinsulinemic euglycemia, with 85% of persons developing diabetes having preexisting insulin resistance (37), constituting a large group of individuals with increased atherothrombotic risk. Inflammatory mediators such as CRP are involved in the atherosclerotic process, with increased coagulation, increased platelet activation and adhesion, and inhibition of fibrinolysis, leading Grant to suggest that we need an extended concept of the insulin resistance syndrome that includes inflammatory atherothrombotic disease. Management, then, must include not only glucose-lowering treatment but also the use of agents to affect the cluster of additional CVD risk factors.

Gordon Lowe (Glasgow, U.K.) discussed the epidemiology of diabetes, insulin resistance, and cardiovascular thrombosis, addressing the mechanisms of the association of the former two abnormalities with thrombosis and whether abnormality of inflammation, hemostasis, and fibrinolysis might in some fashion promote diabetes. It is now well established that diabetes and insulin resistance are related to increased risk of CVD and stroke, as well to venous thromboembolism (VTE). Persons with diabetes have a tripling of CVD rates (38), leading to the concept of diabetes as a CHD equivalent (39), with the diagnosis of diabetes at age 40 years associated with an 8-year reduction in life expectancy (40). There is also an association of the insulin resistance sydrome with CVD (41), perhaps underlying the relationship between A1C well below the diabetic range with adverse outcome (42). Underscoring the association between VTE and atherosclerosis is evidence that persons with a history of the former have a likelihood of plaques on carotid ultrasound ~50% greater than that in control subjects that is not corrected by multivariate analysis including CVD risk factors (43). Furthermore, persons who have had pulmonary emboli have a doubled risk of subsequent cardiovascular events (44), and diabetes is associated with a 50% increase in VTE risk (45). The effect of diabetes and insulin resistance on thrombosis may be mediated by proinflammatory cytokines present in atheromata and in adipose tissue, with IL-6 a key component of these inflammatory processes (46). Diabetes, insulin resistance, and the components of the insulin resistance sydrome are associated with CRP, plasma viscosity, the leukocyte count (white blood cells [WBCs]), fibrinogen, and a variety of clotting factors (47). In a study comparing 325 men with and 2,899 without diabetes between 60 and 79 years of age, the diabetic patients had 20% higher levels of CRP and ~10% higher WBCs, viscosity, fibrinogen, clotting factors, and tissue plasminogen activator (tPA) (48). Among nondiabetic men, BMI and, even more strongly, waist circumference and plasma insulin are associated with CRP, viscosity, clotting factors, and tPA, with a particular relationship of waist circumference with tPA and of insulin with factor VII/von Willenbrand factor (vWF) and tPA, while there is little association of HDL with these inflammatory/thrombotic measures (49). The triglyceride level, however, is strongly associated with viscosity, factors VII and IX, and tPA; the blood pressure shows modest association with CRP, viscosity, and factor VII; and blood glucose is particularly associated with factor VII/vWF (36). Thus, inflammation and the prothrombotic state are associated with diabetes and insulin resistance, clustering with metabolic factors (50), and therefore potentially contributing to the risk of thrombosis. There are potential genetic associations, with first-degree relatives of persons with type 2 diabetes having increased thrombotic factors (51). Insulin and triglyceride may have direct effects on plasminogen activator inhibitor (PAI)-1 (52). Exercise may have a therapeutic effect, with levels of CRP, fibrinogen, WBCs, and platelets lower in persons with greater degrees of physical activity, with or without a history of CVD (53). Lowe noted that a number of meta-analyses suggest that CRP is as strong a marker of CHD risk as fibrinogen, IL-6, vWF, D-dimer, and other hemostatic factors (54–56). Furthermore, persons expressing the 1444C allele have higher CRP levels than those with the 1444TT genotype (57), but they fail to show evidence of increased CVD risk or of hypertension or the insulin resistance sydrome; therefore, although diabetes and insulin resistance are certainly associated with increased risk of CVD and thrombosis, the activation markers are not proven as causes of either thrombosis or diabetes.

Grant discussed insulin resistance

and CVD, addressing the regulation of fibrin structure and function. Venous thromboses are typically platelet poor, while arterial thromboses contain a platelet-rich fibrin mesh. The coagulation cascade ultimately results in the generation of thrombin from prothrombin, leading to activation of factor XIII (XIIIa), as well as leading fibrinogen to change to a soluble form, which, under the influence of factor XIIIa, forms cross-linked fibrin. Cross-linked fibrin breakdown by tPA is limited by PAI-1. With increasing insulin resistance, factor XIIIa levels rise. Scanning electron microscopy may be used to distinguish looser versus more tightly linked fibrin strands, the latter seen in the prothrombotic state. Permeation and turbidity studies and measures of viscoelastic properties of clots are alternative approaches to distinguishing these two types of fibrin. Polymorphisms in factors XIII and fibrinogen as well as changes in insulin sensitivity may further alter fibrinogen. The insulin resistance sydrome is associated with multiple aspects of the prothrombotic state, principally by affecting fibrin and PAI-1. Posttranslational modifications in fibrin and fibrinogen may be important, as glycation, sialycation, oxidation, and acetylation act particularly at the lysine residues involved in the coagulation process. Clot permeability decreases as A1C levels rise (50), and glycation is associated with decreased generation of plasmin, the critical enzyme that breaks down fibrin, so that fibrin lyses more slowly in persons with diabetes. Grant speculated that diabetes and insulin resistance may mediate the moderate heritability of thrombotic risk (58,59), as specific genes coding for variants of clotting factors such as fibrinogen, factor VII, and PAI-1 have not been demonstrated in association with thrombosis. He suggested that genetic influences on insulin resistance, hypertension, and dyslipidemia interact as environmental influences on thrombotic processes, and reminded the audience of the importance of treatments such as aspirin, clopidogrel, and the IIb/IIIa inhibitors.

