Second World Congress on the Insulin Resistance Syndrome

Insulin resistance syndrome and nonalcoholic fatty liver disease

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This is the first in a series of articles on the Second World Congress on the Insulin Resistance Syndrome, Universal City, California, 18–20 November 2004.

Yehuda Handelsman (Tarzana, CA) introduced the Second World Congress on the Insulin Resistance Syndrome, noting the importance of ICD-9 diagnostic code 277.7, which allows one to use insulin resistance syndrome as a specific medical diagnosis, although the nomenclature of the syndrome is complex (1). There is a continuous relationship between the number of risk factors and associated conditions and the severity of insulin resistance, so that it may be incorrect to suggest that a specific number of components is needed to determine the presence of this condition, a potential advantage of the American Association of Clinical Endocrinologists diagnostic criteria, which appears to be more strongly associated with diabetes than other criteria for the insulin resistance syndrome.

Gerald M. Reaven (Stanford, CA) discussed the relationship between obesity and the insulin resistance syndrome, noting that mean fat and energy intake increased between 1990 and 2000 from 81 to 86 g and from 1,969 to 2,200 calories daily, respectively, so that "we're getting heavier because we're eating more." Obesity is associated with increased mortality, with insulin resistance the link between obesity and coronary heart disease. Reaven used 3-h somatostatin, insulin, and glucose infusion to measure the steady-state plasma glucose (SSPG), which is inversely related to insulin sensitivity. There is tremendous variability in healthy individuals, with SSPG in 490 people with normal glucose tolerance <50 mg in the 1st and >300 mg/dl in the 10^{th} decile. The lowest quartile of insulin sensitivity is strongly predictive of development of diabetes and of coronary artery disease. Both BMI and waist circumference correlate with SSPG, but "with enormous variation," as some obese individuals have normal and some lean individuals have high SSPG. Physical fitness, as measured by maximal oxygen consumption, is as powerful as obesity in predicting insulin sensitivity. SSPG has little relationship to LDL cholesterol but is strongly associated with abnormal levels of triglycerides, HDL cholesterol, and fasting insulin (2). Comparing insulin-resistant and insulin-sensitive individuals with similar degrees of obesity (BMI $\sim$32 kg/m^2), glucose, cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol are more abnormal in the former group. Weight loss improves insulin sensitivity and reduces inflammatory markers only in individuals who are insulin resistant at baseline.

Reaven addressed the question, "Which is the culprit?" He contrasted the effects of insulin resistance with those of compensatory hyperinsulinemia, stressing the importance of differential tissue insulin sensitivity. In individuals without diabetes, insulin resistance as measured by the SSPG is strongly associated with the day-long circulating insulin level. The degree of suppression of plasma free fatty acids (FFAs) by insulin shows greater responsiveness at lower levels than does the suppression of glucose production, but both are lessened in individuals with higher SSPG, which is the strongest correlate of FFA levels. Insulin resistance may be associated with both high FFAs and high circulating insulin levels, both potentially increasing hepatic triglyceride secretion (and hepatic lipid deposition). Uric acid clearance is also correlated with insulin sensitivity, so that hyperinsulinemia may be associated with hyperuricemia. Comparing women with and without polycystic ovary syndrome (PCOS), testosterone and androstenedione are higher in the PCOS group, with a further increase among those who are insulin resistant, while sex hormone–binding globulin is lower in PCOS, with further lowering among those who are insulin resistant, with what Reaven stated is "an ovary that is responding to insulin by hypersecretion of androgens."

A number of factors underlie the association between insulin resistance and hypertension. A high-sodium diet increases body weight and urine Na, increases atrial natriuretic peptide, and reduces renin and aldosterone levels. Comparing insulin-sensitive and insulin-resistant individuals, the latter excrete less sodium on the high-sodium diet, although with similar aldosterone, renin, and atrial natriuretic peptide levels. Insulin resistance is also associated with increased sympathetic nervous system activity (3), increasing the heart rate and likelihood of developing hypertension. Some of these abnormalities are mediated by hyperinsulinemia, which, although beneficial from the point of view of protection against hyperglycemia, contributes to a number of abnormalities of the insulin resistance syndrome.

