2nd International Symposium on Triglycerides and HDL

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This is the first of two articles summarizing the 2nd International Symposium on Triglycerides and HDL, organized by the Giovanni Lorenzini Medical Foundation and held in New York, New York, 14–17 July 2005.

Anthony Gotto (New York, NY) gave an overview of the “evolving story” of HDL and triglycerides in cardiovascular disease (CVD) prevention. He noted that statins only reduce clinical events by approximately one-third (although subsequent speakers suggested that with more aggressive LDL targets events may be reduced by half), and recommended targeting HDL and triglyceride in addition to LDL cholesterol to achieve greater degrees of risk reduction. There is as yet, however, no direct evidence of clinical benefit with this approach. In the early 1950s, the higher level of HDL cholesterol in women and the association of low HDL with CVD was first described, with the Framingham Heart Study recognizing low HDL as the “major potent lipid risk factor” in 1977 (1), and with recognition that each 1-mg/dl decrease in HDL is associated with a 2–3% increase in CVD risk later proposed by this group. Triglyceride also has been shown to be associated with CVD, although this is more controversial. In a meta-analysis of 17 population-based prospective studies of 46,413 men and 10,864 women, adjusting for HDL cholesterol and other risk factors, there were increases of 16 and 42% in CVD end points in men and in women, respectively, for every 100-mg/dl increase in triglyceride level (2). The National Cholesterol Education Program Adult Treatment Panel III (ATP III) recommended use of non-HDL cholesterol as a target of therapy if the triglyceride level exceeded 200 mg/dl. Triglycerides were recommended as a “secondary target” if levels exceeded 200 mg/dl, with nicotinic acid and fibrates useful pharmacologic approaches, and specific HDL cholesterol targets were not recommended (3). Using the ATP III definition, there is evidence that the metabolic syndrome, comprising at least three of the five criteria of central obesity (waist >102 cm in men and >88 cm in women), HDL <40 mg/dl in men and <50 mg/dl in women, triglyceride ≥150 mg/dl, blood pressure ≥130/85, and fasting glucose >110 mg/dl (revised to >100 mg/dl), is associated with additional risk to that conveyed by its defining characteristics (4). A number of other groups have given criteria for metabolic syndrome, with the International Diabetes Federation (IDF) giving central obesity (waist >94 cm in men and 80 cm in women) as the main criterion and requiring at least two of the following four additional criteria: triglyceride ≥150 mg/dl, HDL <40/50 mg/dl (men/women), blood pressure ≥130/85 mmHg, and fasting blood glucose >100 mg/dl (5).

Addressing clinical trials, the VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial) studied 2,531 men with CVD treated with gemfibrozil versus placebo (6). HDL cholesterol levels during treatment were associated with outcome, with subsequent analysis showing that persons with diabetes or insulin resistance experienced particular benefit of this treatment (7). Analysis across multiple fluvastatin trials showed that the greatest benefit was seen in persons who had low HDL cholesterol, with each 1% rise in HDL associated with 1–2% lower CVD risk (8). In the UKPDS (U.K. Prospective Diabetes Study), the most potent CVD risk factors were, in order, LDL cholesterol, HDL cholesterol, HbA1c (A1C), systolic blood pressure, and cigarette smoking (9). Triglyceride was a risk factor for CVD among UKPDS participants after adjustment for age and sex but was not a significant factor when the other variables were included.

Based on similar analysis, the European Consensus Panel has recommended the combination of nicotinic acid and a statin, together with lifestyle modification, as a useful strategy to lower coronary heart disease (CHD) risk in patients with diabetes and metabolic syndrome (10), while the American Heart Association and American Diabetes Association have suggested use of fibrates in combination with statins (11). The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study of fenofibrate and the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial of intensive glycemic control (A1C <6 vs. 7–7.9%), HDL triglyceride treatment (fenofibrate plus simvastatin versus simvastatin), and intensive blood pressure control (systolic blood pressure <120 vs. <140 mmHg), with 1,000–1,500 persons in each subgroup (www.accordanc.org), will give further information on this approach in persons with diabetes, while the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes) study will compare simvastatin with simvastatin plus nicotinic acid in a high-risk population of persons with metabolic syndrome.

