Second World Congress on the Insulin Resistance Syndrome

Hypertension, cardiovascular disease, and treatment approaches

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Insulin resistance and hypertension

At a symposium on insulin resistance, hypertension, and cardiovascular disease (CVD) cosponsored by the European Group for the Research of Obesity, Hypertension, and Insulin Resistance, Albert P. Rocchini (Ann Arbor, MI) discussed the relationship of hypertension and insulin resistance in obesity. Potential explanations for the frequency with which insulin resistance and hypertension are associated could be the coincidence of two common abnormalities, the causation of one by the other, or, intriguingly, the existence of a common underlying factor. The first explanation appears unlikely, with a preponderance of evidence suggesting that the two conditions are related (1). It also appears unlikely that hypertension causes insulin resistance, as glucose uptake is not affected in experimental renovascular hypertension and because lowering blood pressure in individuals with hypertension does not necessarily improve glucose uptake. There is, however, greater forearm vascular resistance in obese than in nonobese adolescents, with glucose uptake across this tissue inversely related to vascular resistance, suggesting that vascular resistance may play a role in some aspects of insulin action (2). The converse, that insulin resistance may cause hypertension, appears more likely to be a factor. Fasting insulin levels correlate with systolic blood pressure, and the drop in blood pressure following weight loss is related to the improvement in insulin sensitivity. Interestingly, in hypertensive obese individuals, somatostatin decreases both the insulin level and blood pressure, suggesting an effect of hyperinsulinemia. Insulin can lead to sodium retention (3) and angiotensin II–mediated aldosterone production, can change vascular structure and function, can alter cation flux, and can activate the sympathetic nervous system. In both obese and nonobese individuals during water diuresis, however, sodium excretion decreases with a euglycemic-hyperinsulinemic clamp, so insulin resistance cannot be certainly proposed as the cause of hypertension. Furthermore, improvement in insulin sensitivity need not lower blood pressure, as for example in dogs with high-fat diet–induced hypertension, where the blood pressure is not lowered by high-dose aspirin despite prevention of insulin resistance. Rocchini posited common factors related to obesity, explaining both insulin resistance and hypertension, suggesting activation of the sympathetic nervous system as one such factor. Thus, central and/or peripheral α-2 receptors cause insulin resistance, whereas peripheral α and β receptors cause hypertension. Comparing clonidine with the combination of peripheral α- and β-blockade, both prevented hypertension, while only clonidine prevented insulin resistance in the high-fat–fed dog model.

Arya M. Sharma (Hamilton, Canada) further discussed the question of a causal relationship between insulin resistance and hypertension, particularly addressing the question of whether angiotensin II blockade can be used both for treatment of hypertension and insulin resistance. He noted that “salt-sensitive” people, those whose blood pressure increases with increased sodium intake, show insulin resistance (4), which is present on either a low- or high-sodium diet (5). Furthermore, sympathetic nervous system activity is stimulated by insulin in what appears to be a central effect, suggesting that the hyperinsulinemia accompanying insulin resistance may be directly deleterious. He also cited a number of studies showing that insulin sensitizers decrease blood pressure, a phenomenon seen both with metformin (6,7) and thiazolidinediones (TZDs) (8). Thus, insulin may stimulate sympathetic activity and sodium Na reabsorption, as insulin-induced vasodilatation is reduced in individuals who develop hypertension. Insulin resistance can, however, occur without hypertension, there is no increase in blood pressure with insulin treatment, and insulin is more strongly correlated with body fat than with blood pressure. Another link between obesity and blood pressure is leptin, which increases sympathetic activity and may increase sodium reabsorption and heart rate.

