

Insulin Resistance, Dyslipidemia, and Cardiovascular Disease

ZACHARY T. BLOOMGARDEN, MD

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This is the fourth in a series of four articles on presentations at the World Congress on the insulin resistance syndrome (IRS), reviewing aspects of insulin resistance pertaining to dyslipidemia and cardiovascular disease.

Insulin resistance and dyslipidemia

Ronald Krauss (San Francisco, CA) gave insights in the genetics of the more common forms of IRS based on the understanding of the complex topic of dyslipidemia. There is an intimate relationship between diet and dyslipidemia, and dietary manipulations may be used to understand the mechanisms of these abnormalities. LDL particles exist in multiple subclasses, differing in size, density, and lipid content. Large and medium LDL comprise the most abundant species in plasma of the most healthy individuals, but there are two forms of small LDL, exhibiting reduced receptor binding, greater endothelial transport, greater arterial proteoglycan binding, and greater susceptibility to oxidation.

Small LDL is associated with elevations in triglyceride levels. Traditional models describe a pathway from VLDL

formation in the liver to formation of IDL and then of LDL particles via lipolysis. Actually, there is heterogeneity in size subspecies of VLDL and IDL (1). With low levels of triglyceride transport from the liver, triglyceride-poor particles are exported as IDL, with lipolysis by lipoprotein lipase (LPL) to form LDL1. Under more typical circumstances of triglyceride formation, VLDL2 is formed. These VLDL particles are substrates for LPL, producing LDL2, the most avidly bound substrate of the LDL receptor. LDL1 and LDL2 comprise the larger size LDL particles. When larger VLDL1 is produced, lipolysis by LPL is less efficient, leading to production of remnant particles, which are further acted on by LPL and hepatic lipase (HL) to form LDL3a. This class of LDL particles further is acted upon by cholesterol ester transport protein (CETP), shuttling triglyceride back to remnant particles, and by HL to form LDL3b. A final pathway is with very large VLDL1, which are acted on by LPL to produce highly atherogenic remnant particles, which are either cleared directly or are metabolized by LPL and HL to the smallest LDL4 particles. LDL1 and LDL2 are described as phenotype A and LDL3 and LDL4 as phenotype B particles, the form associated with greater degrees of atherosclerosis.

A given individual's LDL phenotype shows 40–75% heritability, with phenotype B more common in older individuals and males, with adiposity, insulin resistance, and dietary factors as additional determinants. A low-fat, high-carbohydrate diet may have adverse effect in increasing phenotype B expression (2) but, unexpectedly, particularly reduces LDL cho-

lesterol in individuals with phenotype B (3). Those with phenotype A show reduction in LDL1 with increase in LDL3, while with phenotype B there are decreases in LDL1 and LDL2 but increase in LDL4. This diet changes lipid levels in individuals with phenotype A by reducing cholesterol content of LDL particles, without reducing particle number, while individuals with phenotype B show reduced conversion of VLDL2 to LDL2 with increased levels of large VLDL particles, resulting in greater numbers of remnant particles (4). There is an inverse relationship between the amount of dietary carbohydrate and LDL size. Krauss showed studies comparing diets with 54 vs. 39% carbohydrate, similar fat, and 16 vs. 29% protein. Phenotype B prevalence decreased by 25–50%, with benefits of weight loss particularly seen in individuals ingesting greater amounts of carbohydrate, suggesting that either approach, reducing carbohydrate or losing weight, can be used.