Philipp E. Scherer (Bronx, NY) reviewed adipocyte-derived factors and their impact on glucose and lipid metabolism and on inflammation, pointing out that adipocytes are not only fat stores but also the source of a number of hormonal

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Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; FFA, free fatty acid; HCV, hepatitis C virus; MMP, matrix metalloproteinase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PCOS, polycystic ovary syndrome; PPAR, peroxisome proliferator–activated receptor; PUFA, polyunsaturated fatty acid; SSPG, steady-state plasma glucose; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; TZD, thiazolidinedione.

factors. He noted that both excess and deficient fat are associated with insulin resistance, reflecting dysregulation of adipocyte-derived factors as well as abnormality of fat storage. Adipose tissue impacts on energy metabolism, inflammation, infection, and the development of malignancy, with particular importance of local adipose tissue deposits present in the area of malignancy. Adipose tissue has effects on liver, vasculature, muscle, pancreatic β-cells, and brain. The preadipocyte differentiates into a mature adipocyte, producing, among many other cytokines, leptin, adiponectin, resistin, tumor necrosis factor (TNF)-α, interleukin-6, and α1 acid glycoprotein. Although hepatic production is important, C-reactive protein also has substantial production in adipocyte tissue stores.

Adiponectin was not well characterized until 2001. Levels are associated with the degree of insulin sensitivity and are higher in females, lower in obesity (and lipodystrophy), decreased by inflammatory stimuli, increased in type 1 diabetes, decreased in type 2 diabetes and in individuals with cardiovascular disease, and increased by the thiazolidinedione (TZD) peroxisome proliferator–activated receptor (PPAR)γ agonists. Adiponectin mutations and polymorphisms are associated with diabetes and cardiovascular disease. Chromosomal locus 3q27 codes for adiponectin and appears to be associated with insulin resistance and risk for type 2 diabetes. Adiponectin-null mice show evidence of increased atherosclerosis; in humans, higher levels of adiponectin are associated with lower myocardial infarction risk (4). Adiponectin has a number of antiatherosclerotic properties, suppressing the endothelial inflammatory response, decreasing vascular smooth muscle proliferation, decreasing vascular cell adhesion molecule-1 expression, and suppressing conversion of macrophages to foam cells. Thus, adiponectin may be anti-inflammatory and may offer a connection between the insulin resistance syndrome and atherosclerosis.

Adiponectin exists as a trimer, which assembles into hexamers and multimers; the complexity of its circulating forms have made it difficult to determine its physiologic effects. When acutely infused, adiponectin increases hepatic insulin sensitivity and potentiates insulin-induced suppression of hepatic glucose production. This may be one of the mechanisms of the insulin-sensitizing effect of PPARγ activation, although the change in adiponectin with various PPARγ agonists is not strongly related to their degree of glycemic effect. High–molecular weight adiponectin may be the metabolically responsive form of the protein, and specific measurements of this form appear to be required to accurately determine the relationship of adiponectin to insulin action and to assess the effect of TZDs.

There is, however, little correlation of the high–molecular weight forms of adiponectin with peripheral glucose uptake. Scherer suggested that the measurement of the high–molecular weight form of adiponectin may allow early assessment of whether a given person will have clinical glycemic response to TZD treatment. In animal models of overexpression of adiponectin to an extent similar to that seen with TZD treatment, hepatic insulin sensitivity is increased and postprandial triglycerides are decreased, in association with increased LPL activity. Mice lacking adiponectin, in contrast, have decreased hepatic insulin sensitivity and reduced response to administration of TZD. These mice fail to upregulate hepatic adenosine monophosphate kinase with TZD treatment. Although there are also non-adiponectin factors in TZD action, adiponectin appears to be an important global indicator of insulin sensitivity and could, Scherer suggested, become as important as HbA_{1c} in clinical assessment.

In a mouse insulin resistance model with fat apoptosis through triggered activation of caspase (FAT-ATTAC), insulin sensitivity improves. Addressing the question of the systemic versus local contribution of fat to inflammation, the FAT-ATTAC mouse has reduced levels of inflammatory mediators. Scherer noted that macrophages present in adipose tissue play a major role in elevating circulating levels of interleukin-6 and other inflammatory mediators, but noted that it must be adipocytes themselves that have the proinflammatory effect of macrophage activation, suggesting "intense cross talk between the adipocyte and the macrophage," so that the inflammatory effect of adipocytes appears to be basic.

Nonalcoholic fatty liver disease

Under cosponsorship with the American Association for Study of Liver Disease, a symposium was held addressing the complex interrelationship between insulin resistance and hepatic steatosis (5–8). Nathan M. Bass (San Francisco, CA) discussed definitions, epidemiology, and the public health impact of the syndrome. There is debate as to whether the presence of fat in the liver may be a physiologic phenomenon. In some vertebrate species, hepatic fat is regulated and plays an important role, as in certain fish using hepatic fat for adjustment of buoyancy. The presence of fat in >5% of hepatocytes in humans is indicative of pathologic fatty liver.