Mariella Travati (Turin, Italy) presented a fascinating review of the effects of insulin resistance on platelet function. Platelets exhibit complex interactions with other vascular cells and are themselves targets of insulin action, expressing insulin receptors, with insulin reducing platelet aggregation in response to factors such as ADP and arachidonic acid. Insulin decreases platelet-collagen interactions when infused in vivo and modulates platelet calcium flux, a basic regulatory process for platelet aggregation. Insulin also increases platelet NOS via a PI3K pathway, with NO showing effects including vasodilation and inhibition of platelet aggregation. Insulin stimulates platelet phosphorylation of Akt, of AMPK, and of NOS and increases platelet cGMP and cAMP generation, all causing its antiaggregating effect, with the NOS inhibitor L-NMMA preventing these effects. Prostacyclin has antiaggregatory effects mediated by activation of adenylate cyclase, with insulin increasing these effects and upregulating prostacyclin receptors, again blunted by L-NMMA. Thus, insulin acts via the NOS/cyclic nucleotide pathways to inhibit platelet function.

In insulin-resistant states, all of these processes are impaired, with defective antiaggregating effect of insulin in obese persons. Interestingly, lean persons with type 2 diabetes do not demonstrate the abnormality seen in obese persons with or without diabetes. Obesity is associated with decreases in both cGMP and cAMP production and action, and states of insulin resistance are associated with increased platelet cytosolic calcium levels. F2-isoprostane levels are increased in obesity and decreased by weight loss, with evidence of reduced aspirin sensitivity of the proaggregatory pathway (60). In a study of 20 persons following a weight-loss program for 6 months, 10 subjects lost weight and demonstrated decreased waist circumference, BMI, fasting insulin, triglyceride, and CRP levels and increased HDL cholesterol levels. Weight loss restored platelet sensitivity to the antiaggregating effects of insulin and of NO, while no changes occurred in persons not losing weight. Travati noted that obesity induces inflammatory changes in adipose tissue (61) and that the change in platelet NO response after weight loss correlates with the improvement in insulin sensitivity but not with changes in a variety of adipokines. Thus, platelets are targets of insulin action and are affected by insulin resistance. She addressed the question of whether aspirin resistance is seen in individuals with insulin resistance, noting that this does occur and is related to increased isoprostane levels and perhaps also to glycation, with high fibrinogen and vWF markers of aspirin resistance. It is not clear, however, whether a clinically relevant degree of aspirin resistance occurs in diabetes. The Antithrombotic Trialists' Collaboration showed 8 vs. 22% reduction in events in persons with versus without diabetes treated with aspirin, suggesting the potential for this to be an important area for additional intervention (62). Of further note, postprandial platelet activation appears to occur, and may be related to, oxidative stress or to changes in both lipid and glucose levels.

Nikolaus Marx discussed the emerging role of PPARγ activators in insulin resistance, diabetes, and atherothrombotic disorders. PPARγ is a nuclear receptor that heterodimerizes with the retinoid X receptor, binding to promoter regions on genes leading to adipocyte protein synthesis, resulting in changes in cytokine production and fatty acid metabolism (63). There is evidence of PPARγ expression in endothelial cells, macrophages, smooth muscle cells, and CD4-positive lymphocytes (63,64). Atherogenesis is an inflammatory process occurring in the vascular wall, with evidence that TZDs decrease vascular monocyte and T-cell recruitment, decrease T-cell activation and vascular smooth muscle cell migration in fatty streak formation, and reduce inflammatory biomarkers in the atherosclerotic plaque. PPARγ activators have antiatherogenic effects. In a comparison of pioglitazone with glimepiride in persons with type 2 diabetes attaining similar degrees of glycemic control, CRP levels decreased with the TZD (65). Similarly, rosiglitazone decreases serum amyloid A within 2 weeks after administration, suggesting that the anti-inflammatory effects of these agents may be independent of their metabolic effects (66). The normal endothelium generates NO with shear stress, leading to 5–10% vasodilation in healthy persons. Endothelial dysfunction can be demonstrated in persons with diabetes, who fail to show this phenomenon. Following TZD treatment, endothelium-dependent vasodilation is restored, with improvement seen as early as the 1st day of treatment (67).

Restenosis is an important pathologic process seen following vascular intervention and resembles atherosclerosis, with several studies examining the effect of TZD treatment. In persons with type 2 diabetes treated with rosiglitazone (68) and in nondiabetic persons with coronary artery disease treated with pioglitazone (69), restenosis rates have been reduced. In the latter study, there was no effect on glucose, insulin, A1C, or lipids but significant reduction in neointimal volume. In studies of plaque morphology and plaque stability, 24 nondiabetic patients under-

going carotid endarterectomy were randomized to pretreatment with 4 mg rosiglitazone twice daily or placebo, showing histologic evidence of decreased CD4-positive lymphocytes, without change in macrophage content but with decreased macrophage HLA-DR staining, suggesting inhibition of macrophage activation by T-cells. There was a trend to reduction of MMP expression and increased collagen content, suggesting the development of more stable plaques with these agents. Marx noted that both in the restenosis and in the carotid endarterectomy studies, all patients were treated with statins, with benefit of TZD administration nevertheless demonstrated. Whether the TZD effect is mediated by insulin sensitivity is not certain, as it may represent a direct anti-inflammatory action.

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