0163-769X/08/$20.00/0
Printed in U.S.A.

Endocrine Reviews 29(7):939–960

doi: 10.1210/er.2008-0009

Causes and Metabolic Consequences of Fatty Liver

Norbert Stefan, Konstantinos Kantartzis, and Hans-Ulrich Häring

Department of Internal Medicine, Division of Endocrinology, Diabetology, Nephrology, Vascular Disease and Clinical Chemistry, University of Tübingen, D-72076 Tübingen, Germany

Type 2 diabetes and cardiovascular disease represent a serious threat to the health of the population worldwide. Although overall adiposity and particularly visceral adiposity are established risk factors for these diseases, in the recent years fatty liver emerged as an additional and independent factor. However, the pathophysiology of fat accumulation in the liver and the cross-talk of fatty liver with other tissues involved in metabolism in humans are not fully understood. Here we discuss the mechanisms involved in the pathogenesis of hepatic fat accumulation, particularly the roles of body fat distribution, nutrition, exercise, genetics, and gene-environment interaction. Furthermore, the effects of fatty liver on glucose and lipid metabolism, specifically via induction of subclinical inflammation and secretion of humoral factors, are highlighted. Finally, new aspects regarding the dissociation of fatty liver and insulin resistance are addressed. (*Endocrine Reviews* 29: 939–960, 2008)

First Published Online August 21, 2008

Abbreviations: *ADIPOR1*, Adiponectin receptor-1; AMPK, AMP-activated protein kinase; BMI, body mass index; ChREBP, carbohydrate response element-binding protein; CLOCK, circadian locomotor output cycles protein kaput; CoA, coenzyme A; CRP, C-reactive protein; CT, computed tomographic; CYP7A1, cytochrome P450 cholesterol 7a-hydroxylase; D2, type 2 iodothyronine deiodinase; DGAT2, diacylglycerol acyltransferase 2; DNL, *de novo* lipogenesis; ER, endoplasmic reticulum; FACoA, fatty acyl CoA; FFA, free fatty acid; FGF, fibroblast growth factor; FXR, farnesoid X receptor; HDL, high-density lipoprotein; ^{1}H-MRS, proton magnetic resonance spectroscopy; IFN, interferon; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; LDL, low-density-lipoprotein; LXR, liver X receptor; MR, magnetic resonance; MTP, microsomal transfer protein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor κB; NK, natural killer; PGC-1α, PPARγ coactivator 1α; PPAR, peroxisome proliferator-activated receptor; RBP4, retinol binding protein 4; ROS, reactive oxygen species; SNP, single nucleotide polymorphism; SOCS, suppressor of cytokine signaling; SREBP-1c, sterol-regulatory binding protein 1c; VAT, visceral adipose tissue; VLDL, very low-density lipoprotein.

***Endocrine Reviews* is published by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

I. Introduction

THE EPIDEMICS OF obesity, metabolic syndrome, type 2 diabetes, and atherosclerosis are increasing worldwide (1). Nonalcoholic fatty liver disease (NAFLD), for a long time unnoted in the metabolic field, is becoming recognized as a condition possibly involved in the pathogenesis of these diseases. Support for this hypothesis emerges from studies revealing that NAFLD precedes the manifestation of the metabolic derangements (2–4). Today, with a prevalence of about 34% in the United States among adults (5), NAFLD is the most common cause of chronic liver disease, constituting a major risk factor for progression to liver failure, cirrhosis, and hepatocellular carcinoma (6–8). Particularly alarming are the data showing that NAFLD has become the most common cause of liver disease in children (9). Therefore, and because the prevalence of the metabolic syndrome as well as type 2 diabetes continuously rises in children (10–12), a concerted effort of the academic disciplines is requested to study the pathophysiology of fatty liver. Furthermore, the consequences of fatty liver for metabolism need to be carefully investigated. Novel findings from the research in this field may help to implement intervention strategies aimed at preventing and reversing fat accumulation in the liver, as well as its complications.

II. Prevalence and Diagnosis of Fatty Liver

A. Prevalence of fatty liver

The term NAFLD is used to describe a condition of fat accumulation in the liver in the absence of excessive alcohol consumption (less than 20 g/d) and specific causes of hepatic steatosis. Among them, nutritional (*e.g.*, malnutrition, rapid weight loss), metabolic (*e.g.*, abetalipoproteinemia, lipodystrophy), and drug-induced (*e.g.*, glucocorticoids, methotrexate) causes as well as other conditions (*e.g.*, jejunal diverticulitis with bacterial overgrowth, inflammatory bowel disease) are relevant.

A number of epidemiological studies converge in raising the prevalence of fatty liver, measured by proton magnetic resonance spectroscopy (^{1}H-MRS), to more than 30% of the adult general population (5, 13). Fatty liver is more frequent among obese subjects (75%) compared with controls (16%) (14) and among patients with type 2 diabetes (34–74%), whereas it is an almost universal finding in obese patients with type 2 diabetes (15). The prevalence of fatty liver is increasing with age. Nevertheless fatty liver is found even in children and that with increasing rates. Recent data indicate a doubling of the prevalence from 2.6% a decade ago (16) to 5% of normal-weight children, 38% of obese children (17), and 48% of children with type 2 diabetes (18). This makes fatty liver the most common chronic liver disease in westernized societies (15). In particular, males and certain ethnic groups, *e.g.*, Hispanics (5) and Asian-Indians (19), tend to have higher rates of fatty liver.

B. Imaging techniques and histology

The American Association for the Study of Liver Diseases (AASLD) set the limit for the diagnosis of NAFLD at fat accumulation in the liver of at least 5–10% by weight. For practical use, NAFLD is estimated as the percentage of fat-laden hepatocytes observed by light microscopy in liver biopsy (20). Because ^{1}H-MRS, which is considered the most accurate noninvasive method for measuring liver fat, is more often applied, the cutoff limit has been set to 5.56% (hepatic triglyceride level of 55.6 mg/g), corresponding to the 95th percentile of the distribution of liver fat in 345 healthy subjects with no or minimal alcohol consumption (13). Furthermore, computed tomographic (CT) scanning for the low-density hepatic parenchyma, which is produced by the fat infiltration of the liver, can be used to estimate the amount of fat accumulation in the liver (7). Ultrasonography, the method that is most widely used, allows detecting moderate and severe steatosis with a fair sensitivity and specificity only when fat on liver biopsy exceeds 33% (21). Histologically, the liver of patients with NAFLD displays predominantly macrovesicular and microvesicular fat accumulation in hepatocytes. More severe states involving mononuclear cell infiltration and hepatocyte necrosis constitute steatosis with inflammation [nonalcoholic steatohepatitis (NASH)]. NASH may particularly advance to liver fibrosis, cirrhosis, and hepatocellular carcinoma (7, 22). NAFLD and NASH represent advanced stages of hepatic steatosis that are associated with metabolic diseases. However, findings from studies using very precise imaging techniques such as ^{1}H-MRS, which allows detection of fat accumulation in the liver in early stages of steatosis, suggest that already moderate hepatic fat accumulation is associated with multiple metabolic phenotypes (5). Thus, a "low-grade fatty liver syndrome" may exist.