He speculated that there might also be a genetic component to susceptibility to dietary induction of phenotype B. Family studies suggest inherited components to the LDL phenotype, with possible gene associations including polymorphisms in the LDL receptor, apolipoprotein (apo) CIII, apo A-V, and CETP. A short-term 75% carbohydrate diet produced the phenotype B lipid pattern in children having a parent with phenotype B (5). In a subsequent study, the response to high versus low dietary fat appeared to be related to genetic heterogeneity, including the LDL receptor *Nco1* polymorphism, as well as polymorphisms in the CETP promoter and in apo A5*3 (3). The change in VLDL2 was inversely correlated with the change in LDL2 in the apoA5*3 variant, with Krauss raising the possibility that apoA5 promotes LPL-mediated VLDL hydrolysis, explaining the selective effect of high dietary carbohydrate in these individuals. Given these interesting observations, it appears likely that there are many interactions between genetic and dietary factors inducing expression of the common atherogenic lipoprotein phenotype B, a major component of the IRS. Understanding these interactions may allow

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.

Abbreviations: ADMA, asymmetric dimethyl arginine; ALT, alanine aminotransferase; apo, apolipoprotein; CETP, cholesterol ester transport protein; CVD, cardiovascular disease; DDAH, dimethylarginine dimethylaminohydrolase; HL, hepatic lipase; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; LPL, lipoprotein lipase; MAPK, mitogen-activated protein kinase; NOS, nitric oxide synthase; PAI, plasminogen inactivator; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator-activated receptor; RAS, renin-angiotensin system; RXR, retinoid X receptor; SDMA, symmetric dimethyl arginine; TNF, tumor necrosis factor.

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identification of individuals most likely to respond to specific dietary interventions.

Jose Ordovas (Boston, MA) further discussed human genotypes affecting lipid metabolism and reviewed associations between lipid metabolism and cardiovascular disease (CVD) risk. He noted that many mutations have been described in lipoprotein metabolism, both infrequent monogenic mutations with large effect and high-frequency mutations with small individual effect but modest to high population attributable risk. ApoE makes different contributions to cholesterol levels in different countries and has different effects in men and women, suggesting the importance of gene-environment interaction. In Framingham, men with apoE2 had lower cholesterol but similar CVD risk as those with apoE4, while in women those with apoE2 had lower CVD risk, suggesting other contributory factors. In contrast, a CETP polymorphism has been described with increased CVD risk only in males, and LPL polymorphisms lack consistent effect on lipid abnormalities and CVD risk. Other factors, including physical activity, cigarette use, and diabetes, have important additional effects. In Framingham, the effect of apoE phenotype on CVD risk is clearer when stratified by smoking status, with nonsmokers showing increased risk of E2 and E4 compared with E3, while those smoking at least 10 cigarettes daily demonstrate a reduction in CVD with E3. For individuals with BMI <30 kg/m², the apoE phenotype has no effect on glycemia, while for those with BMI >30 kg/m² fasting glucose is lowest in those with E2, higher with E3, and still higher with E4, suggesting a relationship to insulin sensitivity modulated by environmental factors. Carotid intima-media thickness did not vary by apoE genotype in nondiabetic individuals, but those with diabetes and E4 had higher greater evidence of carotid atherosclerosis.

The C/T polymorphism of the HL promoter shows a relationship to HDL cholesterol, which increases with increasing dietary fat in those with the CC phenotype but decreases with increasing dietary fat with the TT phenotype, further revealing the importance of understanding of both genetic and environmental contributions to dyslipidemia. LDL cholesterol levels increase regardless of HL phenotype with increasing dietary fat, so those with the TT genotype are uniquely susceptible to high dietary fat-induced atherosclerosis, while those the CC genotype may have relative protection from in-

creased dietary fat. Since the frequency of CC and TT are similar in blacks and Hispanics, while in Caucasians ~80% of the population have the CC phenotype, this may be an important explanation of ethnic variation in the relationship of diet to atherosclerosis.

Ordovas discussed apoA5 gene polymorphisms, noting their relationship to the effect of diet on triglycerides. With increasing dietary polyunsaturated N6 fatty acid intake, remnant lipoprotein cholesterol levels increase with the apoA5 1131C genotype, while polyunsaturated N3 fatty acids decrease remnant lipoprotein cholesterol with this genotype.

