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The kidney, the liver, and insulin resistance

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This is the third of four articles summarizing presentations at the seventh World Congress on the Insulin Resistance Syndrome, held in San Francisco, California, on 5–7 November 2009. This article pertains to the kidney, the liver, and insulin resistance.

The kidney and insulin resistance

Eberhard Ritz (Heidelberg, Germany) discussed insulin resistance (IR), metabolic syndrome, and the kidney, noting that obesity, which causes IR, is currently at epidemic levels and begins in childhood. Ritz also pointed to the association of obesity with hypertension, dyslipidemia, diabetes, and a variety of complications. Chronic kidney disease (CKD) is associated with obesity (1), with a BMI >25 kg/m^2 in young adulthood tripling the risk of subsequent CKD (2) and end-stage renal disease (3) in a fashion comparable with the more recognized association of obesity with coronary disease. Both high and low birth weight also increase CKD risk (4) since intrauterine growth retardation is a risk factor for decreased renal function among young adults (5). The effect of obesity varies with ethnicity as seen with CKD beginning to increase at a BMI of 22 kg/m^2 among Japanese subjects (6).

The link between obesity and end-stage renal disease appears in part due to diabetes and hypertension (7), but there are also the direct effects of overweight on the kidney (8). Proinflammatory and growth-promoting cytokines associated with obesity might have direct adverse renal effects (9). A mechanism may be the association of obesity and IR with hyperfiltration (10) and the consequent renal damage based on sodium excess, which may cause glomerulomegaly and may be in part an effect of IR. Ritz noted that exogenous insulin does not directly cause these effects (11). Obesity is associated with increased intraglomerular pressure, which increases the filtration fraction (12). Weight loss with bariatric surgery in morbid obesity decreases the glomerular filtration rate and renal plasma flow and reduces albuminuria (13). Renal sensitivity to aldosterone increases in the setting of inflammation and oxidative stress, additional potential causative factors, with adipocyte-derived factors exacerbating podocyte injury from aldosterone overproduction (14), which can be inhibited by aldosterone antagonists such as eplerenone (15). The increased activity of 11-β hydroxysteroid dehydrogenase type 1 in IR and type 2 diabetes leading to increased cortisol action may also play a role. IR is associated with increased total body sodium and with sodium-sensitive hypertension. The sodium reabsorption due to insulin is not, however, lessened by IR, which blocks insulin-induced vasodilation and leads to elevation in blood pressure. Low adiponectin levels may increase albuminuria and oxidant stress in a fashion amplified by diabetes (16). There is evidence that decreased telomere length, indicative of tissue aging, is potentiated in adipose tissue by obesity (17).

The finding of a correlation between waist circumference and albuminuria (18) has led to the notion that visceral fat is particularly injurious to the kidney (19) since the waist-to-hip ratio is superior to BMI as a predictor of CKD risk (20). Metabolic syndrome is associated with renal insufficiency (21). The number of metabolic syndrome factors is associated both with microalbuminuria and CKD (22) and with diabetic nephropathy in individuals with type 1 diabetes (23).

Even very early abnormalities of glucose metabolism that do not reach impaired glucose tolerance/impaired fasting glucose are associated with renal insufficiency (24). A number of pathological features characterize the kidney in obesity (25), including glomerular hypertension, endothelial dysfunction, vasoconstriction, and expansion of mesangial matrix (26). Obesity is associated with reduced podocyte number, segmental glomerulosclerosis, glomerulomegaly, and interstitial and arterial abnormalities (27). Obesity is also associated with renal cancer, nephrolithiasis (28), and focal segmental glomerulosclerosis. There is evidence that obese individuals with IgA glomerulonephritis have poorer outcomes (29).

Urate, fructose, and insulin resistance

Richard Johnson (Denver, Colorado) discussed uric acid, fructose, and the metabolic syndrome, which are the subjects of his book for the general public entitled "The Sugar Fix." He noted that the increase in obesity in the U.S. began in the 1800s (30); that the prevalence of hypertension increased from 10% in 1939, to 25.3% in 1975, 28.9% in 1990, and 31.3% in 2000; and that there has been a dramatic increase in diabetes in the U.S. (31). In Kuwait, 40% of adults have diabetes and there has correspondingly been a tremendous increase in cardiovascular disease (CVD). Angina was rare in the 1880s, with coronary artery disease first described in 1911, but it became increasingly common in the U.S. in the 1920s. According to Johnson, there were only 500 cardiologists in the U.S. in 1950, and today there are more than 30,000. Cardiovascular mortality has recently decreased somewhat, not because of the reduction in CVD but rather because of improvements in the late-stage treatments of the disease.