Gotto discussed the discovery of the nicotinic acid receptor, which is allowing understanding of the mechanism of action of this agent in inhibiting adipocyte lipolysis in vivo, and suggested that polymorphisms in the receptor may explain variations in nicotinic acid response. New evidence that β-hydroxybutyrate activates the nicotinic acid receptor (12) may explain the action of high-protein ketogenic diets in inhibiting lipolysis and decreasing hepatic triglyceride synthesis.

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Abbreviations: apo, apolipoprotein; ATP III, Adult Treatment Panel III; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; IDF, International Diabetes Federation; IDO, inhibitor of NF-kB; IL, interleukin; LPL, lipoprotein lipase; NF, nuclear factor; PPAR, peroxisome proliferator-activated receptor; RIO, Rimonabant in Overweight/Obesity; TNF, tumor necrosis factor; VA-HIT, Veterans Affairs High-Density Lipoprotein Intervention Trial; WHO, World Health Organization.

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There are three major pathways of HDL-mediated cholesterol efflux: passive diffusion, scavenger receptor B1, and ATP-binding cassette transporter 1 (13). Future approaches may be based on understanding of the process whereby ATP-binding cassette transporter 1–transported cholesterol is esterified by lecithin:cholesterol acyltransferase and then transferred to VLDL particles via cholesterol ester transfer protein. The HDL apolipoprotein (apo)A1 production rate appears to be the primary predictor of plasma apoA1 concentration (14). This suggests that therapy to stimulate HDL apoA1 production, as occurs with peroxisome proliferator–activated receptor (PPAR)-α and -γ agonists, may be the most rational option for targeting low HDL levels in the metabolic syndrome. Activation of PPAR-γ in foamy macrophages increases net lipid efflux (15), a process also involving the liver X receptor nuclear receptor, but liver X receptor agonists that have been developed appear to cause toxicity in leading to fatty liver. Another important approach will be the use of apoA1 mimetic peptides to promote atherosclerosis regression. The cholesterol ester transfer protein inhibitor torcetrapib is associated with an increase in HDL (to >40–50% at highest dose) and a decrease in LDL cholesterol (16) and offers another potential approach. Gotto concluded that HDL-based therapy may become an accepted practice over the next decade, although suggesting that “we remain quite a ways” from triglyceride-based therapy.