Sharma pointed out that a potential relationship between blood pressure and insulin sensitivity may be mediated by the renin–angiotensin system (RAS). In HOPE (Heart Outcomes Prevention Evaluation), ramipril decreased the likelihood of development of type 2 diabetes by 34% (9), with a meta-analysis of randomized controlled trials of angiotensin II blockade showing a 22% decrease in diabetes development across a variety of patient groups (10). The adipocyte makes angiotensinogen, with levels regulated by nutritional factors; produces ACE and the...
higher AT1 receptor expression in people with adipocyte biopsy studies showing a version of angiotensin I to angiotensin II, with irbesartan blocking this effect. Thus, an angiotensin II– mediated paracrine effect of adipocytes in impairing recruitment of additional adipocytes may lead to excess visceral fat (12) or to fat storage in tissues other than adipose tissue, such as myocytes, while RAS blockade may allow excess lipids to be partitioned back into adipose tissue (13). Supporting this concept, in a fructose-fed rat model of insulin resistance, RAS blockade with either ACE inhibitors or ARBs reduces insulin levels, triglycerides, and free fatty acids (FFAs) and decreased intramyocellular lipids (14). In addition, there is evidence that the ARB telmisartan may have direct effects in activating the peroxisome proliferator–activated receptor (PPAR)γ nuclear receptor and inducing adipocyte differentiation in a fashion similar to that seen with TZDs. As angiotensin II may therefore decrease adipogenesis and increase lipolysis, both of which cause insulin resistance, as well as increasing norepinephrine release with vasocostrictive effects causing hypertension, Sharma suggested that angiotensin II “may be the common molecule driving both insulin resistance and hypertension.” The TRIM (Telmisartan in Reduction of Intra-Myocellular lipids) study of patients with the insulin resistance syndrome will address these hypotheses. ONTARGET (ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) will compare the agents individually and in combination, and the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) study will contribute further to understanding these concepts.

Ele Ferrannini (Pisa, Italy) discussed insulin resistance, hypertension, and CVD, noting that hypertension was one of the initial core components of the insulin resistance syndrome identified by Reaven in 1988, but that the syndrome is now vastly more complicated. ” He focused on hypertension as one element of the cluster, reviewing the inverse correlation of blood pressure with insulin sensitivity in individuals with normal as well as with elevated blood pressure levels (15). Lean individuals (BMI <25 kg/m²) have lower blood pressure than those with BMI >25 kg/m² for a given level of insulin sensitivity, suggesting that there may be an independent effect of obesity per se adding to the effect of associated insulin resistance. Furthermore, regardless of obesity, hypertensive individuals have ~60% increase in visceral fat, a potential factor underlying the association between insulin resistance and hypertension. The antinatriuretic effect of insulin correlates with its action in reducing uric acid excretion (16), and even if not alone causing hypertension, it may be a contributory factor leading people with diabetes or the insulin resistance syndrome to require diuretic treatment for optimal treatment. Insulin also has a vasodilatory effect, which appears linked to an effect of calcium ion on vascular smooth muscle cell and may be decreased in insulin-resistant individuals, contributing further to blood pressure elevations.

Ferrannini further discussed the link between hyperinsulinemia and the autonomic nervous system, noting that insulin resistance is associated with sympathetic nervous system activation. Heart rate variability measures may be used to assess parasympathetic versus sympathetic tone, with lean individuals showing increased sympathetic tone after insulin infusion, whereas obese individuals already show maximal activation with no further increase following administration of insulin, presumably related to the obese person already being hyperinsulinemic. Indeed, heart rate decreases in association with decline in adrenergic activation during the night in both obese and lean individuals, but this is less marked with obesity, in which the phase of highest sympathetic activity occurs during feeding. Another marker of adrenergic tone is the QT interval of the electrocardiogram, which increases during insulin administration, suggesting an effect on intramyocardial cation levels. Insulin receptors are ubiquitous in the brain, including the cortex, with insulin crossing at least part of the blood brain barrier. Insulin reduces diastolic but not systolic blood pressure, in association with reduction in peripheral vascular resistance, thereby increasing pulse pressure. Heart rate and stroke volume increase, so cardiac output increases. “Obesity may,” Ferrannini speculated, “be the chronic extension of what insulin does acutely,” with insulin’s acute effect similar to the chronic changes associated with insulin resistance (increased epinephrine, norepinephrine, and cortisol; decreased thyroid-stimulating hormone; increased prolactin and adrenocorticotrophic-releasing hormone; and marked increase in corticotropin-releasing hormone), presumably requiring insulin to cross the blood-brain barrier and overall having characteristics of a “stress response.” Ferrannini reviewed a set of concepts derived from the Mexico City Diabetes Study, in which >2,000 people were screened, with 3.25- and 7-year follow-up. Twelve percent of normotensive and 23% of hypertensive individuals had diabetes at onset. Among those originally neither hypertensive nor diabetic, 11% without diabetes developed hypertension. Seven percent of those without hypertension developed diabetes, while 13% of diabetic patients developed hypertension and 19% of hypertensive patients developed diabetes. Obesity was a powerful risk factor, as was waist circumference. Heart rate was greater in all classes of converters. Ferrannini postulated “a common soil” for converters, recognizing that there are subtypes converting to either or both conditions, so that it may be incorrect to assume that one overall underlying type exists. These data suggested both hypertension and diabetes tended to develop fairly quickly rather than there being a gradual rise in levels.