Perilipin is the lipid droplet-associated protein surrounding fat in adipocytes, playing a role in modulation of fat stores, with *ob/ob* mice not expressing perilipin failing to develop obesity. Perilipin polymorphisms were associated with differences in BMI in women, but not in men, in population studies in Spain and the U.S. The 11482G > A polymorphism was found to be associated with resistance to weight loss on a low calorie diet (6). Other perilipin polymorphisms appear to be associated with dietary changes in insulin sensitivity. Ordovas cautioned that these studies of individual genes and individual nutrients may be of limited benefit and represent a "proof of concept" research tool, given the thousands of genes related to nutrition and the thousands of dietary approaches potentially available. Future studies with gene chips may allow greater understanding of the use of genetic information in practical treatment of individuals with various diets and with various degrees of insulin sensitivity. For now, a family history of premature coronary disease may be of as much importance as a gene profile. "These kinds of tests," Ordovas concluded, "are not ready for prime time," although the field of genomic medicine is rapidly developing and may lead to clinically useful tools.

Jorge Plutzky (Boston, MA) discussed endogenous mechanisms of peroxisome proliferator-activated receptor (PPAR) modulation and their implications for inflammation and atherosclerosis. PPARs are members of the steroid hormone nuclear receptor family. In mice, although not in humans, PPAR α activates peroxisomes, leading to the now outmoded name of the receptor group. There are three isoforms, PPAR α activated pharmacologically by fibrates, raising HDL cholesterol and lowering triglyceride levels, PPAR γ activated by thiazolidinediones, and PPAR δ , not yet fully characterized.

The metabolic changes induced by α and γ agonists have anti-inflammatory and lipid and glucose effects, which might influence atherosclerosis, but there is evidence also that there are vascular PPAR nuclear receptors that may play roles in these benefits. Data for CVD benefit of PPAR agonists have been shown in vitro, in vivo in animal models, and in human studies of surrogate measures of atherosclerosis such as carotid intima-media thickness. Clinical trials have not, however, shown clear benefit, with the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) Study showing no difference in coronary heart disease death or nonfatal myocardial infarction with fenofibrate; the PROactive Study giving a positive secondary but not primary end point; and the combined PPAR α/γ agonists muraglitazar causing increased mortality and major adverse CVD effects and teggaglitazar now withdrawn from development.

PPARs are made up of a ligand binding domain, a DNA binding domain, and the AF2 domain allowing *trans*-activation (7). The nature of the ligand is crucial, so that one cannot assume similarity of all the thiazolidinediones or of all the fibrates. We have extensive information on synthetic PPAR agonists, but the nature of the endogenous PPAR ligands is largely unknown. The existing agents have been identified by drug development programs based on binding potency, rather than on clinically important actions. Plutzky suggested that elucidation of pathways activating PPARs to reveal natural endogenous mechanisms might lead to more physiologic and more protective approaches, greater understanding of the roles of the PPARs, and novel and/or safer therapies, as well as the ability to better predict appropriate individuals to be treated with these agents.

The endogenous ligands for PPAR γ appear to be fatty acids. LPL is a key enzyme in triglyceride metabolism, releasing fatty acids for energy, synthesized in adipocyte, muscle, and macrophages, situated on the endothelial surface, and having two effects: first as a lipase in releasing fatty acids from triglyceride but also playing a nonenzymatic role as a fatty acid transport molecule. Studies using PPAR γ ligand binding domain assays show that incubation of VLDL, HDL, and LDL particles alone show little effect but that with addition of LPL there is considerable activation, particularly by VLDL and to a lesser extent by LDL particles (8). LPL,

but not other fatty acid-releasing lipases such as phospholipase A2, activates PPAR α , suggesting that in addition to hydrolyzing triglyceride-rich lipoproteins for fuel, LPL also generates PPAR α ligands, a potential role for triglyceride-rich lipoproteins in activating PPAR α , which could lead to a positive feedback cycle increasing LPL synthesis. This would oppose proatherosclerotic PPAR α -mediated effects of VLDL, suggesting a potential anti-atherosclerotic LPL effect. Plutzky noted that animal models show a protective effect of LPL overexpression against atherosclerosis in mice not expressing the LDL receptor.