The metabolic syndrome
Scott Grundy (Dallas, TX) presented the XXXI Lorenzini Annual Lecture, giving an epidemiological and genetic overview of the metabolic syndrome, a constellation of metabolic risk factors associated with atherosclerosis via triglyceride, acting via atherogenic remnant particles, low HDL cholesterol, indicating lack of reverse cholesterol transport, small LDL particles, more atherogenic by greater penetration into the arterial wall, elevated blood pressure and glucose, with multiple injurious effects on the arterial wall, the hypercoagulable state with increased plasmogen activator inhibitor 1, and increased C-reactive protein (CRP) as indication of inflammation, which is “part and parcel of atherogenesis.” The metabolic syndrome is linked to multiple CVD risk factors, then, and is a precursor of type 2 diabetes, further increasing CVD risk. Grundy noted that Eskil Kylin first recognized the clustering of hypertension, hyperglycemia, obesity, and hyperuricemia in 1923, with Jean Vague describing the association of upper-body adiposity with CVD in 1947. Over the past 7 years, definitions of metabolic syndrome have been offered by the World Health Organization (WHO), European Group for the Study of Insulin Resistance, ATP III, American Association of Clinical Endocrinologists, and IDF have all offered definitions (17). The WHO proposed insulin resistance as the central feature of the syndrome and required evidence of diabetes, glucose intolerance, or abnormal hyperinsulinemic clamp plus two additional factors. The European Group for the Study of Insulin Resistance required hyperinsulinemia plus any two factors of waist, triglycerides or HDL, blood pressure, and fasting glucose. ATP III suggested three of five factors, including waist, triglyceride, HDL cholesterol, blood pressure, and glucose, and most recently the IDF recommendations suggested the need for different sets of risk factors for different groups, requiring ethnic-specific waist circumference measures, which Grundy suggested would best be 102 and 88 cm for men and women, respectively, or European Cauca- sian descent, as recommended in ATP III, although noting the values suggested for this group of 94 and 80 cm, respectively, by the IDF, with the IDF suggesting respective waist circumference cutoffs of 90 and 80 cm for persons of South Asian or Chinese ethnicity and 85 and 90 cm for those of Japanese ethnicity. Grundy described the syndrome as being based on the concept of progression of risk, from obesity through metabolic syndrome (IDF earlier than ATP III), and finally to type 2 diabetes at the highest risk level. The prevalence of metabolic syndrome varies in different populations, in the U.S. among female and male blacks at 26 and 16%, among Caucasians 23 and 25%, and among Hispanics 36 and 28%, so that more than one-quarter of adults have the syndrome. The NHANES III (Third National Health and Nutrition Examination Survey) showed a metabolic syndrome prevalence of 26% among persons with normal glucose, 33% among those with impaired glucose tolerance, 71% among those with impaired fasting glucose, and 86% among those with diabetes (18). In other countries, the prevalence of metabolic syndrome is 14% in Finland, 23% in Ireland, 25% in Scotland, <10% in France, and 25 and 40% among males and females in Iran and Turkey. Grundy pointed out that HDL levels are lower in women in the Middle East, contributing to their very high metabolic syndrome prevalence. In China, after 55 years of age, 11 and 28% of men and women have metabolic syndrome using the ATP III waist criteria (19). In India, the respective prevalences are 32 and 26% (20). In Greece, there is a discrepancy between IDF and ATP III at ~45% and ~25% prevalences, leading Grundy to comment, “I think that there is a debate . . . what should be the waist circumference cut point,” while he noted that in the U.S., the ATP III and IDF criteria give essentially the same prevalences because of the high degree of obesity. The GEMS (Genetic Epidemiology of the Metabolic Syndrome) project is a multicenter family study designed to uncover the genetic basis of the metabolic syndrome, which Grundy described as offering a promising approach. A new candidate gene is that for the adipocyte product cathepsin S, whose expression in human subcutaneous adipose tissue correlates with BMI, serum cathepsin S, and serum triglyceride (21).

CVD mortality is increased in metabolic syndrome, which is associated with at least a doubling of short-term risk and perhaps an even greater increase in long-term risk. The risk of developing diabetes is increased three- to fivefold among persons with the syndrome (22), and there is a complex interaction between metabolic syndrome, diabetes, and CVD risk, with the NHANES study showing persons having neither metabolic syndrome nor diabetes to have 8.7% CVD prevalence, those having diabetes alone to have 7.5% CVD prevalence, but those with metabolic syndrome without diabetes to have 13.9% prevalence and those with both to have 19.2% prevalence. Furthermore, there may be gradations within metabolic syndrome, with the higher CVD risk occurring among persons who have a greater number of components (23). Metabolic syndrome is associated with aortic calcification, the degree again correlating with the number of positive metabolic syndrome components, with the combination of low HDL and high triglyceride doubling the likelihood of increased aortic calcification (24).