The notion of a relationship between diet and CVD has developed over the past century. Ancel Keys addressed a potential mechanism by reviewing the data from a well-known study of the ef-

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fects of dietary fat in seven countries (32). Certainly low-fat diets reduce cholesterol, Johnson commented, but these diets "really don't work" in comparison to control diets, as shown in the huge (nearly 50,000 subjects) Women's Health Initiative Randomized Controlled Dietary Modification Trial (33). A possible mechanism is the relationship of sugar intake to CVD. Haven Emerson, an early exponent of novel approaches to public health, presented data in the early 1900s showing that the prevalence of diabetes in New York had increased from 2.8 to 19 cases per 100,000. There have been parallel increases in obesity and dietary sugar, and Johnson pointed in particular to the effects of high dietary fructose, with the metabolism of fructose by fructokinase not under feedback inhibition by ADP and depending ATP while increasing levels of AMP, which in turn increases uric acid. Fructose also increases triglyceride levels (34).

An association of hyperuricemia with hypertension has long been recognized and Johnson cited an article from 1879 that stated "people who are subject to this high blood pressure…frequently belong to gouty families" (35). It has been suggested that hyperuricemia might be caused by obesity or by factors related to IR, but Johnson discussed the idea that there may be a causal relation of urate to CVD. Most mammals have low levels of urate because of the enzyme urate oxidase (uricase), which is not expressed in man. When rats are given an uricase inhibitor, their blood pressure increases, an effect blocked with allopurinol. Urate has prooxidant intracellular effects, which reduce nitric oxide levels, stimulate the renin-angiotensin-aldosterone system, and induce renal microvascular lesions independent of blood pressure. Renal microvascular disease induces sodium-sensitive hypertension. In animals fed a low salt diet, an uricase inhibitor increases blood pressure and leads to the development of sodium-sensitive hypertension (36). A number of studies show urate levels to be risk factors for hypertension (37). This, Johnson noted, occurs most commonly in cases of newly diagnosed hypertension. Indeed, children with newly diagnosed hypertension have high urate levels (38). Furthermore, when newly diagnosed hypertensive adolescents were treated with allopurinol, two-thirds (86% of those whose uric acid level was <5 mg/dl, perhaps reflecting a group with better adherence) became normotensive (39). Johnson speculated that uric acid reduces nitric oxide and decreases skeletal muscle microvascular blood flow with consequent decreases in glucose uptake, which contributes to IR. Urate also induces a diabetic phenotype in adipocytes (40). In Johnson's studies, allopurinol improved insulin sensitivity, lowered triglycerides, and reduced weight gain.

As might be expected, Johnson said urate is a risk factor for diabetes (41). He suggested that metabolic syndrome is a disease, and the increase in urate over the past century has contributed to the prevalence of the disease. He presented data from a study of 76 men given 200 g fructose daily for 2 weeks, which increased blood pressure and triglycerides and reduced hormone-sensitive lipase and insulin sensitivity. Administration of allopurinol prevented the increase in blood pressure and the development of metabolic syndrome. Fructose may have been a survival factor in aiding hominids to develop IR, allowing adaptation to starvation without giving rise to high urate—but this is not relevant in men on a high sodium, high purine, high fructose diet with elevated levels of urate. According to Johnson, fructose now comprises 15–25% of the U.S. diet and may be the driving force leading to CVD.

Nonalcoholic fatty liver disease and IR

Arun Sanyal (Richmond, Virginia) discussed nonalcoholic fatty liver disease (NAFLD), characterized by nonalcoholic steatohepatitis (NASH), hepatocyte injury, inflammation, fibrosis, and cirrhosis. Steatohepatitis is not simply a combination of fat and inflammation, but involves specific abnormalities including cytologic ballooning, Mallory bodies composed of eosinophilic material, and pericellular fibrosis. We are just beginning to understand the underlying processes causing tissue repair that leads to resolution in some and disease progression to cirrhosis in others (~15–20% of patients) with mechanisms of hepatic fibrosis including oxidative and cytokine stress activating stellate cells, potentially with a fibrosis-increasing effect of insulin. The liver has high regenerative capacity, and the role of hepatic stem cells is being explored.