Insulin resistance, dyslipidemia, and heart disease
At a symposium on insulin resistance, dyslipidemia, and heart disease, Richard C. Pasternak (Boston, MA) speculated that the epidemic of insulin resistance syndrome will prevent our ability to improve rates of CVD, which currently accounts for half of deaths among men and one-third of deaths among women (17). Analysis of the 4S (Scandinavian Simvastatin Survival Study) showing higher event rates among placebo-treated individuals with than without insulin resistance syndrome, as well as showed greater reduction in adverse outcome among...
simvastatin-treated individuals with than without the syndrome (18). The syndrome represents a clustering of risk factors for CVD, including visceral obesity, atherogenic dyslipidemia, increased blood pressure and insulin resistance, and prothrombotic and proinflammatory state. Pasternak suggested that it will be crucial to determine whether insulin resistance causes atherosclerosis or a common factor causes both to develop new approaches to intervention.

All of the available definitions of insulin resistance syndrome appear to be effective in defining the risk of coronary artery calcification, the number of syndrome features correlating with the degree of calcification (19). One problem with the current definitions is that many therapies have the desirable property of improving insulin resistance syndrome criteria, but may change the classification of a given person, while conceptually not changing their underlying diagnosis. There is a correlation between C-reactive protein (CRP) level and the number of syndrome components (20). CRP appears to have additional predictive power, and it has been proposed that it be considered an additional component of the insulin resistance syndrome (21), potentially allowing understanding of the benefits of therapies (e.g., the additive benefit of ezetimibe to simvastatin in lowering CRP).

Sander Robins (Boston, MA) discussed fibrates and CVD event reduction in people with diabetes or insulin resistance, reviewing the selection of individuals who would benefit from these agents and potential mechanisms of their effect. The Helsinki (22) and Veterans Affairs HDL Intervention Trial (VA-HIT) (23,24) studies of gemfibrozil showed respective 17% and nil vs. 52 and 27% reductions in likelihood of cardiovascular events for individuals with BMI <26 vs. >26 kg/m², and Robins noted that the BIP (Bezafibrate Infarct Prevention) study (25) showed event rates increasing versus decreasing by approximately one-quarter in the two groups. Similarly, weight gain predicted benefit of treatment in a trial with clofibrate (26). Thus, the presence of obesity, presumably indicating insulin resistance, appears crucial to the benefit of fibrate therapy.

Further discussing the VA-HIT of 2,531 men with CHD, low HDL and relatively low LDL randomized to gemfibrozil versus placebo, Robins noted that this was a very-high-risk group, with CHD mortality of 9.3% over 9 years. Thirty-nine percent of participants had BMI >30 kg/m², 30% had diabetes, 31% had fasting glucose 100–125 mg/dl, and 32% had high fasting insulin, with high fasting insulin in 17% of the 1,732 people without diabetes. Four hundred-nineteen people had diabetes with and 339 had diabetes without high fasting insulin, and 431 had high fasting insulin without diabetes, with 1,302 study participants having neither diabetes nor hyperinsulinemia. The latter group had 0.9% CVD risk reduction with gemfibrozil compared with 8.2, 7.7, and 6.9% respective risk reduction in three diabetes and/or high fasting insulin groups. Stroke rates did not change with treatment in the nondiabetic, non–high fasting insulin group, while decreasing 2.4% in the diabetic and/or high fasting insulin group. Event rates increased with gemfibrozil among nondiabetic participants in the lowest fasting insulin quartile while decreasing in the 2nd and 3rd quartiles and showing even greater decrease in the 4th quartile (27).

Between 1980 and 1998, there was a decrease in overall CVD mortality but an increase in diabetes mortality (28), leading Robins to suggest that the development of effective approaches for this group is critical for the future. Gemfibrozil decreased CHD mortality 41% among individuals with diabetes in the VA-HIT, with reduction demonstrable at 2 years and a suggestion of widening separation between the placebo and gemfibrozil groups over the subsequent period. There was progressively increasing benefit of gemfibrozil in reducing CVD death in increasing BMI quartiles, at 20, 29, 31, and 46% for BMI <25.6, 25.6–28.1, 28.2–31.5, and >31.5 kg/m², respectively. The benefits of statin therapy for people with diabetes may, Robins pointed out, be less great than usually thought. Analysis of the combined CARE and LIPID trials showed a nonsignificant 17% reduction in risk of myocardial infarction or CVD death among people with diabetes, while the nondiabetic subgroup had a significant 25% risk reduction (29). Robins reviewed seven statin trials, including individuals with diabetes, with the number needed to treat between 28 and 111, while in the VA-HIT the number needed to treat was 12, suggesting a role of gemfibrozil among such patients.