Grundy discussed the assessment and management of patients with metabolic syndrome and abdominal obesity. He suggested that because of the obesity-related abnormality of lipids, blood pressure, insu-
lin resistance, and hypercoagulability, there may be “an opportunity to go beyond the standard risk factors.” He addressed the question of whether the metabolic syndrome should be considered an obesity syndrome or an insulin resistance syndrome, and recalled that Reaven hypothesized the latter, terming the condition the “insulin resistance syndrome.” Grundy, however, postulated that the role of adipose tissue and of adipokines implies that insulin resistance alone is not the entire explanation, with the adipocyte appearing to drive inflammation, hypercoagulability, blood pressure, glycemia, and atherogenic dyslipidemia. Genetic variation in metabolic risk factors may mediate the effect of obesity in causing metabolic syndrome, so it may be that obesity and insulin resistance vary in importance in different populations. The obesity model may be more applicable to the U.S., where the prevalence of metabolic syndrome increases progressively with increasing BMI in all population groups, while in South-Asian populations and among persons with a strong family history of diabetes, even without obesity there is marked insulin resistance, suggesting this to mediate the high prevalence of metabolic syndrome, diabetest, and CVD. The greater degree of insulin resistance and higher levels of free fatty acids, leptin, and CRP and lower adiponectin in the latter group appear “as though,” Grundy said, “the adipose tissue thought it was more obese.” Explanations that have been advanced for this include the thrifty gene hypothesis of polymorphisms in genes regulating insulin signaling (25), the Barker hypothesis of intrauterine malnutrition (26), or the presence of lifestyle factors related to weight gain and sedentary habits with increasing degrees of urbanization. A particularly important example of a population exhibiting reduced insulin sensitivity is seen in the Asian subcontinent, where the prevalence of type 2 diabetes is predicted to increase from 20 million in 2002 to 57 million in 2025. There may be multiple genetic causes of insulin resistance, with a polymorphism in plasma cell membrane glycoprotein ENPP1/PC-1 K121Q appearing to be a candidate gene explaining at least some of the increase in insulin resistance in a number of populations, including Asian Indians (27–29).

Grundy suggested that treatment of the metabolic syndrome might be improved by better assessment of its pathogenesis. Risk assessment is important, particularly the need to determine whether there is evidence of CVD or diabetes, as well as measurement of the Framingham risk score. Lifestyle intervention is appropriate, including weight reduction and maintenance, increased physical activity, and development of antiatherogenic and antidiabeticogenic approaches to diet, with drug therapies appropriate “first line” only for accepted risk reduction interventions, including treatment of LDL, triglyceride, blood pressure, glucose, and the prothrombotic state with low-dose aspirin. Treatment for insulin resistance again includes lifestyle intervention, and although the use of metformin and thiazolidinediones is being considered, it is still uncertain whether these agents will prevent adverse outcome in this population.

Jorge Plutzky (Boston, MA) discussed basic mechanisms and new targets for treatment of atherosclerosis and metabolic syndrome (30). He noted the effects of insulin resistance and hyperinsulinemia, of hepatic factors leading to hypertriglyceridemia and low HDL cholesterol, and of adipose tissue as a source of free fatty acids and inflammatory cytokines, which may mediate the proinflammatory state. Hypertension, small dense LDL, and many additional factors further contribute to atherosclerosis. “Might there be,” he asked, “central targets” for treatment? The PPAR nuclear receptors are ligand-activated transcription factors that may be important targets that in turn alter “an entire cassette of genes” to then modify a variety of metabolic pathways, including fatty acid oxidation and lipid metabolism, as shown by the effects of PPAR-α and -γ ligands, with the latter also affecting adipogenesis and glucose metabolism. PPAR-γ may have effects on wound healing, carbohydrate metabolism, and inflammation. An early step of atherogenesis, the expression of adhesion molecules, may be decreased by PPAR-α agonists, with low HDL associated with high levels of adhesion molecules. This effect is mediated by nuclear factor (NF)-κB, which is a “distal common pathway” through which PPAR effects, as well as those of cytokines, are mediated. When the inhibitor of NF-κB (IκBα) is released from the NF-κB complex, NF-κB is activated, so that both PPAR-α and -γ activation, by increasing IκBα levels, reduce this inflammatory pathway. Interestingly, PPAR-γ agonists induce IκBα only in the presence of PPAR-α, suggesting cross-talk between the two systems. Addressing the endogenous ligands of PPAR-α and -γ, Plutzky noted that lipoprotein lipase (LPL) may have either anti- or proatherogenic effects and that the enzyme acts on circulating lipoproteins to activate PPAR-α (31). LPL may, then, initiate a PPAR-α-dependent positive feedback loop for catabolism of triglyceride-rich lipoproteins. More generally, one can consider a network of different lipoproteins directing different transcriptional responses, with, for example, the anti-inflammatory effects of HDL blocked by the presence of lipase inhibitors, further suggesting a role of LPL. Plutzky suggested that HDL hydrolysis by endothelial lipase also activates PPAR-α. HDL actually represents a heterogeneous group of lipoproteins. Serum amyloid A and paraoxonase are components of different HDL particles, those containing serum amyloid A having opposing effect to that of the apoA1 and paraoxonase-containing HDL particles on inflammation, with the latter having anti-inflammatory and antioxidative actions.