C. Laboratory and clinical findings

Up to 70% of patients with fatty liver do not show laboratory abnormalities (5, 7, 21–23). An increase in serum levels of liver alanine aminotransferase, which correlates with liver fat independently of adiposity, and to a lesser degree aspartate aminotransferase can be found (24, 25). Serum alkaline phosphatase and γ-glutamyltransferase are also associated with liver fat independent of adiposity (26). However, they are not more helpful than aminotransferases for diagnosing steatosis or NASH (7). In general, elevation of liver enzymes can only be used as a crude estimate of the presence of fatty liver. Most patients with liver steatosis or NASH are asymptomatic and have no signs of liver disease at the time of diagnosis. When present, symptoms and findings are nonspecific and do not correlate well with the severity of the disease. Most commonly, fatigue or malaise and a right upper quadrant pain or sensation of fullness are reported. In addition, hepatomegaly can be found in physical examination (7, 27). Other findings relate to the presence of overweight or obesity and other features of the metabolic syndrome. Acanthosis nigricans, which was earlier found in the context of severe insulin resistance (28, 29), is present almost only in children (27, 30). Finally, cirrhosis exhibits signs and symptoms of decompensated liver disease, independent of the original cause. Altogether the diagnosis of fatty liver can be established with a combined approach involving clinical assessment including a careful history and physical examination, laboratory evaluation, imaging techniques, and liver biopsy. More specifically, when clinical, routine laboratory, or anthropometrical findings show abnormalities that are often associated with fatty liver, ultrasonography and specific laboratory tests are commonly used to diagnose liver diseases. Regarding fatty liver, other causes need to be excluded. CT scan, magnetic resonance (MR) tomography, ^{1}H-MRS, and to a lesser extent ultrasonography allow the noninvasive diagnosis of fatty liver. When there are additional findings suggesting NASH or fibrosis (age $>$ 45 yr, alanine aminotransferase/aspartate aminotransferase ratio $>$ 1, visceral obesity, high triglycerides), a liver biopsy to estimate the severity and the prognosis of the disease, as well as to monitor the effectiveness of an intervention, may be useful.

Regarding the treatment of NAFLD, patients should avoid alcohol and other hepatotoxins. The goal of treatment is to reduce steatosis and prevent the development of fibrosis, which may lead to cirrhosis and its complications. Because the progression of NAFLD to more severe clinical conditions may be affected by obesity, the metabolic syndrome, and insulin resistance, these states have been the focus of treatment. In particular, moderate lifestyle intervention is considered the first-line therapy (15, 31, 32). Numerous clinical trials with pharmaceutical agents have been undertaken in the last few years; however, there is no final consensus on the effectiveness of such a treatment (33, 34). Agents affecting redistribution of body fat (thiazolidinediones), insulin sensitivity (thiazolidinediones and metformin), lipid oxidation and food intake (cannabinoid receptor-1 antagonists), and hepatoprotective drugs (ursodeoxycholic acid, betaine, vitamin E) have been tested. Particularly, thiazolidinediones were found to be effective in the treatment of NAFLD and NASH (35). Pilot studies further reveal a potential role of the nonselective phosphodiesterase inhibitor pentoxifylline, which reduces transcription of the TNF gene, in the treatment of NASH (36, 37).

III. Causes of Fatty Liver

A. Body fat composition, hepatic lipid supply, and adipokines

It is widely accepted that behavioral factors are involved in the pathophysiology of fatty liver. In this aspect, an increased energy intake is considered to represent a major player. In addition, diet composition was found to be relevant. Furthermore, studies showed that a sedentary lifestyle with reduced physical activity, independent of diet, represents another determinant for fatty liver. Although these risk factors may successfully be modified by moderate lifestyle interventions, the existence of other risk factors most probably may necessitate more intense treatment. Among them, a disproportionate fat distribution, particularly with increased visceral adiposity releasing humoral factors regulating liver fat, are relevant. Finally, impaired hepatic lipid oxidation as well as dysregulated lipogenesis, factors that are affected by genetics, may be of pathophysiological relevance (Fig. 1).

Liver fat measured by ^{1}H-MRS is closely and positively correlated with measures of total adiposity such as body mass index (BMI) or percentage body fat. Furthermore, the correlation of liver fat with visceral adiposity, measured as waist circumference, is particularly strong. In most studies, the latter association remains statistically significant after adjustment for BMI and is stronger than the relationship between liver fat and BMI (38–40). Even stronger are the correlations between liver fat and visceral adipose tissue (VAT) mass, quantified by means of computed (41) or MR tomography and ^{1}H-MRS (24, 42, 43). Of note, in multivariate analyses with gender, age, waist-to-hip ratio, and VAT as independent variables, only VAT is significantly correlated with liver fat (42). Both, in univariate and multivariate analyses, the respective correlation coefficients generally range between 0.54 and 0.65, suggesting that 30 to 40% of the variation in liver fat content can be explained by the variability in VAT (44). The impact of other body fat compartments, as sc abdominal fat or fat of the extremities, remains to be studied.

A mechanism possibly explaining the relationship of overall and visceral obesity with liver fat is inflammation of hypertrophic adipose tissue. When adipose tissue expands, it becomes infiltrated by macrophages and overflows with proinflammatory cytokines and probably, therefore, is insulin resistant (45–47). The impairment of insulin-mediated suppression of lipolysis then results in an increased release of free fatty acids (FFAs) from adipose tissue (48, 49). In this aspect, VAT is of special importance because it is metabolically more active than sc adipose tissue (50, 51). The increased lipolysis in VAT is thought to result in an elevated flux of FFAs directly into the portal vein and the liver, a process that is commonly referred to as the "portal hypothesis" (48). FFAs are then taken up by the hepatocytes and are bound to coenzyme A (CoA). The fatty acyl CoAs (FACoAs) can react to form hepatic triglycerides but can also interfere with insulin signaling (52). Furthermore, FACoAs can induce intracellular inflammation by stimulating the nuclear factor κB (NF-κB) (53). Moreover, FFAs are ligands of the membrane-bound toll-like receptor 4 and can induce insulin resistance and inflammation virtually by the same intracellular mechanisms, without being converted to FACoAs (54–56).

Hepatic inflammation was previously considered to promote steatosis (57); however, this concept is not supported by other studies (58, 59). In mice selectively expressing active inhibitor κB kinase, which stimulates nuclear translocation and expression of NF-κB and NF-κB target genes, liver fat is not increased but is reduced (59).

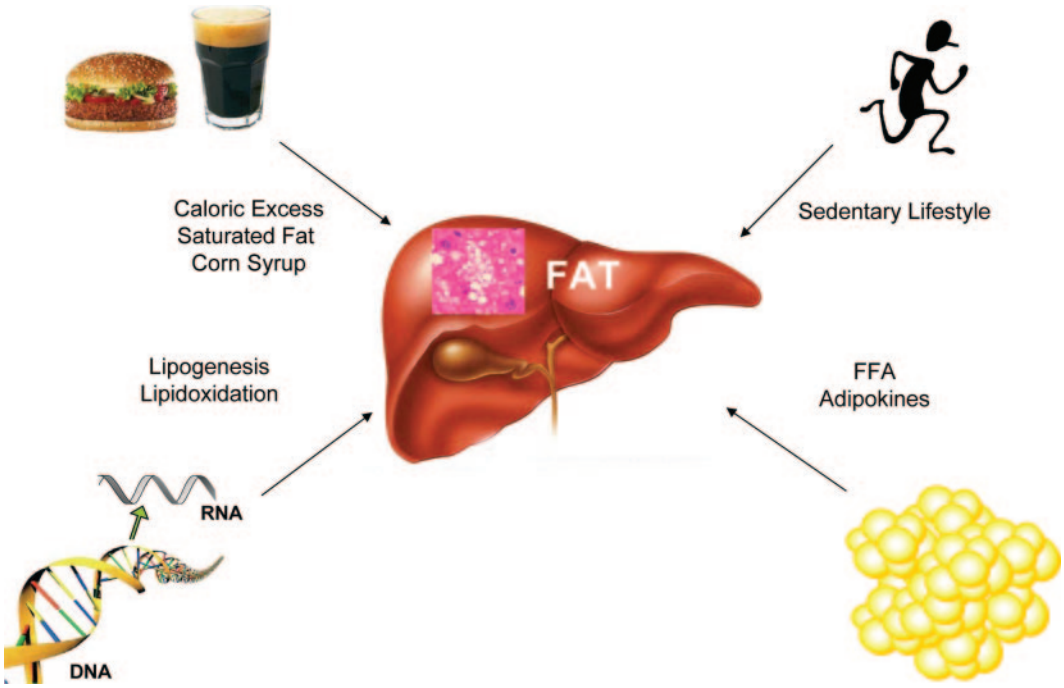

FIG. 1. Major determinants of fatty liver.