In humans, fatty liver, regardless of cause, can lead to cirrhosis and can be an important cause of morbidity and mortality. Nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) have only been recognized since 1980 (9). This is a clinicopathologic condition typically seen in obese individuals with type 2 diabetes, with histology consistent with alcoholic hepatitis in the absence of significant alcohol use, although the exact meaning of "significant" is uncertain, with some alcohol-related disease presumably misclassified as NAFLD (and perhaps, conversely, some NAFLD incorrectly considered alcohol related) (10). Alcohol intake should be reported in assessing whether a person has NAFLD, with suggestions that none, one or less, two, or even three alcoholic beverages daily are compatible with the diagnosis; most authorities would accept no more than 14 alcoholic drinks per week in men and 7 in women.

Fat, inflammation, necrosis, Mallory's hyaline, and ultimately the development of ballooning and fibrosis are seen histologically. Nonalcoholic fatty liver refers to simple fat (steatosis) without inflammation, necrosis, or fibrosis and is largely benign. NASH is associated with evidence of injury with ballooning, inflammation, and fibrosis, and NAFLD refers to the entire spectrum of disease. NASH-cirrhosis represents the end stage, ultimately with fat no longer present and a "cryptogenic cirrhosis" pattern. Individuals with NAFLD have a high prevalence of obesity, diabetes, and hyperlipidemia (11). Other hepatic conditions similar to NAFLD include nutritional disorders, such as that following jejeunoileal bypass, total parenteral nutrition, or rapid weight loss, inborn metabolic errors, such as fatty acid oxidation defects, carnitine defects, and urea cycle defects, metabolic diseases including lipodystrophy and abetalipopro-

teinemia, and toxicities including those caused by glucocorticoids, tamoxifen, amiodarone, and aspirin (Reye's syndrome).

Twenty to 77% of individuals with NAFLD have no symptoms, 25–48% experience right upper-quadrant pain, and 50–75% complain of fatigue. The examination is normal in 19–30%, shows hepatomegaly in 25–50%, and reveals signs of hepatic decompensation in <10% of patients. Usually the alanine transaminase (ALT) exceeds the aspartate transaminase (AST) level, and the converse occurs in advanced disease or with a component of alcoholic liver disease. The alkaline phosphatase is usually normal. Serum iron and ferritin may be elevated but without evidence of iron overload. Sonography shows a "bright liver," computerized tomography shows lower density of the liver than the spleen, and magnetic resonance imaging shows T1 phase shifting. Although liver biopsy is the "gold standard" for diagnosis and probably should be used for enrolling patients in therapeutic trials, clinical indications for biopsy are controversial, as 96% of asymptomatic individuals with negative autoimmune and viral markers, abnormal liver enzymes, and fatty liver on ultrasound have NAFLD (12); Bass suggested that individuals with unexplained ALT/AST elevation and/or hepatic steatosis on imaging, with little or no alcohol intake, should be categorized as having "suspected" NAFLD.

The prevalence of NAFLD varies from 3 to 20% of the population based on elevated transaminase and from 16 to 19% based on ultrasound screening. Autopsy series suggest that 11–36% of the population has NAFLD. NASH is present in 1.2–4.8%, and 0.15–0.37% have cirrhosis. The prevalence of NAFLD is considerably higher in obese individuals, with weight appearing to be synergistic with alcohol in causing fatty liver. Similarly, NAFLD is more prevalent among individuals with type 2 diabetes. There are ethnic differences, with African Americans and Hispanics having two- to threefold greater prevalence of NAFLD. Over 3–9 years of follow-up, approximately one-third progress, with perhaps half this number ultimately developing cirrhosis. Age, diabetes, and obesity predict the development of fibrosis. The high population prevalence of NAFLD contrasts with that of hepatitis C (~2% of the population). All other forms of liver disease have much lower prevalence, so that NAFLD constitutes by far the largest population grouping with liver disease. Bass noted that "cryptogenic cirrhosis," likely the end stage of NAFLD, is the third most common diagnosis in individuals having liver transplantation, as well as being associated with hepatocellular carcinoma, and concluded that some 10–20% of individuals with NAFLD experience adverse consequence of liver disease.