George Steiner (Toronto, Canada) discussed clinical trials to reduce atherosclerosis in the metabolic syndrome. Diabetes is associated with a two- to fourfold increase in CVD risk, with a subset of persons with diabetes having a particular increase in risk: those who have the characteristic findings of metabolic syndrome. The risk of major coronary events is similarly associated with hyperinsulinemia. In a study of 633 men and women with acute myocardial infarction, there was 3.8 vs. 10.7% case fatality among those without versus with metabolic syndrome (32). There is some evidence that the CVD risk of persons with diabetes is similar to that of persons who have had myocardial infarction (33). Although this has been questioned by studies such as the epidemiologic follow-up of the MRFIT (Multiple Risk Factor Intervention Trial) (34), the HPS (Heart Protection Study) placebo group follow-up (35), and other studies (36), in which persons with coronary disease had somewhat greater risk than persons with diabetes, there remains definite evidence of adverse consequence of diabetes, particularly among women (37). Similarly, there is CVD risk associated with metabolic syndrome (4), with some investigators finding residual risk after taking into account all the specific components (38), while others report that the presence of metabolic syndrome itself loses significance after factoring out the specific components of HDL cholesterol, blood pressure, and diabetes (18). Among statin-treated persons in the PPP (Prospective Pravastatin Pooling) project, HDL cholesterol remained a
risk factor after treating LDL (39). The greatest response to simvastatin in the 4S (Scandinavian Simvastatin Survival Study) may similarly have been among persons with high triglyceride and low HDL cholesterol (40), with there also being evidence of greater reduction of coronary artery disease by simvastatin in persons with than without metabolic syndrome in this study (41). Addressing the question of how low the LDL cholesterol should be in persons with diabetes, Steiner noted that recent analysis confirmed better outcome among persons with diabetes treated with 80 rather than 10 mg atorvastatin daily, so that, perhaps, "we ought to be aiming down" and "pursue prevention aggressively" among persons with diabetes, recommending LDL <100 mg/dl for high-risk and lower for very-high-risk persons, triglyceride <150 mg/dl, and HDL cholesterol >40 mg/dl.

Increased triglycerides, decreased HDL cholesterol, and changes in LDL particle size and density characterize metabolic syndrome, with evidence that correcting these lipoprotein abnormalities in persons with diabetes improves risk, whether it be with statins or fibrates. Steiner reviewed a series of fibrate trials, showing that gemfibrozil associated with a 68% decrease in events in the HHS (Helsinki Heart Study) and a 24% decrease in the VA-HIT, bezafibrate associated with 65% decrease in events in the SENDCAP (St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Prevention Study), and fenofibrate decreasing angiographic changes 40% in the DAIS (Diabetes Atherosclerosis Intervention Study). In the WHO clofibrate trial, evidence of benefit was only seen in persons with obesity; in the HHS, benefit was seen in persons with high triglyceride and low HDL cholesterol; in the VA-HIT, persons with either diabetes or hyperinsulinemia had the greatest risk reduction; and analysis of the BIPS (Bezafibrate Infarct Prevention Study) showed that reduction in myocardial infarction and total CVD end points were seen only with this agent among persons with metabolic syndrome, with a 41.8% CVD event reduction (42).

