

# Viewpoints on the Way to a Consensus Session

## Where does insulin resistance start? The liver

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### THE CENTRAL ROLE OF THE LIVER

— Insulin resistance and the insulin resistance syndrome refer to a constellation of anthropometric and metabolic features that may be summarized as overweight/obesity, glucose intolerance, dyslipidemia, and hypertension. These anthropometric and metabolic abnormalities are associated with type 2 diabetes, cardiovascular disease, polycystic ovary syndrome, and nonalcoholic fatty liver disease. The liver plays a central role in the regulation of whole-body glucose, fatty acid, and amino acid metabolism. It is the main source of endogenous glucose production, it is a major site of fatty acid disposal (esterification and oxidation) and of amino acid metabolism, and it is the primary site of insulin degradation.

### Tissue-specific insulin receptor knockout mice

Studies using tissue-specific insulin receptor knockout have demonstrated that mice lacking the muscle insulin receptor alone (MIRKO) are characterized by reduced insulin-stimulated muscle glucose uptake, but total-body glucose homeostasis remained normal (1). Adipose tissue insulin receptor knockout mice (FIRKO) had impaired adipose tissue glucose uptake but were protected against obesity, glucose intolerance, and dyslipidemia and manifested a prolonged lifespan (1). In contrast, knockout of the insulin receptor in the liver resulted in both fasting and postprandial hyperglycemia and the subsequent development of peripheral (muscle) insulin resistance. Collectively, these observations support the view that hepatic insulin resistance is the primary

event and leads to the subsequent development of peripheral (muscle and adipose) tissue insulin resistance.

### The model of nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is part of the broad spectrum of nonalcoholic fatty liver diseases, which also includes steatosis. The distinction between fatty liver and steatohepatitis only can be made by examination of liver histology, which allows the assessment of inflammatory infiltrate, cellular degeneration, and necrosis and fibrosis, and cannot be made on the basis of clinical or laboratory parameters. Despite the weak correlation between liver function tests and the severity of liver disease, epidemiological studies have shown that transaminases, and, in particular, elevated alanine aminotransferase (ALT), even if in the normal range, predict new-onset type 2 diabetes independent of classic risk factors, metabolic syndrome, and C-reactive protein (2). The authors postulated that elevated intrahepatic fat (IHF) content played a central role in liver damage and glucose intolerance. Fatty liver is the most common hepatic disorder characterized by triglyceride accumulation within hepatocytes. Although simple fatty liver is thought to be a benign condition, it is characterized by multiple metabolic abnormalities in organs and tissues that are responsive to insulin. Impaired insulin-mediated inhibition of hepatic glucose production (3,4), reduced insulin-stimulated glucose uptake in skeletal muscle (3,5,6), and decreased inhibition of lipolysis by insulin (3,6) has been doc-

umented in patients with fatty liver disease. Whether the accumulation of fat in the liver is the primary event leading to hepatic and subsequently peripheral (muscle and adipose tissue) insulin resistance is not clear because of the lack of longitudinal data. In support of primacy of the liver, treatment of type 2 diabetic patients with a hypocaloric very-low-fat diet resulted in an 81% reduction in IHF content in association with reductions in both basal and insulin-suppressed hepatic glucose production and a decrease in FPG concentration (7). However, there was no significant improvement in insulin-stimulated peripheral glucose disposal (7). Also, in insulin-treated type 2 diabetic patients, the IHF content was closely correlated with the insulin dose and the sensitivity of endogenous (hepatic) glucose production to insulin and best explained the interindividual variation in insulin requirements (8). Moreover, when the relationship between peripheral glucose metabolism and fatty liver were explored in healthy nondiabetic humans, the correlation between the IHF content and peripheral insulin resistance was much stronger than the correlation with intramyocellular lipid content, visceral fat content, or subcutaneous fat content (9). Stefan et al. (10) recently reported that in the model of the metabolically fit, but obese individuals, preserved insulin sensitivity was more strongly associated with lower IHF content than with other parameters of body adiposity, including intramyocellular lipid content, concluding that ectopic fat in the liver may be more important than visceral fat in the determination of such a beneficial phenotype in obesity. Similar conclusions were also reported in individuals with overt type 2 diabetes (11). In the same line of evidence, we observed that in obese adolescents with fatty liver, there was a greater severity of whole-body insulin resistance compared with that of BMI-matched insulin-resistant obese adolescents with normal IHF content (12).