Robins presented interesting data pertaining to the mechanism of benefit with gemfibrozil. He noted that it is not clear that the effect of gemfibrozil was mediated by an increase in HDL cholesterol levels, pointing out that in compliant patients in the VA-HIT, benefit was seen as long as there was any increase in HDL, suggesting a direct drug effect. Furthermore, there was an inverse linear relationship between the change in HDL cholesterol and fasting insulin, so that the patients with the highest fasting insulin, who had the greatest benefit, had the smallest change in HDL cholesterol. High fasting insulin was strongly associated with waist circumference. CRP was measured in 834 subjects in the VA-HIT, with CVD risk increasing above the median level of 2 mg/l. High CRP did not, however, track with increased waist circumference, with those subjects having both high CRP and high fasting insulin having the highest CVD event rate. Gemfibrozil reduced CRP only in individuals with high fasting insulin, and a fall in CRP was a marker of CVD risk reduction by (34%) in this group but not in those without high fasting insulin. In the placebo group, the fasting insulin was similar at 0 and 12 months, while individuals treated with gemfibrozil had ~20% decrease in fasting insulin at 12 months, suggesting improvement in insulin sensitivity. Although there was modest weight loss with gemfibrozil, it did not appear to explain the change in insulin sensitivity or CRP. Robins noted that most (although not all) studies of subjects with hypertriglyceridemia treated with fibrates do suggest reductions in insulin resistance. Individuals who had both reduction in CRP and reduction in fasting insulin with gemfibrozil had the greatest improvement in outcome. Thus, Robins concluded that for people with diabetes, insulin resistance, and moderate LDL cholesterol elevation, the first choice for lipid therapy may be a fibrate, with benefit possibly related to more reduction in inflammation and insulin than to normalizing lipids, suggesting the quandary that unlike statins the benefit of therapy is not reflected by changes in the usually measured lipid parameters, as triglyceride lowering also was not itself predictive of events in the VA-HIT or in the Helsinki study. Looking at changes in LDL and HDL particle size in VA-HIT, however, Robins did state that "reduction in LDL particle number clearly
predicted a reduction in events." When asked about combining fibrates with statins, he suggested that studies comparing effects of each agent alone with the combination are needed to determine risks and benefits.

Fredrik Karpe (Oxford, U.K.) discussed postprandial lipid metabolism and the insulin resistance syndrome. Although most lipid measurements are made in the fasting state, we spend most of the day in the nonfasting state, implying that it is important to understanding normal lipid homeostasis. In a normal person, peak triglyceride levels double or triple following meals, with different levels after different meals and a tendency of triglycerides to accumulate during the day, leading Karpe to suggest that "we have to broaden our views a little bit.

Postprandial lipid transport involves production of chylomicrons, with the hallmark protein apolipoprotein B (apoB)-48, which is only expressed in the small intestine. Lipoprotein lipase (LPL) leads to tissue uptake of fatty acids, with uptake of chylomicron remnants by the liver. The endogenous pathway of lipoprotein metabolism involves hepatic VLDL particles containing apoB-100 and following a similar pathway. Determinants of postprandial lipemia include the amount of dietary fat and endogenous triglyceride production as well as the rates of degradation of triglyceride-rich lipoproteins.

In a study of the incorporation of 1,13C[palmitate] from a mixed meal into VLDL particles using immunonaffinity capture with monoclonal antibodies to separate apoB-48 from apoB-100, the dietary fatty acid was rapidly incorporated into VLDL, with lipids containing only apoB-100 beginning to appear ~2 h after meal consumption (30), suggesting that >20% of VLDL triglycerides are derived directly from dietary fat within hours of eating, indicating that there is rapid recirculation of dietary fat. FFA levels, in contrast to triglycerides, are suppressed from fasting levels to the postprandial state and remain suppressed until the next morning, while FFA levels are elevated throughout the day in people with diabetes. FFAs are both taken up by and generated in adipose tissue. LPL is highly expressed in the fed state on the surface of the endothelium, but in individuals with insulin resistance there is “spillover” of FFAs generated by LPL back into the circulation rather than their undergoing uptake by adipocytes.