HDL may have anti-inflammatory effect, inhibiting adhesion molecule expression. In tumor necrosis factor (TNF) α -treated leukocytes either a PPAR α agonist or HDL inhibits leukocyte adhesion, an action that can be prevented with a lipase blocker. Endothelial cell lipase appears to be the major enzyme mediating this anti-atherosclerotic effect, preferentially hydrolyzing HDL to generate PPAR α activators at physiologic HDL concentrations, with the combination activating PPAR γ and, to a lesser extent, PPAR δ as well. In experimental studies, TNF α causes leukocyte adherence to endothelial cells, an effect blocked by PPAR α agonists, and by HDL particles, with the latter effect not evident in the presence of a lipase inhibitor or in cells not expressing PPAR α (9). Thus, the beneficial vascular effects of HDL may in part be mediated by generation of endogenous PPAR α agonists.

The PPARs exist as heterodimers with the retinoid X receptor (RXR). The endogenous agonists of RXR are metabolites of carotenoids, fat-soluble aliphatic hydrocarbons consisting of a polyisoprene backbone. β -Carotene cleavage forms retinoic acids and the apocarotenals, which appear to play roles in PPAR signaling, with one of these molecules, apocarotenal-14, markedly decreasing PPAR γ activation, suggesting it to be an endogenous PPAR γ antagonist. Adiponectin and aP2 are adipocyte PPAR γ -regulated targets, with apocarotenal-14 repressing expression of these PPAR γ responses. Apocarotenal-14 also inhibits PPAR α responses and is proinflammatory, with the inflammatory effect not seen in mice not expressing PPAR α . Thus, the situation is made even more complex by the existence of apocarotenals as endogenous inhibitors of PPAR and RXR responses.

Cardiovascular disease and insulin resistance

Andrew Selwyn (Boston, MA) reviewed aspects of the relationship between IRS and CVD, noting the increasing prevalence of type 2 diabetes from the 1970s to the 1990s, with its far stronger association with CVD than with the traditional microvascular complications such as visual loss, renal failure, and amputation (10). Analysis of individuals developing diabetes in the Nurses' Health Study led to the development of the "ticking clock hypothesis," in which the pre-diabetes state is one associated with increased CVD risk, with macrovascular atherosclerotic disease developing in many cases a decade before diabetes becomes manifest (11). There is increasing awareness of the clinical phenotype of metabolic syndrome/IRS based on glucotoxicity and lipotoxicity and of its association with a variety of abnormalities of inflammatory mediators. Selwyn pointed out that the focus on lowering LDL overlooks the potential that at-risk individuals may have a proatherosclerotic increase in small LDL particle number, potentially underlying the increased CVD risk of metabolic syndrome (12). Further evidence of the association between IRS and CVD are the high prevalences of impaired glucose tolerance (IGT) and undiagnosed type 2 diabetes among individuals admitted with acute myocardial infarction (approximately two-thirds [13]) or stroke (approximately two-fifths [14]).

Insulin resistance has both genetic and environmental components, the latter dramatically shown in the Cardia Study of 3,031 adults, with a direct association between "fast food" habits and both weight gain and insulin resistance (15). There is similarity of the pathways leading to insulin resistance and to atherosclerosis, with elevations both in glucose and in free fatty acids causing oxidant stress, activation of mitogenic and proinflammatory pathways, cytokine release, prothrombotic effects, and dyslipidemia. Similarly, there is overlap between insulin resistance and cardiovascular risk conditions such as hypertension (16), type 2 diabetes, and low HDL/high triglyceride. Selwyn concluded by stressing the importance of control of all of these risk factors among individuals with diabetes, noting that there is less clear evidence favoring glycemic control to reduce CVD than for the benefits of blood pressure and lipid treatment.