Arthur McCullough (Cleveland, OH) discussed aspects of the relationship between insulin resistance and hepatic steatosis, suggesting that the disease involves two pathogenic abnormalities, with both the presence of insulin resistance and that of FFAs and adipokines required for hepatic fat deposition. Individuals with NAFLD have the same degree of insulin resistance as those with type 2 diabetes, both in terms of peripheral glucose disposition and of suppression of lipolysis, although there is increased hepatic FFA flux and triglyceride synthesis (8,13). An important question is the direction of the causal relationship between NAFLD and insulin resistance.

NAFLD is seen in 50–70% of individuals with type 2 diabetes and in 95% of those who are obese. Hepatic LPL overexpression increases liver fat and attenuates insulin-induced suppression of basal hepatic glucose production. In a canine model, increasing dietary fat intake increases omental, subcutaneous, and presumably hepatic fat deposition, in association with hepatic insulin resistance, although not with resistance to peripheral glucose uptake. In a population-based study of >2,000 individuals having magnetic resonance spectroscopy, more than one-third of the population had evidence of elevated hepatic triglycerides (14), with 30% of these individuals (as opposed to 8% of those without increased liver fat) having insulin resistance syndrome, suggesting insulin resistance to be the primary factor. Other studies have shown increases in body weight to precede the development of NAFLD, again suggesting insulin resistance to be the primary abnormality.

Addressing the mechanism of the relationship between insulin resistance and hepatic steatosis, lack of suppression of lipolysis may increase influx of fatty acids to the liver, leading to increased hepatic triglycerides. Adiponectin levels are decreased with NAFLD, and the level of adiponectin is inversely correlated with hepatic fat content. An interesting observation is that adding insulin to peritoneal dialysis fluid may cause a form of hepatic steatosis occurring on the surface of the liver, suggesting high local insulin levels to contribute to development of NAFLD (15). A number of studies have been performed with insulin sensitizers, with evidence that there may be benefit with metformin (16), and that rosiglitazone decreases hepatic steatosis as well (17), with metformin appearing of less benefit than rosiglitazone, perhaps correlating with the increase in adiponectin with the former but not the latter agent (18).

Arun J. Sanyal (Richmond, VA) further discussed the pathogenesis and mechanisms of development of steatohepatitis (19), addressing the question of whether the basic abnormality is accumulation of fat via increased production or decreased export, with evidence that apolipoprotein B synthesis is decreased in NASH, suggesting the latter (20), and that there may be increased de novo hepatic lipogenesis in NAFLD (21), which favors the former explanation. Recognizing that increased substrate can contribute to increased lipogenesis, Sanyal noted that fructose can be particularly dangerous in bypassing intracellular regulatory steps and directly increasing triose phosphate levels. He pointed out that there has been increasing fructose intake over the past 4 decades, correlating with population weight gain (22) and with the increasing prevalence of NAFLD.

In hepatic steatosis there is down-regulation of the effect of the insulin-sensitive transcription factor sterol regulatory element–binding protein-1c in increasing acetyl CoA disposition to synthesis of cholesterol rather than triglycerides. This is regulated by liver X receptor-α, suggesting a role of PPARγ, which has potential cross talk with liver X receptor. The "two-hit" hypothesis states that some individuals develop NASH, while others only show increased hepatic fat deposition, because of the effect of oxidative stress, which may be caused by mitochondrial dysfunction, cytochrome p450 activation, peroxisomes, and/or iron overload. Mitochondrial structural abnormality, with depletion of mitochondrial DNA and abnormality of the electron transport chain (13), has been shown to exist in NASH, with consequent evidence of decreased hepatic ATP stores

(23). Mallory bodies, the classic pathologic markers of alcoholic and nonalcoholic fatty liver disease, represent heat-shock protein colocalized with ubiquitin, which is a peptide that functions as a marker for intracellular protein transport and degradation and is produced in response to oxidative stress (24). There is additional evidence that NASH is associated with increased apoptosis (25), with increased expression of cytokines such as TNF-α (26), of leptin in causing hepatic fibrosis (27), and of the interrelationship between inflammation and insulin resistance.