In a patient with PPARγ mutation-induced lipodystrophy who had hypertriglyceridemia and hyperinsulinemia, there was a marked postprandial increase in triglyceride levels, with high fasting FFAs failing to show the normal rapid postprandial drop, in part due to exaggerated FFA spillover from LPL into the bloodstream, presumably leading to adverse consequence in development of ectopic fat deposition in muscle and liver via increased flux of substrate for triglycerides. Karpe addressed the effect of insulin sensitizers on the lipid phenotype of the insulin resistance syndrome. In a study of rosiglitazone treatment, BMI increased modestly, HbA1c (A1C) decreased from 7.4 to 7.0%, and fasting FFA levels did not change, although there was some reduction in postprandial FFAs, with increased rapidity of the postprandial decline in plasma triglycerides (31). There was no difference in adipose tissue or skeletal muscle removal of triglycerides, suggesting the dyslipidemia of the insulin resistance syndrome to be related to increased levels of production, with the T2D acting to reduce VLDL production. Thus, Karpe noted, factors that determine the plasma triglyceride levels all are related to insulin effects, including triglyceride production, based on VLDL secretion, FFA generation from VLDL substrate, and fatty acid oxidation in liver and muscle, and triglyceride removal based on LPL action.

Alexandros N. Vgontzas (Hershy, PA) discussed sleep apnea as a manifestation of the insulin resistance syndrome, noting that while obesity changes anatomic factors, altering the mechanics of respiration, the majority of adult apneics do not have structural abnormality, with Vgontzas suggesting that apnea may also be a manifestation of insulin resistance, having a strong association relationship with male sex and android obesity. The sleep apnea syndrome may have a progressive course, with weight gain progressing to further increase in snoring and apnea leading to excessive daytime sleepiness (EDS), worsening weight gain. Sleep apnea has a number of insulin resistance-related systemic effects, particularly increasing blood pressure, with the failure of mechanical treatment approaches with surgery furthering the concept of apnea as a systemic illness rather than a local abnormality. Levels of tumor necrosis factor-α and interleukin (IL)-6 are elevated in sleep apnea as in narcolepsy, with cytokine elevations independent of the degree of obesity. Sleep apnea is associated with increased plasma insulin and glucose levels, with insulin resistance present even in nonobese apneics and even in mild forms of sleep apnea. Cross-sectional computer tomography scanning shows increased visceral, but not subcutaneous, fat in sleep apneics compared with weight-matched control subjects, with evidence that sleep loss leads to insulin resistance and obesity. Addressing the question of whether sleep apnea is more common in all states of insulin resistance, Vgontzas reviewed studies comparing women with versus without polycystic ovarian syndrome (PCOS), showing 17 vs. <1% sleep apnea, accompanied by EDS not explained by obesity alone (32). Continuous positive airways pressure (CPAP) treatment is often difficult to tolerate and may not always be effective. In a study of effects of CPAP, 16 obese men with obstructive sleep apnea were compared with 13 obese men without the condition and 16 normal-weight control subjects. CPAP did not decrease levels of IL-6 or of fasting glucose or insulin. Individuals with sleep apnea had markedly lower levels of adiponectin than either control group, again without effect of CPAP. Furthermore, there was no effect of CPAP on the high visceral adiposity levels. CPAP did somewhat improve EDS and hypercortisolism, but this and other studies show no benefit in low-grade inflammation, insulin resistance, or visceral fat accumulation, suggesting inflammation and insulin resistance to be primary factors. There is a complex association between EDS and sleep apnea. The apnea/hypopnea index (number of >10-s apneic episodes/h) is not always clearly associated with the degree of EDS, suggesting that daytime sleepiness may have other determinants. In a study of 73 obese and 45 control subjects without sleep-disordered breathing, the obese individuals were sleepier during the day and less sleepy during the night. The prevalence of EDS increases exponentially above BMI ~28 kg/m2, with age and the apnea/hypopnea index also having significant association with EDS. Clinically, depression, obesity, and diabetes are the major determinants of EDS and appear to be of greater importance than sleep apnea per
se. There is heterogeneity of sleep apnea phenotypes. Vgontzas suggested distinguishing between symptomatic (EDS and/or hypertension) and asymptomatic sleep apnea. Although the overall prevalence of sleep apnea increases linearly with age, there is a peak of symptomatic sleep apnea at age 50 in men and 60 in women that appears to resemble the age distribution of the insulin resistance syndrome. In a study of the tumor necrosis factor-α antagonist etanercept in sleep apnea among eight obese men with symptomatic apnea, sleep latency increased from ~12 to 16 min with active treatment, suggesting an improvement in EDS, with IL-6 levels also decreasing. In contrast, in a study of ~500 people treated with CPAP, sleep latency changed by <1 min. Vgontzas described a study of 1,104 men and women age 30–60 showing an apnea/hypopnea index of 2.8 vs. 5.3 in those exercising versus not exercising at least 7 h/week.