James Leiper (London, U.K.) dis-

cussed endogenous inhibitors of nitric oxide (NO) synthesis in the setting of insulin resistance. NO regulates vasodilatation, synthesized by endothelial cells and diffusing into vascular smooth muscle cells, with NO production from L-arginine, leading to production of citrulline as a side product, tightly regulated by endothelial NO synthase (NOS). There are two endogenous analogs of the competitive inhibitor of NOS, L-NMMA (L-N-monomethylarginine), asymmetric and symmetric dimethyl arginine (ADMA and SDMA, respectively). SDMA is not active, while ADMA shows similar action to L-NMMA in inhibiting all three forms of NOS (17). ADMA elevates systemic vascular resistance and blood pressure, and chronic ADMA administration in rodent models accelerates atherosclerosis (18). Among individuals who have had a CVD event, the ADMA level predicts future cardiovascular risk. Increased ADMA has been reported to be associated with hypercholesterolemia, hypertension, diabetes, and CVD, as well as with insulin resistance (19,20).

Leiper reviewed evidence further suggesting that ADMA is causally related to vascular disease. Dimethylarginine dimethylaminohydrolase (DDAH), which exists in two isoforms, hydrolyzes ADMA, generating citrulline. DDAH is widely expressed in mammalian cells. Its levels decrease in isolated vascular cells incubated in high glucose media, a process attenuated by antioxidant administration, and DDAH levels are reduced in streptozotocin-induced animal models of diabetes (21). In vivo, mice heterozygous for deletion of DDAH and those administered either of the low-molecular weight DDAH inhibitors, L-291 and L-257, show a 20% increase in ADMA, without change in SDMA, with impaired vasodilatory response to acetylcholine and increased vasoconstriction with phenylephrine, suggesting decreased endothelial NOS activity. Blood pressure and systemic vascular resistance are increased, while heart rate and cardiac output are decreased. The ADMA/DDAH pathway may, then, be a target for drug development, with intriguing evidence of increased DDAH activity and decreased ADMA with inhibitors of the renin-angiotensin system, thiazolidinediones (19), aspirin, retinoids, and erythropoietin, although not with statins.

Peter Grant (Leeds, U.K.) discussed insulin resistance, thrombosis, and acute coronary syndrome, noting that less at-

tention is currently being given to thrombosis than to other abnormalities but that there is strong correlation between the severity of acute coronary syndromes and increasing thrombotic markers, suggesting these abnormalities to be of considerable pathogenic importance. Among individuals with diabetes, females lose vascular protection, and outcomes are generally poorer, with 80% dying of vascular disease. Thrombosis overlaps with inflammation. Abnormal coagulation is involved in the development of unstable angina, with occlusion of the vascular lumen leading to release of tissue factor k, which in turn activates factor VII causing further coagulant activation. NO has anticoagulant/antiplatelet and vasodilatory effects, all of which decrease with insulin resistance. At the same time, migration of macrophages into the subendothelial layer leads to foam cell formation with the CD-36 receptor, which internalizes oxidized LDL, increased in the proinflammatory state of insulin resistance. Insulin resistance is associated with increased factor XII, both directly as an effect of insulin and indirectly via hypertriglyceridemia. Insulin resistance similarly acts in to increase levels of factor VII, fibrinogen, and plasminogen inactivator (PAI)-1, all increasing likelihood of thrombosis. Clotting shows specific characteristics in diabetes, with increased fibrin clot density. The fibrin structure is more tightly cross-linked, in part related to lysine residue modification by oxidation, glycation, and acetylation, decreasing plasmin-induced clot lysis, with a linear relationship between A1C and clot permeability. Furthermore, glycated fibrin reduces tissue plasminogen activator clot binding and decreases the formation of plasmin from plasminogen (22), leading to decreased fibrinolysis.