Hepatic fat in NAFLD is predominantly triglycerides made up of n-7 fatty acids with decreases in the n-3 and n-6 precursors, which perhaps reflect abnormalities of intrahepatic metabolism with increased utilization of arachidonic acid and production of proinflammatory lipoxygenase products (42). This suggests increased stearoyl CoA desaturase activity under the influence of hyperinsulinemia, which is not downregulated in IR. The balance of fat synthesis and import against utilization and export determines hepatic fat content (43) so that the histologic findings of a fatty liver may be regarded as representing the protective responses to large amounts of potentially toxic fatty acids entering the liver. Transcriptional regulation of this process include the nuclear receptors liver X receptor, farnesoid X receptor, and the peroxisome proliferator–activated receptors, which in turn are regulated by insulin, adiponectin, tumor necrosis factor-α, resistin, and many other cytokines, which Sanyal summarized as being "anything but simple!"

A potentially important finding in NAFLD has been an increase in hepatic free cholesterol, perhaps produced by upregulation of hydroxymethylglutaryl-CoA reductase and sterol regulatory element–binding protein 2, related to downregulation of the microRNA mir122 (44) and inducing apoptosis. Free cholesterol is usually esterified to cholesterol ester. In NAFLD, reverse esterification of cholesterol ester to free cholesterol occurs with a reduction in the export of free cholesterol to LDL because of decreased LDL-receptor levels, while the conversion of free cholesterol to bile acids is downregulated. There is also downregulation of cholesterol efflux via the transport systems ATP-binding cassette A1 and G1, creating "a perfect storm" for exacerbating liver injury.

Further mechanisms of hepatocyte injury include oxidative stress (45), reflecting increased lipid peroxidation from mitochondrial dysfunction, iron overload, and perhaps reduced antioxidative defense mechanisms. Abnormalities of mitochondria in NAFLD are seen with paracrystalline inclusions on microscopy, suggesting a defective electron transport system leading to increased free radical expression. Lipid-induced apoptosis leads to ceramide accumulation, causing further apoptosis (46,47). The unfolded protein response, a cellular process occurring with overload of the endoplasmic reticulum, occurs in states of high protein synthesis and inadequate ATP availability and leads to an adaptive response with decreased protein synthesis and increased

protein degradation. In NAFLD, the inositol-requiring enzyme-1 pathway mediating this process shows particular abnormality in ~20% of patients. These patients may comprise the subset with the increased likelihood of progression to cirrhosis as reduction in protein synthesis appears to promote recovery while increased protein degradation leads to further cellular toxicity. This may be mediated by two other microRNAs, mir-34A and mir 451 (45).

Jeff Schwimmer (San Diego, California) discussed clinical consequences and diagnostic challenges in NAFLD, distinguishing fatty liver from NAFLD and, in turn, NAFLD from NASH. NAFLD includes a spectrum of disorders ranging from steatosis to steatohepatitis with or without degrees of fibrosis extending to cirrhosis. Most children with NAFLD are overweight or obese. Analysis of liver histology from >1,000 autopsy specimens mainly obtained after motor vehicle accidents showed the presence of NAFLD in ~10% at age 10–14 years and 18% at age 15–19 years. There was a greater frequency in boys than girls and a lower frequency in blacks and a somewhat higher frequency in Hispanics than in whites and Asians. Of those with NAFLD, 60% were obese, 20% overweight, and 20% normal weight (48). Short of histology, with fatty liver defined by >5% fat content (normal liver fat content is 1%), clinical testing is imperfect. Although alanine transaminase (ALT) tends to be elevated in NAFLD, and the majority of obese adolescents with ALT >35 have fatty liver (based on magnetic resonance imaging [MRI]) and the majority of obese adolescents with ALT <35 have a normal MRI (49), Schwimmer noted, "Being obese and having an elevated ALT does not automatically equal NAFLD." Further, MRI studies show that "the ability to distinguish none from mild [on ultrasound] is actually quite poor" (50,51). MRI assessment of liver fat, although useful, requires high technical accuracy that may not be achieved in all clinical settings. Cytokeratin-18 fragment, derived from a cysteine endopeptidase playing a role in regulating inflammation and apoptosis, appears to be a good marker of NASH (52), although Schwimmer commented that "this is not perfect technology yet." A NAFLD fibrosis risk score has been proposed using age, BMI, diabetes, ALT, aspartic acid transaminase (AST), platelets, and serum albumin level (53), and there is evidence that this can be made more accurate with measurements of procollagen III and hyaluronic acid levels (54).

Given these caveats, it is important to realize that NAFLD is associated with adverse prognosis (55). Age-standardized mortality is fourfold greater in subjects with NAFLD based on liver biopsy; diagnosis based on ALT testing is associated with ~1.5-fold increase in mortality (56). This does not reflect liver disease alone. Controlling for obesity, there is a strong association of NAFLD with metabolic syndrome factors (57), the development of diabetes (58), coronary artery disease mortality (59), and death from malignancy.