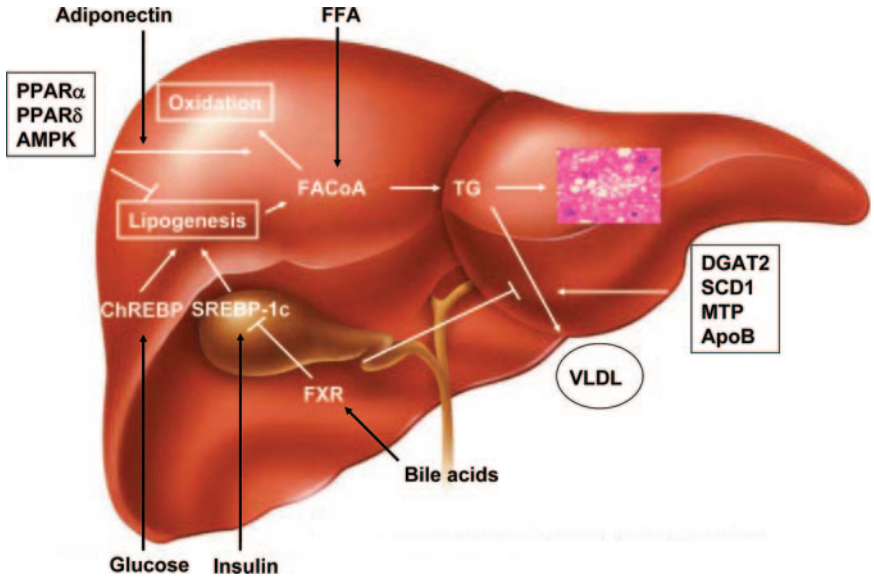

FIG. 2. Pathophysiology of fatty liver. Among the mechanisms involved in the pathophysiology of fatty liver, hyperglycemia and hyperinsulinemia are considered to induce lipogenesis via ChREBP and SREBP-1c, respectively, thereby increasing the hepatic pool of FACoA. This pool is also increased by increased delivery of FFA through either the diet or lipolysis in adipose tissue. FACoAs are assembled to triglycerides (TG) that remain in the liver or are secreted in the form of VLDLs. The latter pathway is regulated by several factors, among them the two enzymes stearoyl-CoA-desaturase (SCD) and acyl:CoA:DGAT2, as well as the MTP and the availability of apolipoprotein B. FACoAs can also be oxidized in the liver, involving the transcription factors PPARα and PPARδ. In addition, the AMPK is involved. The adipokine adiponectin stimulates fatty acyl oxidation via AMPK activation and PPARα induction. AMPK is also involved in the suppression of lipogenesis. Furthermore, bile acids activate the FXR that inhibits SREBP-1c. The role of insulin signaling in the pathophysiology of fatty liver needs to be elucidated further.

The "portal hypothesis" was challenged when the contribution of VAT lipolysis to the pool of FFAs drained into the liver, measured by isotope dilution and arteriovenous sampling methods, was found to be only 5–10% in normal-weight subjects and only up to 25% in viscerally obese individuals (60). The main origin of the FFAs in the systemic plasma pool in the fasting state is considered to be sc fat (60, 61). Whereas in the fasting state hepatic fatty acids originate predominantly from the systemic plasma FFA pool (62), the portal FFA supply to the liver may be substantially increased postprandially (63). Nevertheless, irrespectively of the origin of the FFAs, increased hepatic lipid supply is most probably contributing to hepatic fat accumulation (31, 49) (Fig. 2). This hypothesis is further supported by studies showing that exogenous lipid infusion and high-fat diet increase liver fat content and hepatic insulin resistance, whereas low-fat diets and treatment with fatty acid-lowering medication have the opposite effects (32, 49).

Furthermore, inflamed adipose tissue in obesity secretes high amounts of proinflammatory cytokines as TNF-α and ILs, particularly IL-6 (45–47), which suppress the production of the insulin-sensitizing adipokine adiponectin (64, 65). The imbalance in the secretion pattern of these adipocytokines is considered to represent another link between obesity and fatty liver (49). Although plasma levels of TNF-α and IL-6 are increased in obesity (47, 66, 67), they are low compared with their tissue concentrations (68, 69). In particular, TNF-α is likely to have predominantly paracrine effects in terms of increasing insulin resistance in the adipose tissue (31, 47). In contrast, circulating adiponectin closely correlates with liver fat content (43, 70) and hepatic insulin resistance (70). Furthermore, treatment with thiazolidinediones, which increase circulating adiponectin, results in a decrease in liver fat content (35). In addition, genetic variability in the adiponectin receptor gene affects hepatic fat accumulation (71), supporting the important role of adiponectin signaling in the pathophysiology of fatty liver in humans. Mechanisms of adiponectin action include increase in lipid oxidation in liver and skeletal muscle via activation of AMP-activated protein kinase (AMPK) and induction of peroxisome proliferator-activated receptor (PPAR)-α (65, 72, 73). Furthermore, adiponectin decreases the activity of enzymes involved in fatty acid synthesis as acetyl-CoA carboxylase and fatty acid synthase (74).

Leptin is considered another important regulator of liver fat, although the mechanisms of the protective effect of this adipokine are not fully understood. Besides the hypothalamic effects of leptin in the regulation of food intake, it most probably has direct antisteatotic effects by enhancing lipid oxidation and inhibiting lipogenesis in tissues (75). This hypothesis is supported by data from studies with administration of recombinant adenovirus-receptor constructs containing the normal leptin receptor in obese Zucker diabetic fatty rats. Because most of the infused adenovirus-receptor construct is taken up by the liver, the reduction in hepatic triglycerides under treatment is thought to be predominantly mediated by direct antisteatotic effects of endogenous leptinemia (75). However, effects of this intervention on other tissues cannot be ruled out.

In line with findings from studies on lipoatrophy (76), both aforementioned hypotheses, the hepatic FFA oversupply and altered adipokine release, suggest that fat distribution may strongly be involved in the pathogenesis of hepatic steatosis. More specifically, it is hypothesized that when sc adipose tissue is absent or deficient, the excess of calories cannot be stored in this insulin-sensitive tissue. Thus, expansion of visceral fat mass, as well as ectopic fat accumulation in liver and skeletal muscle results from the inability of the body to adequately store energy, a state that is driven by insulin resistance of sc adipose tissue (77). Fatty liver would then rather be secondary to peripheral insulin resistance.

Whether hyperinsulinemia is only an innocent bystander, resulting from skeletal muscle insulin resistance-mediated hyperglycemia and thus, insulin hypersecretion from the β-cells, or whether it may also contribute to the pathogenesis of liver fat accumulation has been a matter of discussion. Insulin is a potent activator of sterol-regulatory binding protein 1c (SREBP-1c), a transcription factor regulating the ex-

pression of enzymes involved in the synthesis of fatty acids in the liver (31, 49, 78, 79) (Fig. 2). At first view, it seems contradictory that in hepatic insulin resistance, which is strongly associated with hepatic steatosis (44, 49, 80), insulin may still be able to stimulate lipogenesis. However, in the presence of profound insulin resistance in animals, insulin does stimulate hepatic SREBP-1c transcription. This is associated with increased rates of *de novo* lipogenesis (DNL) (81, 82), possibly mediated by a mechanism involving Foxa2 signaling (83–85). Alternatively, as discussed by Biddinger *et al.* (86), DNL may also become insulin resistant but may be stimulated by other factors such as carbohydrates.

In this aspect, glucose activates carbohydrate response element-binding protein (ChREBP), which exerts, similarly to SREBP-1c, stimulatory effects on the expression of genes involved in lipogenesis and triglyceride synthesis (79, 87, 88). ChREBP also stimulates pyruvate kinase, thus increasing the glycolysis of glucose into pyruvate, which forms acetyl-CoA and then malonyl-CoA, which is required for FFA synthesis (89). The activities of both transcription factors (ChREBP and SREBP-1c) are increased in animal models of fatty liver (81, 90) (Fig. 2).