Ronald Krauss (Berkeley, CA) discussed the pathogenesis and assessment of cardiovascular risk in metabolic syndrome, recognizing that it represents a cluster of CHD risk factors and suggesting that multiple pathophysiological processes are present, with insulin resistance a unifying underlying process. Insulin resistance itself can directly trigger atherogenic dyslipidemia. It also is associated with inflammatory changes, which in turn lead to the prothrombotic state. There is also an association of autonomic dysfunction with insulin resistance, contributing to the raised blood pressure of the syndrome. All of these components also are modified by genetic susceptibility, which may explain the clustering of risk factors, with additional factors such as obesity, age, diet, stress, and lack of physical activity further contributing to the complex presentation of the syndrome. Reviewing the ATP III definition of metabolic syndrome, he pointed out that the incorporation of elevated fasting glucose as a measure of insulin resistance justifies the use of 100 mg/dl as a new cut point for the syndrome, with the number of risk factors present proportional to the risk of CHD in a population-based study. The definition of the IDF further highlights the importance of central obesity as a critical component of the syndrome, adding ethnic differences in waist circumference criteria and the potential to use glucose tolerance testing to assess glycemic abnormality. He noted that age contributes greatly to the prevalence of metabolic syndrome and commented on the question of whether the presence of the syndrome is more important than its components, "I'm not sure that it is necessary... The main importance is to call attention to the concordance of the various components"; lipid abnormality is particularly important. The characteristic LDL abnormality is that of smaller particle number, so that the plasma LDL level underestimates the number of LDL particles, with apoB measurement being another approach to address this characteristic. There are distinct population groups with large and small LDL particle distribution, with an independent relationship of the small LDL particle cholesterol mass to CAD risk independent of total LDL cholesterol, apoB, and triglyceride levels (43). A final factor that Krauss suggested should be considered a component of metabolic syndrome is plasma CRP, with high CRP and metabolic syndrome being independent CVD risk factors among women (44). Effects of diet and physical activity have been examined in studies modifying these lifestyle factors, with the Finnish Diabetes Prevention Program (DPP) showing benefit of diet and physical activity in reducing diabetes risk (45) and with favorable effects of lifestyle change in the DPP. In the DPP, lifestyle, with a goal of 7% weight loss and exercise 150 min/week, reduced progression to diabetes 58% over lifestyle and 39% over metformin, with the cumulative 3-year development of metabolic syndrome 51% with placebo, 47% with metformin, and 34% with lifestyle intervention (46). Krauss suggested that lifestyle change, LDL reduction, blood pressure treatment, aspirin, and treatment of elevated triglyceride and low HDL cholesterol are all relevant. Further targets include pharmacologic approaches to weight loss such as orlistat (46a) and rimonabant.

**Obesity-related aspects of metabolic syndrome**

Benoît Lamarche (Sainte-Foy, Canada) discussed the use of waist circumference and triglyceride levels as screening tools to detect patients with increased abdominal adiposity—the “hypertriglyceridemic waist phenotype.” He mentioned that both the ATP III and WHO definitions of metabolic syndrome may be difficult to use, suggesting the need to identify more simple screening tools. Certainly, persons with the traditional risk factors of high LDL cholesterol and triglyceride and low HDL cholesterol are associated with a fourfold increase in risk, but those persons who also have a “nontraditional” risk triad of high insulin, high apoB, and the small dense LDL pattern have a 20.8-fold increase in risk (47). Lamarche presented additional evidence that persons with high LDL cholesterol have a tripling of CVD risk without the nontraditional factors, but a five- to sixfold increase in risk with two elements of the triad, even without high traditional risk factors. Increased waist circumference is associated with higher apoB and insulin levels, and increased triglyceride is associated with the small dense LDL pattern, suggesting that high waist and high triglyceride could be used as surrogate measures of the metabolic triad, with waist >90 cm and triglyceride >2 mmol/l as cutoffs, the presence of both associated with 83% prevalence of the triad, with hypertriglyceridemic waist also strongly associated with angiographic evidence of CAD (48). A survey carried out by Lamarche’s group showed that 19% of the male population, and 29% of those aged 40–65 years, had hypertriglyceridemic waist, with BMI, waist circumference, and HDL cholesterol and triglyceride levels similar to those of persons having diabetes, suggesting this to be a very high-risk group (49). In another population analysis, insulin
sensitivity was lower among persons with than without the two abnormalities, and those persons with hypertriglyceridemic waist had 25.4% diabetes prevalence, while diabetes was present in 8% of those without either abnormality (50). Analysis of another group of >4,000 persons showed that waist >95 cm and triglyceride >160 mg/dl was associated with a markedly higher prevalence of risk factors of lipids, blood pressure, and obesity (51). The pattern is associated with postprandial hypertriglyceridemia (52) and with 1.8- and 2.7-fold increases in CVD risk among persons with normal and elevated glucose levels, respectively (53), so that compared with persons with normal glucose, triglyceride, and waist circumference, those with the hypertriglyceridemic waist have a 5.4-fold increase in CVD risk and those with both hypertriglyceridemic waist and glucose 110–125 mg/dl have an 8.4-fold increase in CVD risk (54). Comparing hypertriglyceridemic waist with ATP III metabolic syndrome, in 560 women there were 2.2- and 1.8-fold increases in CVD, as well as increased aortic calcification score with both (55), so that the hypertriglyceridemic waist may be as good a predictor as the somewhat more complex determination of metabolic syndrome, although of course after persons at high risk are identified by either approach, one should then measure blood pressure, glucose, other lipids, etc., to determine the required treatment (56).