Christopher Day (Newcastle, U.K.) discussed the role of genetic factors in the progression of NAFLD. The well-established risk factors of obesity, insulin resistance, hypertriglyceridemia, etc., are well-known, with the number and severity of risk factors predicting severity of NAFLD. However, only a minority (<20%) of individuals with risk factors develop NASH (i.e., more than steatosis). Responsible factors might include dietary saturated fat and deficient levels of dietary antioxidants (28), exercise levels, small intestinal bacterial overgrowth (as seen following jejeunoileal bypass [29]), or even episodic hypoxia, potentially explaining the association between NASH and sleep apnea. Genetic factors are suggested by family clustering (30), by twin studies showing steatosis on CT scanning, and by ethnic differences, although it is uncertain whether there are specific NASH genes rather than obesity/type 2 diabetes genes. Candidate gene association studies have been carried out, with some evidence of association with 11-β-hydroxysteroid dehydrogenase, the insulin receptor, and PPAR genes. Antioxidant genes may be abnormal in the syndrome, and there may be gene abnormalities causing excess hepatic fat. Microsomal triglyceride transfer protein, which plays a role in the synthesis and secretion of VLDL particles, may be another factor, with some evidence of a promoter region polymorphism associated with NAFLD. Other studies suggest a cholesterol ester transfer protein polymorphism to be associated with NAFLD.

Endotoxin plays a role in alcoholic liver disease, and the development of NASH in individuals undergoing jejeunoileal bypass with creation of a blind loop of bowel, which could be prevented with antibiotics, suggests this as a potential contributory factor. Polymorphisms in the endotoxin lipopolysaccharide toll-like receptor (TLR)4 may reduce inflammatory responses to endotoxin and appear to be risk factors for NASH. NOD2 is a cytosolic protein expressed by monocytes, with gene mapped to chromosome 16q12, functioning as an intracellular receptor for lipopolysaccharide. NOD2 polymorphisms are associated with Crohn's disease, perhaps via impaired gut mucosal innate immune response favoring chronic bacterial overgrowth. Day showed that individuals with polymorphisms in NOD2, in TLR4, and in both have 2.3-, 4.1-, and 37-fold increases, respectively, in risk of development of NASH.

Genes causing excess hepatic fibrosis may be related to development of NASH, with candidates including adipocytokines such as leptin, adiponectin, angiotensin, transforming growth factor (TGF)-β, and matrix metalloproteinases (MMPs). TGF-β and angiotensinogen polymorphisms are associated with greater likelihood of NASH in individuals undergoing obesity surgery. Day summarized his presentation by presenting the concept that NASH is caused by environmental factors including alcohol, obesity, and small bowel bacterial overgrowth and by genetic factors such as cholesterol ester transfer protein increasing hepatic fat. Further genetic factors such as TLR4 and NOD2 may mediate the transition from steatosis to steatohepatitis, and polymorphisms in TGF-β and other profibrotic genes may be involved in progression from steatohepatitis to cirrhosis.

Stephen H. Caldwell (Charlottesville, VA) discussed diagnostic and management strategies for the assessment of NASH. Elevations in aminotransferases are important markers, as discussed by Bass. Normal aminotransferases, however, may be seen in individuals with severe histological abnormality, and insulin sensitizers may normalize transaminase levels without resolving residual injury such as fibrosis. Hyperferritinemia is also common; it is elevated in 30–40% of patients with NASH and associated with the degree of fibrosis, perhaps reflecting oxidative stress. Hepatic ultrasound may be limited by lack of sensitivity to hepatic fat below the 20–30% level and is unable to detect fibrosis, ballooning, or Mallory bodies. Fibrosis markers include blood collagen VI, procollagen III, TGF-β, MMP, and tissue inhibitor of MMP, but these are not reliable in detecting mild degrees of disease. Magnetic resonance spectroscopy remains investigational but offers the potential to give a variety of biochemical parameters of liver function. Caldwell suggested that liver biopsy may be used to confirm the diagnosis and stage of injury, to address medication issues, to avoid the limitations of surrogate markers such as transaminases, and for assessment of populations with a significant burden of disease. Forms of NAFLD are those with fat alone (type 1), fat and inflammation (type 2), bridging fibrosis (type 3), and cirrhosis with regenerating nodules (type 4), although small sampling size may limit the accuracy of a biopsy, with a study of correlation between two simultaneous 3-cm core biopsies suggesting that these are inaccurate in ~10% of cases. A number of clinical findings should be sought in determining whether a patient has cirrhosis, including palmar erythema, spider angiomata, splenomegaly, and platelet levels near or below 150,000. If cirrhosis is present, treatment may need to be changed, recognizing for example that fatigue may represent encephalopathy, that ACE inhibitors may worsen fluid retention with ascites, and that screening may be needed for hepatocellular carcinoma and for esophageal varices.