Support from data in humans showing that hyperinsulinemia alone is not a major driving force for fat accumulation in the liver comes from a study in patients with type 2 diabetes. In that study, 7 months of insulin therapy resulting in systemic hyperinsulinemia actually was found to decrease liver fat content (91). Furthermore, a study addressing the effect of high-fat, low-carbohydrate *vs.* low-fat, high-carbohydrate diets on hepatic DNL in lean, obese insulin-sensitive and obese insulin-resistant subjects shows a major effect of carbohydrate intake on lipogenesis (92). On the high-fat diet, DNL increases only in obese, insulin-resistant subjects (but not in obese, insulin-sensitive subjects), supporting the finding that hyperinsulinemia is involved in DNL in humans. Moreover, and of particular importance, on the high-carbohydrate diet DNL is highest in lean insulin-sensitive subjects, and hyperinsulinemia has no additional effect on DNL. Altogether, these human data support, first, that hepatic DNL is up-regulated in insulin resistance; and second, that intake of carbohydrates has a more profound effect than hyperinsulinemia. Certainly, further studies are needed to precisely clarify the magnitude of these effects in human metabolism.

B. Nutrition

Nutritional factors affect the hepatic fatty acid pool in several ways. Dietary fatty acids enter the liver either through the uptake of intestinally derived chylomicron remnants or in the form of FFA from chylomicrons hydrolyzed at a rate in excess of what can be taken up by tissues (spillover) (62, 79). Dietary glucose, as mentioned above, and fat are important regulators of DNL via activation of ChREBP and SREBP-1c (79, 87, 88). Postprandially, both dietary fat supply to the liver and DNL increase and can provide more than 50% of the FFAs entering the liver (63). In the fasting state, DNL accounts for less than 5% of hepatic fatty acids in healthy subjects (93), but lipogenesis may substantially increase in subjects with fatty liver (62, 94). Moreover, it is likely that the fatty acid pattern modulates the activity of ChREBP and SREBP-1c, with saturated and trans-unsaturated FFAs increasing and mono- as well as polyunsaturated FFAs decreasing their expression and activity (95–98).

In human studies, individuals with fatty liver have higher intake of calories as well as saturated fat and cholesterol compared with healthy controls. They also have lower intake of polyunsaturated fat, fiber, and antioxidant vitamins such as vitamin C and E (99–101). In trials with only caloric restriction in severely obese individuals, an improvement in liver enzymes and in liver steatosis is found in those subjects who lost weight (102, 103). Furthermore, a low-calorie diet is associated with improvement in liver histology in overweight patients with NASH (104). In intervention studies investigating the effect of fat intake, high-total fat diets cause an increase in liver fat content. In contrast, low-fat diets result in a decrease in liver fat content as well as in markers of insulin resistance. These effects occur under isocaloric (105) as well as hypocaloric diets (106–108). The restriction of saturated fat intake is particularly effective (108, 109). Many of these studies are relatively small and do not assess the effects of such diets on the improvement in liver fat content using precise measurement techniques such as histology, ^{1}H-MRS, or CT scans. Nevertheless, strategies aimed at weight reduction by restriction of total and saturated fat intake, combined with an increase in physical exercise, are now considered to constitute the most appropriate initial treatment for fatty liver (15, 32). A moderate weight loss by 5–10% of baseline weight or 0.5–1.5 kg/wk is recommended (31, 34). This is important because rapid weight loss was found to deteriorate liver histology, possibly due to increased lipolysis (15, 31, 110).

There are also human studies supporting the findings in animals regarding the role of dietary carbohydrates in the pathophysiology of fatty liver (111–113). A low-carbohydrate, ketogenic diet (<20 g/d) is associated with a greater weight loss, a better lipid profile, and clearly improved steatosis and inflammation in liver biopsies after 6 months than low-fat diets (113). Among the carbohydrates, fructose appears to have the strongest effects on lipogenesis (114, 115). In a study in seven young healthy males, a high-fructose diet for 6 d was found to increase the fractional hepatic DNL 6-fold as well as hepatic insulin resistance and plasma triglycerides. Interestingly, fish oil supplementation reversed dyslipidemia and tended to reduce DNL (116). However, in another study a 4-wk high-fructose consumption (1.5 g/kg·d) resulted in an increase in plasma triglycerides, but not in hepatic fat content, suggesting that the excess of triglycerides formed in the liver was exported as very low-density lipoprotein (VLDL) triglycerides (117). Because consumption of high-fructose corn syrup has tremendously increased in the last decades in the westernized world, it may have contributed to the respective increase in the incidence of fatty liver disease (118).

Other nutritional factors may also be of importance in the pathophysiology of hepatic steatosis and hepatosteatitis. Antioxidant vitamins, because of their ability to prevent oxidative stress and inflammation, may have beneficial effects particularly in the pathogenesis of steatohepatitis and fibrosis. In support of this hypothesis, obese patients with NASH

were found to consume less antioxidant vitamins C and E compared with obese controls (100). In addition, vitamin E supplementation as add-on treatment of NASH reduces liver fat content (119, 120). However, these are rather small trials, and the magnitude of the effect of vitamin supplementation on liver fat still remains to be clarified.

Furthermore, agents regulating bile acid metabolism may be important in the regulation of fat accumulation in the liver. Bile acids, by binding to the G protein-coupled receptor TGR5, or mBAR, induce PPARγ coactivator 1α (PGC-1α) transcription, thereby increasing mitochondrial activity and β-oxidation (121). Furthermore, bile acids via G protein-coupled receptor increase cAMP production and activate the cAMP-protein kinase A pathway, resulting in an increase of cAMP-dependent thyroid hormone activating enzyme type 2 iodothyronine deiodinase (D2) activity. This enzyme converts T_4 to T_3, which binds to thyroid hormone receptor and uncouples electron transfer in the respiratory chain from oxidative phosphorylation. Thus, this bile acid-TGR5-cAMP-D2 signaling pathway increases energy expenditure and oxygen consumption and finely regulates energy homeostasis. These mechanisms are operative in the most thermogenically important tissues in rodents (brown adipose tissue) and humans (skeletal myocytes) (121, 122). Whether such a mechanism also takes place in the human liver, thereby possibly contributing to an increased oxidation of fatty acids and reducing liver fat, is unknown.

In addition, bile acids are the major ligands of the farnesoid X receptor (FXR) (Fig. 2), a nuclear receptor that plays a key role in protecting the liver and the intestine against bile acid toxicity (123, 124). In this context, FXR down-regulates cytochrome P450 cholesterol 7a-hydroxylase (CYP7A1) gene expression and thus, bile acid synthesis via up-regulation of the atypical nuclear receptor small heterodimer partner (SHP) (121, 125, 126). Another pathway leading to suppression of *CYP7A1* involves bile acid-mediated activation of FXR of the ileum, which induces the local expression of fibroblast growth factor (FGF)-19 (FGF15 in rodents) (127, 128). FGF19 is absorbed in the bloodstream and is able to activate FGF receptor isotype 4 in hepatocytes. Activated FGF receptor isotope 4 represses *CYP7A1* expression via a c-Jun N-terminal kinase (JNK) pathway (127, 129–131). Liver FXR also down-regulates expression of polypeptides acting as bile acid import pumps, up-regulates bile acid export pumps, and inhibits intestinal reabsorption of bile acids (121, 127).

Furthermore, FXR has significant effects in modulating postprandial energy metabolism and particularly lipoprotein metabolism (130). A natural FXR agonist, chenodeoxycholic acid, has been known for several decades to reduce plasma triglycerides in humans (132). In animals, both this natural agonist (133) and the synthetic FXR agonist GW4064 reduce plasma triglycerides and the rate of VLDL production, as well as blood glucose (134). Although the mechanism of bile acid sequestrants (resins)-induced hypertriglyceridemia was unknown for a long time, recent findings indicate that a reduction in FXR ligands is involved. The reduction of triglycerides is, at least partially, attributed to the down-regulation of SREBP-1c (133, 135) and up-regulation of PPARα, leading to a reduced hepatic fatty acid and triglyceride synthesis and an increased fatty acid oxidation (121). The latter effect may also be mediated by bile acid-induced production of FGF19 (136). Another mechanism includes induction of apolipoprotein C-II expression, which is a coactivator of lipoprotein lipase, the enzyme that hydrolyzes serum triglycerides (127, 137).