Robert Chilton (San Antonio, TX) discussed therapeutic implications of the relationship between insulin resistance and the development of atherosclerotic plaques. Among children, associations can be found between carotid intima-media thickness and decreased flow-mediated vasodilatation, increased C-reactive protein, increased triglyceride, decreased HDL cholesterol, and increased insulin levels. Endothelial dysfunction, as measured by flow-mediated vasodilatation, is strongly related to insulin resistance and to a family history of diabetes (23). Similarly, coronary vasomotor abnormality progressively worsens in the progression from insulin sensitive to in-

sulin resistant to IGT to frank diabetes (24). There are a number of similarities between the effects of PPAR γ agonists and those of statins (25,26). Comparing the effects of pioglitazone versus glimepiride on carotid intima-media thickness (27), improvements with the former are similar to those occurring with high-dose atorvastatin (29). The atherosclerotic lesion of individuals with diabetes shows increased macrophage infiltrate (29), suggesting the linkage to inflammation.

Ralph DeFronzo (San Antonio, TX) reviewed interventional strategies for IRS. In the Prospective Cardiovascular Münster (PROCAM) Study, the incidence of myocardial infarction increased with increasing risk factors. Insulin resistance is associated with coronary artery disease, to an extent similar to that seen in lean individuals with type 2 diabetes, with obesity, hypertension, and hypertriglyceridemia all more than doubling the risk of CVD (30). DeFronzo suggested that the CVD risk of type 2 diabetes is mediated by insulin resistance rather than by hyperglycemia, although the major defect appears to be in glycogen synthesis, rather than in other insulin actions, leading to the question of what accounts for the insulin resistance phenotype and for the presence of insulin resistance in all these individuals. There is a cascade of insulin binding to and activating the insulin receptor, then leading to insulin receptor substrate-1 activation, with consequent activation of the receptor P85 subunit of phosphatidylinositol 3-kinase (PI3K), promoting protein, lipid, and glycogen synthesis and GLUT4 translocation to the cell membrane. A defect in many individuals with insulin resistance is at the level of p85, the response element of PI3K, with the p110 catalytic subunit intact. In compensation, the insulin level ultimately increases, leading to an increase in an alternative insulin receptor pathway activity, turning on mitogen-activated protein kinase (MAPK), a central step in a mitogenic/proatherosclerotic pathway. Administration of thiazolidinediones increases activity of the PI3K pathway and represses the MAPK pathway. This represents a common site of multiple related metabolic abnormalities, with DeFronzo giving as an example the effect of angiotensin-II in causing insulin receptor substrate-1 serine phosphorylation, reducing insulin receptor substrate-1 activity while activating MAPK. He noted that PI3K activation activates NOS as well as the metabolic effects of insulin, so that insulin resistance is associated with a

vasoconstriction phenotype. Another mechanism of insulin resistance is obesity, increasing tissue fat, with increased fatty acid-CoA activating serine kinases and inactivating insulin receptor substrate-1. This is associated with increased diacyl glycerol, leading to activation of protein kinase C and to elevation in ceramide levels, also decreasing PI3K activity. Fatty acid-CoA is a powerful activator of the nuclear factor- κ B, with nuclear nuclear factor- κ B entry in the nucleus, increasing serine kinases, TNF, inflammatory cytokines, and growth factors.

Insulin resistance has been shown to predict the risk of developing cardiovascular risk factors such as hypertension (31) and to predict future CVD (32–34). In the San Antonio Heart Study, insulin sensitivity was associated with CVD in nondiabetic individuals, after adjusting for age, sex, blood pressure, LDL, HDL, triglyceride, smoking, exercise, and other variables (35). The presence of metabolic syndrome is associated with greater CVD risk than are dyslipidemia, hypertension, high homeostasis model assessment of insulin resistance, or obesity taken individually (36). However, the risk for individuals with insulin resistance is not high, so that statistical power calculations show that a study of 8–10,000 individuals with IRS followed for 8–10 years would be required to demonstrate whether improvement in insulin sensitivity resulted in prevention of CVD.