Nathan Bass (San Francisco, California) discussed two current approaches to the treatment of NASH, both based on its hepatic prognosis, to prevent progression to cirrhosis (at which point hepatic fat may be reduced) and hepatocellular carcinoma. Because of this association and the potential causative relationship of NAFLD with CVD, Bass discussed recognizing that NASH worsens hepatic IR. NAFLD affects 12–15% of the U.S. population, 82% (~30 million individuals) with fatty liver alone, 16.4% (~6 million) with NASH, and 1.6% (~600,000) with cirrhosis. Over time, approximately 15–30% of individuals with NASH progress to cirrhosis. The presentation is typically with an incidental finding of elevated AST/ALT or with fatty liver on abdominal imaging, but patients may present with a complication of cirrhosis. Biopsy is useful in determining the grade and stage of NAFLD, allows greater confidence in diagnosis, and may motivate the patient to lose weight and guide intervention. Biopsy is needed for participation in a treatment trial. There is, however, some risk, and biopsy may be inaccurate because of sampling error. Furthermore, noninvasive diagnosis is relatively accurate, and the natural history of NAFLD is benign in most individuals, with no established treatment beyond standard lifestyle interventions. Bass suggested that biopsy be performed on subjects with age >45 years, diabetes, AST > ALT or ALT >three- to fivefold above the upper limit of normal, or difficulty excluding other diagnoses in individuals who are not obese and do not have metabolic syndrome. Iron overload, findings suggesting cirrhosis, and support of a major treatment decision such as bariatric surgery would be additional indications.

The standard of care includes treatment of dyslipidemia, hypertension, and diabetes. Bass suggested that patients be monitored for ALT, AST, alkaline phosphatase, bilirubin, albumen, prothrombin time, platelet count (which he termed a "foolproof early warning marker") or cirrhosis, and abdominal ultrasound, and that patients be referred if there is evidence of marked hepatic dysfunction. Patients with NASH should avoid excessive acetaminophen, tamoxifen, amiodarone, occupational solvents, iron supplements, and vitamin A (in the absence of deficiency). Some supplements, including milk thistle, S-Adenosylmethionine (SAMe), and betaine, appear safe. Although alcohol, cannabis, and tobacco should not be used, modest wine drinking is associated with decreased prevalence of suspected NAFLD, which Bass thought "is going to be very interesting." Statins are considered safe, and of course may be beneficial, based on a number of studies in NAFLD.

According to Bass, specific interventions are based on the notion that progression of NAFLD is due to "two hits" of steatosis followed by many different sequential steps, such as oxidative stress causing inflammation and leading to fibrosis, which in turn gives rise to cirrhosis. He considered NAFLD "the hepatic component of the metabolic syndrome," for which lifestyle modification is appropriate. In a review of 10 studies of 626 patients, although only 123 had sequential biopsy, strong evidence of stabilization or reversal of fibrosis was lacking with any intervention (60). In a study of 50 patients following a 1,500 calorie diet and treated with vitamin E plus orlistat, orlistat was not associated with greater weight loss or other benefit. Those patients with >4% weight loss did show improved insulin sensitivity and reduction in steatosis on biopsy at entry and at 36 weeks. Those with >8% weight loss also showed improvement in ballooning and inflammation. Although lack of physical activity is undesirable, there is no evidence that this is effective as an intervention. Bariatric surgery has been of interest. Malabsorptive procedures such as jejunoileal bypass are no longer used and worsen liver disease, but restrictive and Roux-en-Y tend to have favorable effects with improvement in fibrosis in 66% and in fat and inflammation in 81% (61). No pharmacologic treatment has been found effective in long-term treatment. Bass noted "the other confounding factor is that there is a 15–30% placebo effect." Initial studies of treatment with met-

formin were encouraging, but there is no evidence of improvement in histology. There is experimental evidence that thiazolidinediones improve fibrosis, and clinical studies suggest improvement in liver enzymes (62). Although pioglitazone led to greater reduction in steatosis and ballooning necrosis than placebo, there was no clear reduction in fibrosis. Bass described a recently completed study of 247 patients with biopsy-proven NASH randomized to pioglitazone (30 mg), vitamin E, or placebo for 96 weeks. In the study, ALT and AST improved with both active treatments and IR improved with pioglitazone, but there was weight gain with pioglitazone and histologic improvement was greater with vitamin E. Neither significantly improved fibrosis (63). IR, then, is important, "but not the whole story," said Bass. Other hepatoprotective strategies must be explored, with "fibrosis … a tough end point but … the one that matters most," he said.

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