**Treatment of the insulin resistance syndrome**

Paul Jellinger (Hollywood, FL), representing the American Association of Clinical Endocrinology, introduced a session on treatment by noting that “we do not have, today, clear direction as to how to treat this syndrome,” as opposed to our treatment of specific components of the syndrome. Edward Horton (Boston, MA) discussed effects of lifestyle modification on vascular reactivity and endothelial function in the insulin resistance syndrome, pointing out that this represents early intervention directed at the prevention of complications of the syndrome, and emphasizing the need to use lifestyle modification in appropriate combination with pharmacologic treatment. He reviewed projections of the diabetes epidemic, the “epicenter” of which will be the Indian subcontinent. Currently, 65% of Americans are overweight and 21% obese, with 24% having the insulin resistance syndrome (33). The lifetime risk of developing diabetes for people born in 2000 is 33% for men, 39% for women, and 50% for Hispanic women. The approach of Adult Treatment Panel (ATP)-III has been to focus on obesity, particularly abdominal obesity, which in the setting of environmental factors (physical inactivity and aging) leads to insulin resistance, which in turn causes atherogenic dyslipidemia, hypertension, and hyperglycemia, as well as the many other complications and associated conditions of the insulin resistance syndrome. “The real question is,” Horton stated, “can we stop the progression to diabetes and cardiovascular disease?” A number of studies have addressed aspects of lifestyle modification. The Da Qing IGT and diabetes study involved 577 subjects with impaired glucose tolerance (IGT), in which clinics were assigned to no additional treatment, to diet, to exercise, or to diet and exercise, with each intervention applied to all patients in the clinic. The active lifestyle treatment strategies were associated with 42–45% 5-year diabetes rates, as opposed to the 68% rate for the control clinics. The Finnish Diabetes Prevention Program (DPP) involved 522 middle-aged overweight individuals with IGT randomly assigned to control or intervention groups, the latter exercising at least 4 h weekly, and with diet aimed at decreasing fat and increasing fiber. The intervention group had 4.2 and 3.5 lb weight loss at 1 and 2 years, respectively, with a 58% reduction in diabetes risk directly linked to lifestyle change so that individuals who lost ≥5% body weight had a 74% reduction in diabetes and people who exercised >4 h weekly had 80% reduction in diabetes. In the U.S. DPP, 3,234 subjects were studied, with intensive lifestyle (exercise goal 150 min/week, reduced fat and calorie diet), metformin 850 mg twice daily, or no intervention. Diabetes conversion rates were 11.5%/year in the later group, with 31 and 58% reductions in this rate with metformin and the lifestyle intervention, respectively. Approximately half of the DPP cohort developed the insulin resistance syndrome based on the ATP-III criteria, with 17 and 41% respective reductions in progression to insulin resistance syndrome with metformin and with the lifestyle intervention. Horton reviewed evidence that endothelial dysfunction occurs in diabetes, describing studies showing that leg blood flow change during methacholine infusion is reduced either with obesity or with type 2 diabetes and flow-mediated brachial artery dilatation is reduced and levels of von Willebrand factor, vascular cell adhesion molecule, and endothelin-1 elevated in people with type 2 diabetes, with IGT, or with relatives having type 2 diabetes. In a 6-month DPP-like lifestyle study of individuals with normal glucose tolerance, IGT, and diabetes, insulin sensitivity improved, although to a lesser extent in people with diabetes, and all had improvement in flow-mediated vasodilatation to an extent proportional to the weight loss (34). IL-6, plasminogen activator inhibitor-1, and leptin levels decreased. In the Look-AHEAD (Action for HEAlth in Diabetes) study of intensive lifestyle intervention in overweight individuals with type 2 diabetes, ~5,000 participants with BMI >25 kg/m² have been placed on 10% caloric restriction and 175 min/week exercise; the study will analyze outcome over a 10-year follow-up period. Comparing a small number of control versus lifestyle patients in his center, 6 vs. 10% weight loss was seen, with HDL cholesterol increasing in both groups, although A1C decreased only in the intervention group. Flow-mediated vasodilatation showed no change in the control group but improved in the intervention group, correlating with weight loss. Thus, if lifestyle modification can be sustained over long periods of time in a cost-effective fashion, reduction in conversion to diabetes and improvement in clinical outcome may be expected.