J.-P. Després (Sainte-Foy, Canada) discussed the potential benefits of modest weight loss, suggesting that these are related to the much greater proportionate decrease in visceral fat mass. Fibrate effects occur via increases in HDL and in apoA1 and -A2, from increasing LDL size and LPL, and from decreasing apoC3 and triglyceride. Després noted that in the VA-HIT, the gemfibrozil-treated group had decreased events at all levels of HDL increase, and that persons with hyperinsulinemia and/or diabetes did have benefit but those with neither failed to have benefit of gemfibrozil treatment, so that there are effects of fibrates “unlikely to be mediated by increased HDL.” Similarly, reanalysis of the BIPS showed that although the overall group failed to show event reduction, those who met the criteria for metabolic syndrome did show significant reduction in myocardial infarction and had decreased glucose, non-HDL cholesterol, and triglyceride and increased HDL cholesterol (42). In the QCS (Quebec Cardiovascular Study), persons with either high fasting insulin or elevated CRP had similar risk and those with both had additively higher risk, with Després showing evidence that both gemfibrozil and fenofibrate lower CRP, perhaps particularly in hyperinsulinemic rather than in normoinsulinemic patients. The presence of small LDL particles predicts CVD risk, and persons with small LDL particles and high apoB have the greatest benefit of fenofibrate treatment, which increases LDL size.

Luc F. Van Gaal (Antwerp, Belgium) discussed new data from the RIO (Rimonabant in Overweight/Obesity) diabetes study on the use of this agent as an approach to the improvement of metabolic parameters. The endocannabinoid system appears to act in the hypothalamus and nucleus accumbens on increasing food intake, with the CB-1 blocker rimonabant being an effective approach to decreasing food intake. A total of 6,625 persons were studied in the four RIO studies. Rimonabant versus placebo led at 1 year to a decrease in waist circumference by 8.5 vs. 4.5 cm and to weight loss of 8.6 vs. 3.6 kg. HDL cholesterol increased 27 vs. 17%, and triglyceride decreased 11% compared with a 6% increase (57). In the RIO-Europe trial, there was significant improvement in insulin sensitivity with rimonabant. In a 2-year follow-up, there was maintenance of weight loss, HDL cholesterol increase, and triglyceride decrease, with similar benefit among those with low HDL and with high triglyceride at baseline. Of nondiabetic study participants, 35–54% in the different trials had metabolic syndrome, with approximately half receiving rimonabant versus one-third receiving placebo reverting to normal after treatment. Systolic blood pressure decreased with rimonabant as well. There was also a slight but significant increase versus decrease in LDL particle size with treatment versus placebo and an increase in adiponectin with treatment. In the RIO-diabetes study of >1,000 persons treated with metformin or a sulfonylurea, there was a 0.6 decrease compared with a 0.1% increase in A1C, with 42.9 vs. 20.8% achieving A1C <6.5%. Xavier Pi-Sunyer (New York, NY) discussed evidence of there being a weight loss–independent effect of rimonabant on HDL cholesterol and triglyceride levels. Initial investigations of the CB-1 receptor showed it to be present in the hypothalamus and nucleus accumbens, where blocking would decrease food intake, but there is now evidence of adipose tissue, muscle, liver, and gastrointestinal tract receptors, and pair-feeding animal studies suggest direct peripheral effects. In the liver, CB-1 activation increases sterol regulatory element–binding protein and acetyl-CoA carboxylase. In adipose tissue, adiponectin production is stimulated by rimonabant, and rimonabant inhibits LPL. The question of whether rimonabant has a direct effect was addressed by factoring out the effect of weight loss in placebo-treated persons. At 1 year, in the RIO–North America study, the placebo group lost 2.8 kg, while persons treated with 20 mg daily lost 8.7 kg. HDL increased 16.1 vs. 7.2%, and triglyceride decreased 5.3% compared with an increase of 7.9%. Using linear regression, 44% of the increase in HDL and 53% of the decrease in triglyceride could be attributed to weight loss, with the remainder appearing to be a direct effect of rimonabant. At 2 years, the placebo group lost 1.2 vs. 4.8 kg with 20 mg rimonabant, HDL increased 7.8 vs. 14.1%, triglyceride increased 6.6% compared with a 1.9% decrease, again with approximately half of the effect attributable and half not attributable to weight loss. Pi-Sunyer noted that the drop-out rate was 49% in the placebo group and 45% in persons treated with 20 mg rimonabant, with 7% of placebo vs. 13% of rimonabant-treated patients discontinuing treatment for adverse events, mainly mood change, nausea, and headache.