Finally, the lack of adipose tissue in the congenital lipodystrophy is characterized by extreme insulin resistance associated

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with massive hepatic fat accumulation; intervention with subcutaneous leptin administration in these patients improved whole-body insulin sensitivity mainly due to the mobilization of the excessive fatty liver content (13).

These findings in humans suggest that IHF content has an important systemic consequence to adversely affect insulin sensitivity. The above-described observations in humans are consistent with studies in animal models. When an isocaloric moderate-fat diet was given to dogs, a modest degree of peripheral insulin resistance was triggered; meanwhile, a complete inability of insulin to suppress hepatic glucose production during the clamp developed (14). In rodents, increasing or decreasing IHF content had the opposite effect on muscle insulin sensitivity, suggesting that fat accumulation in the liver may be the primary event leading to peripheral insulin resistance (15). When liver-specific enhancement of fatty acid oxidation was implemented in rats fed a high-fat diet, insulin-stimulated peripheral glucose uptake was enhanced even though intramyocellular lipid content actually increased in some muscle types. More recently, selective hepatic overexpression of glycerol-sn-3-phosphate acyltransferase 1 in rats caused hepatic steatosis and hepatic insulin resistance in the absence of obesity and, surprisingly, triglycerides accumulated in the gastrocnemius muscle in concert with development of insulin resistance in that tissue (16). It has been proposed that the liver might release a humoral factor that sensitizes skeletal muscle to insulin (17), and this suggestive hypothesis is supported by the observation that liver extracts enhanced glucose uptake in the isolated rat hindquarter (18). According to this scenario, peripheral insulin resistance may develop as the result of intrahepatic fat accumulation, resulting in the lower release of these humoral factors that impair insulin sensitivity in peripheral (muscle) tissues. Alternatively, it is possible that fatty liver might interfere with insulin degradation (19); the resultant hyperinsulinemia may potentially be able to impair insulin action in peripheral (muscle and adipose) tissues, as shown in benign insulinoma-induced hyperinsulinemia (20). This hyperinsulinemia-induced mechanism may be justified also based on the finding of the reverse experiment: when the prolonged infusion of ocreotide was administered to extremely insulin-resistant cirrhotic individuals, the correction of hy-

perinsulinemia was paralleled by the restoration of normal insulin sensitivity (21).

### The liver in the phenotype of the insulin resistance syndrome

**Proinflammatory features.** NAFLD is considered the hepatic equivalent of the metabolic syndrome (3,22). This is not surprising since NAFLD is closely associated with obesity, diabetes, dyslipidemia, and insulin resistance (the main features of the metabolic syndrome). Recently, it has been reported that excessive accumulation of fat in the liver rather than in the muscle is associated with features of the metabolic syndrome (23). Liver fat was shown to be fivefold higher in individuals with the metabolic syndrome than in those without the metabolic syndrome, and this finding was independent of obesity (23). No differences in intramyocellular lipid content was observed between subjects with and without the metabolic syndrome. Another feature common to both NAFLD and the metabolic syndrome is the presence of a low-grade inflammatory state in adipose tissue and in the liver. The potential link between inflammation and the metabolic syndrome may well be the increased amount of circulating and intracellular fatty acids concentration that are associated with an increase in the intranuclear and total cellular nuclear factor (NF)- $\kappa$ B (24). Of note, liver biopsy of individuals with fatty infiltration were characterized by increased expression of genes involved in monocyte/macrophage recruitment and inflammation, and this was proportional to the severity of IHF accumulation (25). An attractive hypothesis to account, not only for the metabolic but also for the proinflammatory effects of fatty acids in the liver, is that increased concentrations of intracellular fatty acid metabolites (diacylglycerol, fatty acyl CoAs, etc.) activate I $\kappa$ B kinase (IKK)- $\beta$  and NF- $\kappa$ B (26). Chronic inflammation of the liver secondary to triglyceride infiltration could thereby increase the production of factors that cause systemic insulin resistance. Results in animal models also support this hypothesis. Transgenic activation of the inflammatory mediators IKK- $\beta$  and NF- $\kappa$ B in the liver induce systemic insulin resistance, increase circulating levels of interleukin (IL)-6, and upregulate IL-6 target genes in peripheral tissues, including muscle (27). Conversely, administration of antibodies to neutralize circulating IL-6 normalized IL-6 target gene expression and corrected the insulin resistance.