In addition, activation of FXR is associated with a decrease in blood glucose. This effect is thought to be mediated by suppression of hepatic gluconeogenetic genes (130, 138). Therefore, it is reasonable to assume that an FXR agonist could decrease liver fat as well as plasma triglycerides and possibly glucose levels (139). On the other hand, an antagonist of FXR would be expected to lower low-density-lipoprotein (LDL) cholesterol by promoting conversion of cholesterol into bile acids (140). Furthermore, FXR activation seems to decrease high-density lipoprotein (HDL) cholesterol levels and regulate HDL remodeling. Possible mechanisms include repression of apolipoprotein A-I gene, up-regulation of hepatic scavenger receptor B1 (stimulation of hepatic HDL uptake), and up-regulation of the phospholipid transfer protein (125, 130, 139, 141, 142) and the cholesterol ester transfer protein (121) genes. These data derive principally from animal studies but are in line with the known moderate HDL cholesterol-increasing effect of bile acid sequestrants. In any case, the precise effects of FXR on LDL and HDL remain to be elucidated.

Liver X receptor (LXR, isoforms α and β) is another nuclear receptor that is an attractive target for new drugs. LXR in macrophages and in the liver plays a critical role for cholesterol reverse transport (the transport of cholesterol from macrophages to HDL particles and into the liver). Therefore, agonists of LXR are emerging as drugs potentially reducing atherosclerosis. However, they increase hepatic steatosis and plasma triglyceride levels, possibly by up-regulating SREBP-1c (125). It needs to be investigated whether selective hepatic LXR antagonists could have favorable effects on liver fat without accelerating atherosclerosis.

C. Exercise and mitochondrial function

It is still a matter of discussion whether there is a positive direct effect of exercise on liver fat (108, 109, 143, 144). Habitual physical activity is negatively associated with liver fat, independent of BMI (145, 146) but not independent of visceral adiposity (145). These data suggest that exercise intensity is not an independent determinant of liver fat. In contrast, mitochondrial function, which can be estimated by measurement of aerobic fitness, may be involved in the pathophysiology of hepatic steatosis. The association of maximal aerobic capacity with liver fat was investigated in three cross-sectional studies. In a relatively small study, no significant difference in maximal aerobic capacity between subjects with high *vs.* low liver fat was found (147). Two larger studies showed a close relationship of aerobic fitness, both with liver fat (148) and the prevalence of fatty liver (39). In 170 subjects, we found a strong predictive effect of high fitness at baseline on the reduction in liver fat during a lifestyle intervention (149). This effect was not only larger than the impact of total or visceral fat on change in liver fat, but it was also independent of these parameters, supporting

the hypothesis that aerobic fitness and hepatic lipid metabolism have a common background. In agreement with this assumption, in a recent study involving a cohort of 2603 adults that were followed up for a mean of 12 yr, fitness and BMI predicted mortality, independent of several established risk factors. Most notably, the effect of fitness was independent of total and abdominal adiposity (150). As discussed the effect of fitness on mortality may have been mediated by liver fat (151).

Mechanisms explaining the relationship between fitness and liver fat possibly include factors regulating hepatic lipid oxidation (152–156). Fitness is associated with enlargement of and increase in mitochondria in skeletal muscle and the generation of type I fibers (157). These effects may be regulated by genetics (152). Indeed, genetic variability in PGC-1α and PPARδ genes regulate mitochondrial function and the response of fitness to physical activity (153). Moreover, the same single nucleotide polymorphism (SNP) in the PPARδ gene (PPARD) is associated with change in liver fat (158). Mitochondria play an important role in hepatocyte metabolism, representing the primary site for the oxidation of fatty acids and oxidative phosphorylation. Hepatocytes are rich in mitochondria, occupying about 18% of the liver cell volume (159). Thus, the aforementioned findings strongly suggest that mitochondrial function is a major regulator of liver fat. In addition, when mitochondrial function is impaired or even when an excess of substrate (FFA) is available, as is often the case in fatty liver, reactive oxygen species (ROS) can arise leading to oxidative stress, which is thought to be important for the progress to NASH and fibrosis (83). In fact, multiple functional abnormalities and even morphological changes have often been observed in mitochondria of patients with NASH (160, 161).

D. Genetics

The role of genetics in the pathogenesis of body fat distribution has been elegantly described in animal models (162). So far, there is not much information about the genetics of fat distribution in humans. Beyond that, there is little information about the impact of genetics, independent of body fat distribution, in the pathophysiology of fatty liver. A study in monozygotic twins even revealed that liver fat was different among the siblings; however, the twins also displayed different levels of total and visceral adiposity (163). On the other hand, the fact that the prevalence of fatty liver is different between ethnic groups, *e.g.*, higher in Hispanics compared with European Americans and African-Americans (5), suggests that the disease has a genetic component.

In recent years, microarray and PCR techniques for analyzing differential expression of genes in fatty liver and controls were widely used. Several genes involved in pathways of fatty acid metabolism in the liver such as uptake, *de novo* synthesis, and oxidation of fatty acids as well as synthesis and secretion of VLDL have been identified as candidates. However, the results thus far are largely inconsistent and are not replicated in large studies (164–170).

In contrast to the microarray approach determining merely expression of genes in fatty liver, the investigation of SNPs in candidate genes may be more promising in the search for the impact of genetics. In this respect, the G/T SNP at position −493 of the promoter of the gene encoding microsomal triglyceride transfer protein (MTP), a protein critical for the synthesis and secretion of VLDL, was found to be associated with hepatic steatosis (171). Among factors affecting fatty acid oxidation, adiponectin serum levels and adiponectin signaling are of particular importance (64, 65). We found that variants in the genes encoding adiponectin receptor-1 (*ADIPOR1*) are associated with insulin sensitivity and liver fat content, both in cross-sectional and longitudinal analyses (71). The data on the impact of genetic variants of *ADIPOR1* on metabolism are supported by two other studies showing an association of SNPs of *ADIPOR1* with type 2 diabetes and the metabolic syndrome (172, 173). Such associations were not found in a study including relatively lean subjects (174). In agreement with the data showing that gene-environment interaction is important for adiponectin signaling in mice (175, 176), human studies suggest that the relationship of adiponectin and adiponectin signaling with insulin sensitivity and liver fat are stronger with increasing adiposity (43, 177–179).

As discussed above, mitochondrial dysfunction, which in skeletal muscle is implicated in the pathogenesis of insulin resistance and type 2 diabetes (180), could be a fundamental abnormality in the process of liver fat accumulation (83, 159). Mitochondrial biogenesis and activity are, among others, transcriptionally regulated by PGC-1α and PGC-1β (181, 182). Expression of PGC-1α and PGC-1β is low under normal conditions but is up-regulated under fasting conditions, thereby activating fatty oxidation by induction of PPARα expression (183). Furthermore, PPARδ is considered to interact with PGC-1α in regulating fatty acid oxidation. In a recent study, the rs2267668 A/G SNP in *PPARD* was found to be a determinant of mitochondrial function in cultured myotubes and, together with the Gly482Ser SNP in the PGC-1α gene (*PPARGC1A*), to be associated with the effect of aerobic exercise training to increase aerobic fitness, an effect probably mediated by mitochondrial function (153). In agreement with the aforementioned hypothesis, the SNP in *PPARD* was also associated with liver fat (158).