Vivian Fonseca (New Orleans, LA) reviewed potential approaches to pharmacological management of the insulin resistance syndrome in people without diabetes, including those with IGT, obesity, lipodystrophy, previous gestational diabetes, CVD, PCOS, inflammatory conditions (such as psoriasis), nonalcoholic fatty liver disease, or use of drugs such as glucocorticoids, protease inhibitors, and antipsychotic agents. Treatment could be designed to improve surrogate markers, decrease inflammation, prevent diabetes, treat PCOS, and decrease development of CVD, as well as cirrhosis, cancer, and other non-CVD complications.

Both available sensitizers, metformin and TZDs, might be of benefit in treatment of the insulin resistance syndrome. In the DPP, metformin decreased diabetes progression 31%, and in the TRIPOD (Troglitazone in Prevention of Diabetes) study of 236 subjects, 400 mg troglitazone daily decreased diabetes by ~55% (5.4 vs. 12.1% annually). In DPP, metformin had little effect on weight. The PCOS clearly responds to metformin, with a large multicenter study perhaps needed to more clearly delineate its benefits. In TRIPOD, persistent β-cell benefit was noted during 8-month follow-up and...
carotid intima-media thickness showed stabilization, suggesting an antithrombotic benefit, as has been reported for the other TZDs in individuals with existing diabetes. Bezafibrate also appears to have an effect in decreasing diabetes development (35). The ACT-NOW (Actos Now for the Prevention of Type 2 Diabetes) and DREAM studies will address diabetes prevention with pioglitazone and rosiglitazone. Interestingly, there are 3- to 5-mmHg reductions in blood pressure in subjects receiving TZDs, both with diabetes and with insulin resistance without diabetes, with evidence that the change in blood pressure is proportional to that in insulin sensitivity (36). The TZDs also decrease albuminuria (37), further suggesting a role in the prevention of complications of the insulin resistance syndrome. Both PPARα and -γ agonists decrease CRP, endothelin-1, and fibrinogen, the PPARγ agonists perhaps with greater benefit. Given the evidence that chronic inflammation precedes the onset of type 2 diabetes (38), it may be beneficial to direct treatment toward markers of inflammation, a potential TZD benefit, with rosiglitazone having been shown to decrease CRP and MMP-9 in people with diabetes (39) and to decrease oxidative stress, monocyte chemotactrant protein, and CRP in obese individuals without diabetes. TZDs may also reduce endothelial dysfunction, as improvement in flow-mediated brachial artery vasodilation has been demonstrated in people with and without diabetes (40). Both pioglitazone (41) and rosiglitazone (42) have been shown to reduce intimal hyperplasia and restenosis in people with diabetes following angioplasty and stent placement. Thus, insulin sensitizers appear of potential benefit in reducing CVD. Studies with TZDs in the nondiabetic population will be of importance.

Other potential treatments of the insulin resistance syndrome include α-glucosidase inhibitors, insulin and its secretagogues, blockade of the RAS, weight loss agents, and anti-inflammatory agents. In the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus), 1,429 individuals received 100 mg acarbose three times daily or placebo, with a decrease in progression to diabetes by 25% (43). There is intriguing evidence that secretagogues may prevent the development of diabetes. In a study of what has been termed type 1-1/2 diabetes, glipizide was shown to prolong remission (44), with similar effects of the agent reported in a small study of African-American individuals with IGT (45). Among 267 subjects with IGT followed for 10 years, diet plus tolbutamide prevented diabetes, while 13% of those with diet plus placebo and 29% of those receiving no treatment developed diabetes (46). The NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Study) research will assess the effect of nateglinide in preventing progression from IGT to both diabetes and CVD. ACE inhibition was shown to reduce development of diabetes in the HOPE study with ramipril, as well as in a number of other investigations, with further analysis of this approach in the DREAM study. The ARBs decrease inflammatory marker levels, an effect perhaps not seen with ACE inhibitors (47), with the NAVIGATOR study also addressing the potential effect of valsartan in the prevention of IGT progression to diabetes and of CVD development. The weight loss–promoting agent orlistat also decreases the likelihood of worsening of glycemia in individuals with IGT (48), and there is intriguing evidence that aspirin at the high dosage of 12 g daily may have an insulin-sensitizing effect (49).