**Proatherosclerotic features.** Subjects with features of the metabolic syndrome are at risk of developing cardiovascular disease and coronary heart disease (28), and recent evidence suggests that individuals with NAFLD also are at high risk for coronary heart disease. In a prospective study, the 14-year risk of mortality from cardiovascular causes was doubled in patients with biopsy-proven NAFLD compared with a reference population (29). In the Hoorn Study, elevated ALT at baseline increased the 10-year risk of coronary heart disease events, even after adjustment for the components of the metabolic syndrome (30). Cardiovascular risk factors tend to cluster in patients with NAFLD, who exhibit more advanced atherosclerosis than control subjects (31). Recently, we reported that cardiac metabolic remodeling in young men with fatty liver is an early event and occurs before the development of diastolic dysfunction and is independent of known risk factors for cardiovascular disease (age, obesity, hypertension, diabetes, exercise habits) (32). This finding was associated with alteration of surrogate markers of endothelial dysfunction as previously detected (33). Finally, it has been demonstrated that 100% of mice with selective liver knockout of the insulin receptor gene (LIRKO)—a pure hepatic insulin resistance—develop the metabolic syndrome with severe dyslipidemia and atherosclerosis within 12 weeks after being placed on an atherogenic diet. None of the control mice developed the metabolic syndrome or atherosclerosis (34).

### The model of liver cirrhosis

Patients with liver cirrhosis are characterized by impaired glucose metabolism (35); 60–80% are glucose intolerant and 10–15% develop overt diabetes (36–38). The development of diabetes in patients with liver cirrhosis occurs relatively rapidly; over a period of 5 years, ~15–20% of cirrhotic patients develop frank hyperglycemia (39). Diabetes complicating liver cirrhosis, known as hepatogenous diabetes, and the common form of type 2 diabetes are the result of a marked reduction in insulin action and a  $\beta$ -cell secretory defect that is not able to compensate for the severity of insulin resistance (40). Peripheral insulin resistance plays a major role in its pathogenesis (41,42). The peripheral insulin resistance in these patients has been assessed with positron emission tomography of the skeletal muscle and has been shown to be associated

with both impaired glucose transport and glycogen synthesis (43). The important role of peripheral insulin resistance in the glucose tolerance of cirrhosis is highlighted by the observation that liver transplantation, when the dosage of immunosuppressive agents is reduced and corticosteroids withdrawn, is able to restore normal insulin sensitivity not only in the liver but also at the level of the skeletal muscle and adipose tissue (44) and normalizes glucose tolerance in most patients with diabetes (40).

**CONCLUSIONS** — In support of the supremacy of the role of the liver in the onset of insulin resistance and insulin resistance syndrome, we state the following: 1) NAFLD is the hepatic equivalent of the metabolic syndrome. 2) Even though there are no longitudinal data showing that the development of NAFLD is primary and precedes the onset of whole-body insulin resistance, it is plausible, based on animal studies, that the development of peripheral insulin resistance and proinflammatory state is secondary to hepatic fat infiltration and hepatic insulin resistance. 3) Models in which hepatic dysfunction is known to be the primary disturbance provide strong support that insulin resistance in peripheral tissues develops secondary to the liver disease; this is manifested in humans in patients with hepatic cirrhosis.

A final consideration is that insulin resistance is often defined based on measurements of glucose metabolism, but insulin also regulates the anabolism and storage of fat, protein synthesis, and non-metabolic process such as cell growth and differentiation. In the insulin resistance syndrome, it is important to emphasize that not all insulin-dependent processes and tissues are equally resistant to insulin. Metabolic pathways at the liver site are a good example of this behavior. Accili and coworkers (45) proposed that, when insulin signaling in hepatocytes is impaired, the transcription factor forkhead box O1 (FoxO1) may play a pivotal role in sustaining this mixed state of resistance versus sensitivity to insulin. This heterogeneous phenotype (insulin resistance with respect to glucose metabolism and insulin sensitivity with respect to lipogenesis) seems to be a typical behavior of the liver able to explain simultaneously all the metabolic features (dysglycemia and dyslipidemia) of the insulin resistance syndrome.

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