Among polymorphisms of other genes involved in fatty acid oxidation, SNPs in the gene encoding the hepatic isoform of carnitine palmitoyltransferase were recently investigated. This enzyme regulates the transport of long-chain fatty acids into mitochondria. However, no associations of the SNPs with liver fat or type 2 diabetes were found (185).

Furthermore, hepatic lipase plays a central role in hepatic lipid metabolism (186). In the hepatic lipase gene (*LIPC*), the −514C/T SNP in the promoter is associated with decreased activity of the enzyme (187) and with the plasma lipid profile (188, 189). Carriers of the T allele of this SNP have higher liver fat and insulin resistance, independent of established risk factors for these disorders (190). Furthermore, this SNP displays gene-gene interactions with the common Pro12Ala SNP of *PPARG* (190), which is well known to be involved in the pathogenesis of type 2 diabetes and lipid metabolism (191), and with the upstream transcription factor usf1s2 G/A SNP (192), which is associated with familial combined hyperlipidemia and atherosclerosis (193, 194).

Another interesting candidate gene for fatty liver is the

circadian locomotor output cycles protein kaput (CLOCK) gene. *Clock* mutant mice display hyperphagia, obesity, the metabolic syndrome, and hepatic steatosis. In agreement with the animal data, in humans, SNPs in the CLOCK gene are associated with fatty liver and histological severity of liver damage (195). Furthermore, the phosphatidyl-ethanolamine N-methyl-transferase gene (*PEMT*) catalyzing hepatic *de novo* synthesis of phosphatidylcholine (196) may be involved in the regulation of fat accumulation in the liver in humans. *PEMT* knockout mice develop fatty liver under a choline-deficient diet (197), and in humans a functional SNP (V175M) is associated with fatty liver (198).

In summary, the genetic effects observed so far are rather small. Once available genome-wide association studies, similar to those that occurred in the field of type 2 diabetes (199) and atherosclerosis (200), may reveal new and possibly more important genes. Such efforts, however, are still limited by the relatively small existing databases containing precise measurements of liver fat and information about the diagnosis of NASH.

IV. Metabolic Consequences of Fatty Liver

A. Dyslipidemia

It has been shown convincingly that fatty liver is associated with insulin resistance, atherosclerosis, and the metabolic syndrome (15, 44, 49, 201–204). Furthermore, fatty liver predicts future cardiovascular events (3, 201). It is thought that a pro-atherogenic serum lipid profile, which is commonly observed in subjects with fatty liver, is in part responsible for these relationships. This profile consists of low HDL cholesterol and high triglyceride levels, small, dense LDL particles, and high apolipoprotein B100 levels (4, 78, 205–208). An increased rate of hepatic triglyceride synthesis and VLDL particle production, which secondarily results in low HDL cholesterol and increased LDL particle density (78, 209, 210), is considered to be causative for this type of dyslipidemia. Furthermore, a decrease in lipoprotein lipase activity may also be involved (211, 212). Although there is evidence that insulin resistance is a strong underlying mechanism for this dyslipidemia (78, 207, 209, 210, 213–215), other studies suggest that fat accumulation in the liver may also have an independent effect on dyslipidemia. In the study by Toledo *et al.* (206), plasma insulin was higher in subjects with steatosis compared with controls, but insulin was much weaker correlated with serum triglycerides than hepatic steatosis. However, in that study hepatic insulin resistance was not measured, leaving the question open whether liver fat correlated with triglycerides also independent of hepatic insulin resistance. Regarding HDL, not only quantitative, but also qualitative and compositional alterations are related to its antiatherogenic properties (216–219). Circulating HDL_2 was particularly found to protect from atherosclerosis (220, 221). We could recently show that fatty liver correlates more strongly with circulating HDL_2 and the HDL_2/HDL_3 ratio than with total HDL (222). Moreover, the correlation of liver fat with HDL_2 and the HDL_2/HDL_3 ratio remains statistically significant even after adjustment for whole-body insulin resistance and circulating adiponectin that is associated with both dyslipidemia and liver fat (64, 65). In agreement with the data from Toledo *et al.* (206) and with the limitation that hepatic insulin resistance was not directly measured, these findings suggest that there may be a direct link between fatty liver, dyslipidemia, and thus atherosclerosis.

B. Inflammation

Besides its metabolic functions, the liver is involved in immune responses (47, 223). Although the hepatocytes represent approximately two thirds of the total cells in the liver, other cell types are biliary epithelial cells, sinusoidal endothelial cells, Kupffer cells, stellate cells, dendritic cells, and lymphocytes (224, 225). The Kupffer cells and lymphocytes are the main cell types involved in the hepatic immune response. Kupffer cells represent the largest group of fixed macrophages in the body and account for about 20% of nonparenchymal cells in the liver (226). They are derived from circulating monocytes that arise from bone marrow progenitors (227). In the liver, Kupffer cells clear endotoxins (lipopolysaccharides) from the passing blood, and phagocyte debris and microorganisms. Furthermore, they are in close contact with blood lymphocytes and other resident antigen-presenting cells.

Kupffer cells produce cytokines that play a key role in cell differentiation and cell proliferation. This process is modulated by the membrane-bound bile acid receptor TGR5/mBAR (228). Kupffer cell-derived IL-12 and IL-18, for example, regulate natural killer (NK) cell differentiation and promote the local expansion of cytotoxic NK cell subpopulations that express large amounts of antiviral interferon (IFN)-γ (229). Other Kupffer cell-derived cytokines such as IL-1β, IL-6, TNF-α, and leukotrienes promote the infiltration and antimicrobial activity of neutrophils (230). Because NK T cells are capable of releasing IFN-γ and IL-4 (231), they are thought to modulate the local and systemic adaptive immune responses to either a proinflammatory type I (IFN-γ, TNF-α) or an antiinflammatory type II (IL-4, IL-10, IL-13) profile (224, 225). The increased production of TNF-α is considered to have a particularly major role in the pathogenesis of hepatic insulin resistance (232, 233).

In this aspect, the gastrointestinal tract may be important for hepatic inflammation and the pathophysiology of NASH. This is supported by data from animal studies (234) and from jejunoileal bypass surgery for morbid obesity in humans showing that NASH and fibrosis are encountered as a complication of this procedure (235, 236). Furthermore, small intestinal bacterial overgrowth was more frequently found in patients with NASH than in controls (237). Such derangement of the gut flora, which plays an important role in the prevention and treatment of infections as well as in immune functions, is also thought to be mediated by the consumption of manipulated and processed foods, *e.g.*, high amounts of refined sugar and saturated fat and a decrease in fiber, vitamins, and antioxidants (238). Small intestinal bacterial overgrowth results in the production of ethanol in animals (239) and humans (240–242) as well as in the release of bacterial lipopolysaccharides (243). Both ethanol and lipopolysaccharides activate TNF-α production in Kupffer cells, thereby, inducing hepatic inflammation (244). In agreement

with this hypothesis, antibiotics (245) and probiotics (246) targeting the gut flora positively affect hepatic inflammation in animals as well as in humans (235, 247).

Furthermore, hepatic inflammation is induced by hepatic steatosis. Hotamisligil (47) and Shoelson *et al*. (223) hypothesize that hepatic steatosis might induce a subacute inflammatory response in liver that is similar to the adipose tissue inflammation, after adipocyte lipid accumulation. Part of this process is considered to be attributed to endoplasmic reticulum (ER) and oxidative stress. The ER is a membranous network responsible for the processing and folding of newly synthesized proteins. Besides hypoxia, toxins, infections, and other insults, nutrient fluctuations and excess lipids pose stress on the ER that is accompanied by accumulation of unfolded or misfolded proteins (248). ER stress in liver and adipose tissue is generated in mice with genetic or diet-induced forms of obesity. This is largely mediated by activation of JNK resulting in impairment of insulin signaling (249). Furthermore, ER stress is associated with activation of multiple stress responses and with the specific activation of CREBP, a hepatocyte-specific bZip transcription factor that may have an important role in hepatic acute-phase response such as the induction of transcription of the serum amyloid P-component and C-reactive protein (CRP) genes (250).