DeFronzo suggested two potential approaches to treatment: treating each individual component, such as hypertension, dyslipidemia, and hyperglycemia, or treating the underlying condition, insulin resistance/hyperinsulinemia. He pointed out that although hypercholesterolemia is not part of the syndrome, insulin resistance is associated with an increase in LDL particle number and triglycerides, and reduction in HDL cholesterol, the atherogenic lipid profile accounting for a large part of the cardiovascular risk. In the bezafibrate infarction prevention study, individuals with triglyceride >200 mg/dl showed benefit of the intervention (37), and in the VA-HIT (Veterans Affairs HDL Intervention Trial), CVD risk reduction was seen particularly in diabetic rather than nondiabetic individuals, as well as in nondiabetic hyperinsulinemic versus normoinsulinemic individuals (38). In the FIELD Study, however, the baseline triglyceride level was 150 mg/dl, with a larger number of individuals in the placebo group initiating statin therapy, suggesting that the nega-

tive results of the study were explained by the investigators “pick[ing] the wrong people” (39). Similarly, most of the large antihypertensive trials have shown greater benefit of treatment in individuals with diabetes than in nondiabetic individuals, which DeFronzo suggested reflects the effect of insulin resistance.

Obesity, DeFronzo said, drives diabetes, and “dwarfs everything else,” with fat overload leading to increasing CVD. The abnormality of fat distribution in individuals with type 2 diabetes has led to the overflow hypothesis, that adipocyte fat storage capacity is exceeded, leading to ectopic deposition of fat, in muscle causing insulin resistance, in liver increasing glucose production, and in the vascular wall causing atherosclerosis. Modest (5%) weight loss has major benefit. In XENDOS (XENical in the prevention of Diabetes in Obese Subjects) Study, orlistat was associated with a 6.9% weight loss over 4 years, exceeding the 4.1% weight loss in individuals randomized to placebo plus lifestyle instruction, with a 37% reduction in the rate of development of diabetes (40) and similar reduction in the development of metabolic syndrome. There is evidence that such an approach particularly decreases insulin resistance.

There are two potential pharmacologic approaches to improving insulin sensitivity. Metformin was effective in the Diabetes Prevention Program, and in the UKPDS obesity subgroup study decreased myocardial infarction, stroke, and death by 39, 41, and 42%, exceeding the 29% decrease in microvascular end points. Metformin decreases glucose, triglyceride, cholesterol, weight, insulin, insulin resistance, PAI-1, and endothelial dysfunction, suggesting a benefit. “It’s a pretty safe drug,” DeFronzo commented, “so would not be a bad choice for an interventional trial.” Thiazolidinediones lower glucose, insulin, and triglycerides, particularly with pioglitazone; reducing small dense LDL levels; lowering PAI-1; reducing inflammatory cytokines; improving HDL cholesterol and insulin sensitivity; having beneficial effects on vascular smooth muscle proliferation, migration, and adhesion; and decreasing endothelial cell proliferation. These agents increase adipocyte differentiation with consequent increases in fat storage and decreased ectopic fat, activating peroxisome proliferator-activated γ coactivator-1 and negative regulatory factor, a repressor of nuclear factor- κ B, “the master switches that activate oxidation of fat.”

In the PROactive Study, DeFronzo stated that the combined end point of mortality, myocardial infarction, and stroke was decreased by 16%. Among individuals with prior myocardial infarction, events decreased by 19% and among individuals with prior stroke there was 47% decrease in recurrence. The Diabetes Prevention Program, the Troglitazone and Pioglitazone In Prevention Of Diabetes Study, and the DREAM (Diabetes REduction Assessment with rampril and rosiglitazone Medication) Study (see below) all suggest benefit of these agents (41). DeFronzo suggested exenatide as another potential treatment approach. He described a 30-week study, with reduction in A1C and body weight, with evidence of progressive additional weight loss over 80 weeks, correlating with improvement in blood pressure, triglyceride, and HDL cholesterol levels. He concluded by recommending that individuals with insulin resistance use pioglitazone, given its lipid effects, evidence of cardiovascular protection and β -cell preservation that they use metformin, based on the findings reported in the UKPDS, and that they use exenatide, based on the evidence of weight loss and associated benefits. “We recognize,” he said, “that this disease starts with insulin resistance . . . [we] need to treat IGT with insulin resistance and β -cell failure.”