Further treatment approaches for metabolic syndrome

Peter Ganz (Boston, MA) discussed approaches other than cholesterol lowering in the management of metabolic syndrome, noting it to include visceral obesity, insulin resistance, raised blood pressure, proinflammatory and prothrombotic states, as well as dyslipidemia, leading to both type 2 diabetes and atherosclerosis. The increased obesity of the U.S. will, given the endocrine and paracrine products of adipocytes, be expected to lead to changes in the phenotype of the population. Adipose tissue products linking insulin resistance and atherosclerosis include cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, chemokines such as monocyte chemotactrant protein 1, and growth factors such as transforming growth factor β. Other adipocyte mediators discussed at the meeting are resistin, which reduces insulin sensitivity, with plasma levels correlating with TNF-α, IL-6, and phospholipase A2 (58), and visfatin, a small
endogenous insulinomimetic peptide that may be specific for visceral fat, inducing triglyceride accumulation in preadipocytes in a fashion similar to that of insulin (59,60). Visceral fat levels are increased in nonobese hypertensive persons without diabetes, with subcutaneous fat similar to that in normotensive control subjects (61), suggesting that visceral fat plays a role in hypertension. Both exercise and metformin enhance insulin sensitivity by increasing GLUT-4 via activation of the AMP kinase pathway (62), with thiazolidinediones another potential approach to increasing insulin sensitivity, both for prevention of diabetes (63), decreasing CRP (64), and having direct antiatherosclerotic effects, with evidence that these agents decrease carotid intima-media thickness (65).

William Harris (Kansas City, MO) presented a study of effects of ω-3 fatty acid treatment in improving cardiac autonomic tone. Plasma ω-3 levels measured ~15 years before were associated with reduced risk of sudden death (66), and in the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico)-Prevenzione study of 11,324 persons treated <3 months after myocardial infarction, 1 g ω-3 polyunsaturated fatty acid decreased total and cardiovascular mortality 14 and 17% over 3.5 years (67). Harris studied 18 men >1 year (17) following myocardial infarction, with ejection fraction <40%, without arrhythmia, treated with an ω-3 preparation composed of eicosapentaenoic acid plus docosahexaenoylphosphatidic acid (810 mg daily) versus placebo in a cross-over study. There was no change in triglyceride or LDL or HDL cholesterol, in CRP, TNF-α, or IL-6 or in measures of large- or small-artery elasticity or blood pressure. The heart rate was consistently reduced by 5 bpm, and the decline in heart rate after exercise was greater, both suggesting increased vagal and/or decreased sympathetic tone, a potential mechanism for reduction in arrhythmia with this treatment.

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References


44. Ridker PM, Buring JE, Cook NR, Rifai N; C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation 107:391–397, 2003