In addition, the ER is involved in the generation of ROS and, consequently, oxidative stress (251). Furthermore, ROS are formed in the mitochondria by impaired mitochondrial respiratory chain capacity. Particularly an increase in cytosolic fatty acids results in increased fatty acid oxidation and, thus, ROS production (252, 253). In agreement, in humans with NASH, increased levels of by-products of lipid peroxidation are found, suggesting increased oxidative stress (254). Finally, under conditions of oxidative stress, NF-κB and JNK pathways are activated, representing a link between oxidative stress and insulin resistance (47, 223, 255).

Altogether, the close interaction of immune cells with the metabolically active hepatocytes (47, 223) may trigger local but also systemic subclinical inflammation, a process that is strongly regulated by PPARα (256). Systemic subclinical inflammation can be estimated by measurement of circulating CRP. The plasma levels of this acute-phase protein are very low under healthy conditions but increase in response to a pathological inflammatory process. Because of its relatively low half-life of 18 h, CRP represents a useful, early nonspecific marker of inflammation (257). Plasma CRP is produced predominantly by hepatocytes and is under transcriptional control by IL-6 and other proinflammatory cytokines. However, other sites of local CRP synthesis and possibly secretion have also been suggested (258). Circulating CRP is positively correlated with liver fat (259–262). Moreover, CRP levels are higher in patients with histologically proven NASH compared with simple steatosis (262). Of interest, circulating CRP most probably is not merely an indicator of systemic inflammation but is also involved in the pathogenesis of atherosclerosis (257). These data suggest that fat accumulation in the liver may be involved in the pathophysiology of atherosclerosis via induction of systemic inflammation.

C. Insulin resistance

Fatty liver and obesity are strongly associated with insulin resistance (263, 264), the condition that plays a predominant role in the pathophysiology of type 2 diabetes (47, 255, 264–266) and cardiovascular disease (67, 267–270). Animal studies reveal that fat accumulation in the liver inhibits insulin signaling in hepatocytes. In particular, hepatic insulin resistance can be attributed to impaired insulin-stimulated insulin receptor substrate (IRS)-1 and IRS-2 tyrosine phosphorylation resulting in increased gluconeogenesis (263, 271, 272). In humans, a strong relationship exists between fat accumulation in the liver and whole-body insulin resistance (4, 71, 80, 106, 146, 190, 273–285) (Fig. 3). More importantly, liver fat correlates with insulin resistance independent of visceral adiposity (147, 286), a major regulator of both liver fat and insulin resistance (77, 287). Euglycemic, hyperinsulinemic clamp studies with tracer methods to measure the suppression of endogenous glucose production, an estimate of hepatic insulin sensitivity, show that liver fat is particularly strongly correlated with hepatic insulin sensitivity (41, 106, 147, 280, 288, 289).

Interestingly, hepatic steatosis is also associated with myocardial insulin resistance. In patients with type 2 diabetes, liver fat measured by ^{1}H-MRS is the strongest predictor of insulin-stimulated myocardial glucose uptake, compared with other determinants such as visceral fat mass and whole-body glucose uptake (290). Moreover, liver fat is also strongly associated with myocardial perfusion, which is affected by coronary artery function (290). It needs to be determined whether fat accumulation in the liver induces myocardial insulin resistance via humoral mechanisms, as recently discussed (291), and/or mainly reflects myocardial steatosis and abnormal cardiac metabolism, parameters that strongly correlate with liver fat content (292).

It has not been determined whether fatty liver is mainly a result of insulin resistance of adipose tissue and skeletal muscle or whether fatty liver may also develop independent of the aforementioned conditions. Animal studies provided the first evidence that the latter could also be the case. Insulin resistance can be induced *in vivo* by overexpression of suppressor of cytokine signaling (SOCS)-1 or -3 in liver (293). SOCS proteins attenuate insulin signaling by binding to the insulin receptor and reducing its ability to phosphorylate IRS proteins (294–296). This hepatic overexpression of SOCS proteins is associated with an increase in SREBP-1c and hepatic steatosis (293). Conversely, suppression of SOCS-1, SOCS-3, or both in liver partially rescues impaired insulin sensitivity and ameliorates hyperinsulinemia in diabetic *db/db* mice. More importantly, suppression of SOCS proteins, especially SOCS-3, markedly improves hepatic steatosis. In summary, these findings suggest that fatty liver may also develop by alteration of hepatic insulin signaling and/or by direct effects of SOCS proteins on SREBP-1c in the liver (293, 297, 298). Thus, fatty liver may develop independent of skeletal muscle and adipose tissue insulin resistance.

Furthermore, there are human data showing that fatty liver may even have a primary role in the pathophysiology of skeletal muscle insulin resistance. In patients with type 2 diabetes, the PPARγ agonist rosiglitazone, as well as met-