At a satellite symposium before the 4th World Congress on the Insulin Resistance Syndrome, Stephen Davis (Nashville, TN) reviewed the DREAM Study, which was simultaneously published in *Lancet* (42) and the *New England Journal of Medicine* (43). Lifestyle intervention can reduce diabetes development by more than half, metformin and acarbose have been shown to prevent diabetes, and there is evidence of diabetes prevention with both classes of agents suppressing the renin-angiotensin system (RAS), ACE inhibitors, and angiotensin receptor blockers, as well as with thiazolidinediones. Inhibition of the RAS reduces mortality, myocardial infarction, and stroke in individuals with CVD with and without heart failure, as well as in those with diabetes and additional CVD risk factors, with a 14% overall reduction in diabetes development (44). Angiotensin receptor blocker studies have shown a similar benefit. Earlier studies of benefits of angiotensin-directed therapy did not include glucose tolerance testing, so they may have missed diabetes at baseline and/or on follow-up. Different definitions of new diabetes were used, participants were of

high CVD risk but intermediate diabetes risk, and diabetes prevention was not the primary outcome.

In the DREAM trial, 8 mg rosiglitazone, 15 mg ramipril, both agents, or neither were administered to 5,269 individuals aged at least 30 years, including 58% with just IGT, 14% with just impaired fasting glucose, and 29% with both. Baseline BMI was 30.9 kg/m² and blood pressure 136/83 mmHg, making this “a relatively well cohort.” Adherence was lower to ramipril (75%) than to placebo (81%), with cough appearing to reduce compliance, and blood pressure decreased 8/5 mmHg, which is considerably more than in the Heart Outcomes Prevention Evaluation Study, and perhaps related to the higher ramipril dose. Alanine aminotransferase (ALT) showed a slightly greater fall with ramipril, suggesting an effect on hepatic steatosis. There was a trend to lower weight gain with ramipril than placebo, and diabetes development decreased nonsignificantly by 8% with ramipril. Davis noted, however, that dosing was increased gradually and that the study was terminated early, so that few patients were treated >2 years with the full dose. There was a significant 16% greater rate of normalization of the glucose tolerance testing in the ramipril than the placebo group, and fasting glucose showed a trend to lower levels, while the 2-h glucose was significantly lower, by 5 mg/dl, with ramipril treatment. Individuals in the DREAM trial may have had a less “activated” RAS because of their lower CVD risk, they may have been less likely to receive drugs raising glucose, and there was low power to detect outcome differences in CVD because of the relatively short duration of treatment and the low baseline CVD risk.

In contrast to the findings with ramipril, patients randomized to rosiglitazone had a robust decrease in ALT levels, a 2/0 mmHg decrease in blood pressure, and a 60% reduction in development of diabetes. For 1,000 individuals treated for 3 years, 144 cases of diabetes would be prevented, with the preventative benefit greatest in heavier patients. There was somewhat lower adherence to rosiglitazone than placebo, because of edema and weight gain, with a trend to an increase in CVD and a significant excess in heart failure, occurring in 14 vs. 2 individuals receiving rosiglitazone versus placebo, respectively. Davis noted that 12 individuals receiving ramipril, but only 4 receiving the ramipril placebo, developed

heart failure, quite the opposite of what one might predict. Ultimately, then, the DREAM Study is difficult to interpret and may not have clearly provided a rationale for either more or less use of either study agent.

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