A number of therapeutic strategies have been proposed for NASH. Early therapy at the steatohepatitis stage, with goals of normalization of aminotransferases, reduction in liver fat content on ultrasound or other imaging studies, or, for research, histological improvement. Lifestyle modification approaches include exercise and weight loss with diet, medications, or surgery. Conditioning exercise in individuals with NASH alters the lactate threshold and improves insulin sensitivity (31). In a small study of individuals with NAFLD, ALT and insulin sensitivity improved with this approach (32). A study of weight with orlisat showed reduction in steatosis, although not in fibrosis (33). Surgical weight loss has been shown to be effective in NASH (34), although Caldwell noted that caution is needed because rapid weight loss may cause NASH (35).

Several pharmacological agents have been studied as potential NASH treatments. Dietary polyunsaturated fatty acid (PUFA) supplementation may increase insulin sensitivity, and in animal models decrease sterol regulatory element–

binding protein-1 and hepatic fat content. Caldwell described a report of the effect of administration of 1 g PUFA daily suggesting a decrease in hepatic fat on ultrasound, although noting that there is a potential adverse interaction of PUFA with alcohol in worsening NASH and that there are potential hepatotoxic effects of the PUFA linoleic acid. Ursodeoxycholic acid has hepatic anti-inflammatory effects and reduces ALT and steatosis, although not fibrosis or inflammation. A controlled trial performed in 168 patients with NASH did not show benefit, although not conclusive (36). Vitamin E may have benefit (37), and there are studies suggesting beneficial effects of the alkaloid betaine, which is found in sugar beets (38).

There has been great interest in treatment of NASH with insulin-sensitizing agents. Metformin has been shown to ameliorate NASH in *ob/ob* mice (39) and humans (16). There is increasing evidence of the benefits of TZDs. Administration of rosiglitazone leads to a decrease in hepatic fat as measured with magnetic resonance spectroscopy (40). Similar studies have shown benefit of administration of troglitazone (41) and pioglitazone (42), and a study comparing rosiglitazone with metformin suggests that the former leads to greater benefit in NASH (17). In addition to allowing mobilization of hepatic fat, TZDs may alter fibrosis as well (43). A National Institutes of Health–sponsored clinical trial of treatment with these agents is in progress.

Joel Lavine (San Diego, CA) discussed the spectrum of NAFLD in children, which is seen more frequently in boys than in girls and more in Hispanic and Caucasian than African-American children. The vast majority of children with NAFLD have BMI exceeding the 95th percentile. In a San Diego county population-based prevalence study of 278 children ages 2–19 years who died suddenly from homicide, suicide, or accident, fatty liver was present in 17% of 8–19 year olds, 19% in boys and 12% in girls, with somewhat higher prevalence among Hispanic children and modest correlation with subcutaneous abdominal fat. Acanthosis nigricans and hepatomegaly are typically found on examination, and an echogenic liver on ultrasound. In Lavine's clinical series, the mean ALT was 129 IU/l, AST 77 IU/l, alkaline phosphatase 201 IU/l, triglycerides 218 mg/dl, and insulin 41 μU/ml. Lavine contrasted two different patterns of NASH, both containing hepatic steatosis: the "adult type" with ballooning degeneration, peri-sinusoidal fibrosis, and lobular inflammation versus the "pediatric type," which lacks these features, has more steatosis, and has portal inflammation and fibrosis. He noted that effective therapies in adults may not be appropriate for children. At present, he recommended lifestyle modification, with obesity the main therapeutic target.

Sanyal concluded with a discussion of the interactions between NAFLD and hepatitis C virus (HCV). There are several different HCVs (44); genotype 3 is more associated with hepatic steatosis than the common type (~80%) in the U.S., genotype 1 (45). Individuals with both HCV and NAFLD are typically obese, with hypertension, diabetes, and hypertriglyceridemia, suggesting that their NAFLD is simply related to its prevalence in the population of individuals with insulin resistance. HCV genotype 3 infection may decrease VLDL secretion, accounting for hepatic fat accumulation, with the HCV core protein altering retinoid X receptor–related gene expression by increasing conversion of retinoic acid to *cis*-9 retinoic acid, which is the natural ligand for retinoid X receptor. HCV also may induce insulin resistance by serine phosphorylation of insulin receptor substrate-1 via a TNF-α–mediated pathway (46). In many studies, steatosis is associated with increased HCV fibrosis, particularly in overweight individuals, perhaps mediated by an insulin-induced increase in collagen formation. Hepatic steatosis is associated with lesser response to anti-HCV therapy (47), perhaps because insulin blocks interferon-induced suppression of HCV replication, so that insulin sensitizers may improve the response of individuals with both conditions to therapy.

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