Robert Misbin (Rockville, MD) of the Food and Drug Administration (FDA) addressed aspects of the challenge of developing drugs to treat insulin resistance and asked what is needed to decide to treat the insulin resistance syndrome itself rather than its components. He noted that there are regulatory/bureaucratic reasons that developing new indications for treatment are difficult, as the FDA has difficulty even processing such applications, whereas it is much easier to develop new treatment approaches for recognized conditions. He suggested, however, that physicians should not consider it the role of the FDA to decide upon criteria for effective treatment, as this should be the consensus of experts, after which recommended treatment approaches can be developed. Challenges for drug development include definitions of insulin resistance, measurement of insulin resistance, trial design, and regulatory issues. He suggested that proponents must demonstrate benefit in clinical trials, such as by demonstrating reductions in CVD. Drugs for the indication must have an acceptable risk profile, and a sponsor must submit a New Drug Application. This is not a trivial point, as for example metformin in many ways has optimal characteristics but is indicated “on label” only for diabetes, and as a generic substance “no one has an interest in the pharmaceutical industry for developing further applications” for this agent. Traditionally, we evaluate drugs for benefit versus risk in individual diseases, but benefit versus risk considerations for diabetes and for PCOS are, for example, quite different, given the differences in risk of the two conditions. Misbin pointed out the great influence of the DCCT on the FDA, as its establishment of A1C as a surrogate marker for microvascular disease in patients with type 1 diabetes treated with insulin was extrapolated to the use of metformin, acarbose, miglitol, the TZDs, repaglinide, and nateglinide as glucose-lowering agents for the treatment of type 2 diabetes. Data-based evidence must be put forward to accept new approaches to treatment and to accept a new surrogate end point. Such an end point must have predictive value for an important outcome, must have a standardized methodology for measurement, and must be stable, reproducible, and suitable for a prospective DCCT-like study. "This is the kind of thing," Misbin stated, "that we need for the insulin resistance syndrome." Trial design would require defining a patient population with insulin resistance syndrome, with the major efficacy measure one clearly of major benefit, such as prevention of CVD events, and a surrogate end point for insulin resistance assessment. Misbin asked what he termed a "difficult question": What do you do about other treatments? In clinical practice, one must treat diabetes, dyslipidemia, PCOS, hypertension, IGT, steatohepatitis, and subjects in the placebo arm of the trial might require treatment for diabetes, for hypertension, and so on, which could influence insulin resistance. Thus, the concept of the insulin resistance syndrome does not lend itself in a straightforward fashion to the development of clinical trials.

Gerald Reaven (Stanford, CA) presented an analysis of approaches to identifying obese patients who will benefit from treatment. He noted that rather than establishing diagnostic criteria, it may be more appropriate to establish approaches for individuals with insulin resistance, recognizing that insulin resistance itself is not a disease but a physiologic state. Fur-
thermore, insulin resistance is not itself the only cause of the constituents of the “insulin resistance syndrome,” so that for example there are causes of hypertriglyceridemia having nothing to do with abnormality of insulin action. Recalling his studies of distribution of insulin sensitivity in the population, he suggested that one should ask: Who is at risk of adverse outcomes? With this approach, recognizing that 25–35% of the population is at increased risk of CHD, which he agreed was the most important adverse outcome, one can begin to identify levels of insulin resistance at which treatment might be appropriate. BMI and waist circumference alone do not appropriately identify people who are really at risk, as one-third of the most-insulin-sensitive tertile are overweight or obese and one-sixth of the least sensitive tertile have normal weight. At any BMI, insulin resistance is associated with higher triglycerides and glucose and lower HDL. Reaven pointed out that triglycerides are as good a correlate of insulin sensitivity as is the insulin level, so that a useful approach is to find obese individuals with the typical dyslipidemia. Hypertension is not as good a marker, as people with hypertension without dyslipidemia do not have high CHD risk, whereas those who do have dyslipidemia have quite high risk. He showed, using receiver operator curves (plots of sensitivity vs. 1-specificity), that triglycerides, fasting insulin, and the triglyceride–to–HDL cholesterol ratio are all effective discriminants of obese individuals with and without insulin resistance syndrome. Getting to the issue of “who do you treat,” in a population with approximately two-thirds overweight, only half of these will be in the upper tertile of insulin resistance, so that twice as many people would be in the upper tertile of insulin resistance vs. 1-specificity), that triglycerides, fasting insulin, and the triglyceride–to–HDL cholesterol ratio as the entry criterion and consider comparing any new “drug X” with, say, gemfibrozil, based on studies such as those described by Robins.

References