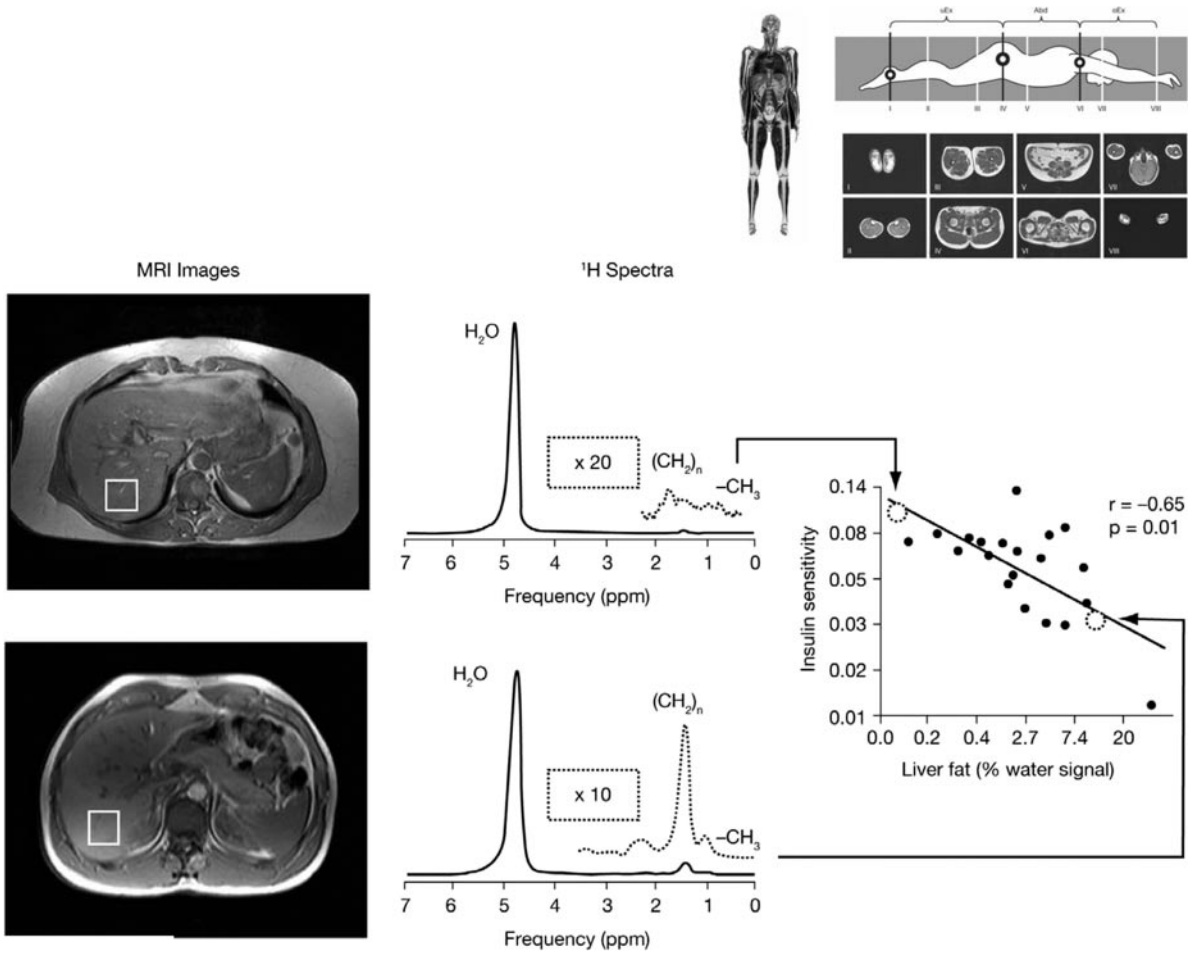

FIG. 3. Relationship of liver fat, measured by ^{1}H-MRS, to insulin sensitivity. Liver fat content was quantified by localized ^{1}H-MRS using a 1.5-T whole-body imager. Although there is no clear difference in gray shade in the liver between the individuals, the signal from the ^{1}H-MRS shows that liver fat content is obviously different. These two individuals also behaved differently when insulin sensitivity was measured during the euglycemic-hyperinsulinemic clamp. The individual with higher liver fat content had lower insulin sensitivity. To correct this relationship for the confounding factors total body fat and body fat compartments, whole-body MR imaging for quantification of these parameters (*inset*) is a precise technique. [Adapted from N. Stefan *et al.*: *Horm Res* 64(Suppl 3):38–44 (285), with permission from S. Karger AG.]

formin, increases hepatic insulin sensitivity via activation of AMPK (299). However, a decrease in liver fat is only seen in subjects receiving thiazolidinediones. More importantly, insulin sensitivity of glucose disposal increases only in the thiazolidinedione group (300). Because skeletal muscle is not a major target of PPARγ action (301), these data support the notion that the increase in skeletal muscle insulin sensitivity in the thiazolidinedione group may be mediated by the decrease in liver fat.

A study by Hwang *et al.* (289), with quantification of fat in liver and skeletal muscle by ^{1}H-MRS and measurement of visceral fat by MRT and of endogenous glucose production and insulin sensitivity of glucose disposal by tracer methods, further supports a role of hepatic fat accumulation in the pathophysiology of skeletal muscle insulin resistance. In that study, the negative correlation between liver fat content and skeletal muscle insulin sensitivity is exceptionally tight (289). The authors discuss the fact that their data, together with previous studies (302–304), suggest that the liver releases factors that regulate insulin sensitivity in skeletal muscle.

Fetuin-A [former name for the human protein, α_2-Heremans-Schmid glycoprotein (AHSG)] may represent one of these factors. Fetuin-A is predominantly expressed in the liver, and to a lesser degree in the placenta and the tongue (305). Because placental expression is only relevant during pregnancy and the tongue is not an organ with endocrine activity, the liver is the only organ regulating circulating fetuin-A levels. This protein is a natural inhibitor of the insulin receptor tyrosine kinase in liver and skeletal muscle (306–310). Furthermore, mice deficient for the gene encoding fetuin-A display improved insulin signaling (311), suggesting that fetuin-A may play a major role in the regulation of insulin sensitivity in animals. In humans, SNPs in the fetuin-A gene (*AHSG*) are associated with type 2 diabetes (312). However, the role of this protein in the natural history of type 2 diabetes was unknown for a long time. Of note, severe liver damage as in cirrhosis, acute viral hepatitis, and cancer is associated with a decrease and not an increase in circulating fetuin-A (313). Thus, no liver dysfunction was known to be associated with elevated fetuin-A production in humans. Recently, fetuin-A mRNA expression was found to be in-

creased in fatty liver in mice (281), which is in agreement with previous data from rats (314). In addition, circulating fetuin-A correlates positively with liver fat in humans in cross-sectional and longitudinal analyses. Circulating fetuin-A also correlates negatively with insulin sensitivity (281, 315). Moreover, high fetuin-A plasma levels predict change in insulin sensitivity, measured by the euglycemic, hyperinsulinemic clamp in prospective analyses (281) and are associated with incident type 2 diabetes (316, 317). In agreement with the notion that circulating fetuin-A is increased in fatty liver and insulin resistance, plasma fetuin-A is associated with the metabolic syndrome and correlates positively with CRP levels (316). Furthermore, fetuin-A promotes cytokine expression in monocytes and adipocytes and represses the production of the insulin-sensitizing adipokine adiponectin (317). Thus, these data support the hypothesis that fetuin-A may be one of the factors that mediate effects of fatty liver to other tissues. Such factors may be referred to as "hepatokines."

Another protein that is preferentially produced by the liver is FGF21 (318). It has beneficial effects on lipid metabolism, as well as insulin sensitivity and pancreatic β-cell function (319–321). These effects of FGF21 on metabolism in animal models are not accompanied by changes in body weight (319). This finding is interesting because a profound synergy between the effects of FGF21 and the thiazolidinedione rosiglitazone, which induces weight gain, exists in stimulating glucose uptake in 3T3-L1 adipocytes (322). In addition, FGF21 regulates hepatic steatosis. FGF21 expression in the liver in the fasted state is induced by PPARα. Accordingly, FGF21 expression in the livers of fasted mice is absent in PPARα-deficient animals. These animals have fatty liver and serum hypertriglyceridemia (323–326). Furthermore, a decrease in endogenous FGF21 expression by RNA interference induces fatty liver and hyperlipidemia (323). So far, there is little information on the relationship of FGF21 with metabolic traits in humans. In a cross-sectional study in 200 subjects, circulating FGF21 levels correlated positively with components of the metabolic syndrome, but not with insulin sensitivity estimated from fasting serum glucose and insulin levels, independent of obesity (327). Whether hepatic FGF21 expression and production are affected by hepatic steatosis needs to be investigated.

Another very interesting protein, retinol binding protein 4 (RBP4), is expressed in adipose tissue and in the liver and is secreted into circulation (328). The first evidence that RBP4 has major effects on metabolism was found in adipose-specific knockout of glucose transporter 4 mice (329) that display insulin resistance in skeletal muscle, liver, and adipose tissue (330). In these animals, expression of *Rbp4* in adipose tissue and serum RBP4 levels are increased. In addition, increase in serum RBP4 concentrations by transgenic overexpression or by injection of purified RBP4 protein into wild-type mice causes insulin resistance (329). Furthermore, *Rbp4* knockout mice display enhanced insulin sensitivity, and lowering of serum RBP4 with the synthetic retinoid fenretinide improves insulin sensitivity and glucose tolerance in mice on a high-fat diet (329). Moreover, in humans high circulating RBP4 is associated with insulin resistance in cross-sectional studies (331–336). In addition, a strong relationship between changes in circulating RBP4 and insulin sensitivity is shown in longitudinal studies (331, 333). Recent data suggest that the elevated circulating RBP4 in insulin-resistant states is a result of increased production from the increased visceral fat mass (332), as well as fatty liver (333).

Altogether, there is strong support to show that fatty liver produces humoral factors affecting insulin signaling in insulin-responsive tissues. Thus, further efforts are warranted to identify these hepatokines.

D. Dissociation of fatty liver and insulin resistance

Although hepatic fat accumulation, both in animals and in humans, is strongly associated with a decrease in insulin sensitivity, a large variability in this relationship exists that cannot be explained by other parameters regulating insulin sensitivity such as overall obesity, body fat distribution, or circulating adipokines. In other words, for the same amount of hepatic steatosis, subjects can be identified who have very high and very low insulin resistance (Fig. 4), suggesting that a dissociation of fatty liver and insulin resistance exists. The paradox of this finding may be due to lipotoxicity. This term was mainly devised by Roger Unger to describe the deleterious effects of lipid accumulation in various tissues (75, 337). According to this concept, triglycerides are probably the least toxic form in which the lipid excess can be stored in ectopic tissues, at least in the short term. The incorporation of fatty acids into triglycerides, as well as their oxidative degradation, thus represents protection from lipotoxicity. However, when these compensatory mechanisms are overwhelmed, fatty acids induce damage to cells resulting in impaired metabolism (75, 249, 337, 338) (Fig. 5).

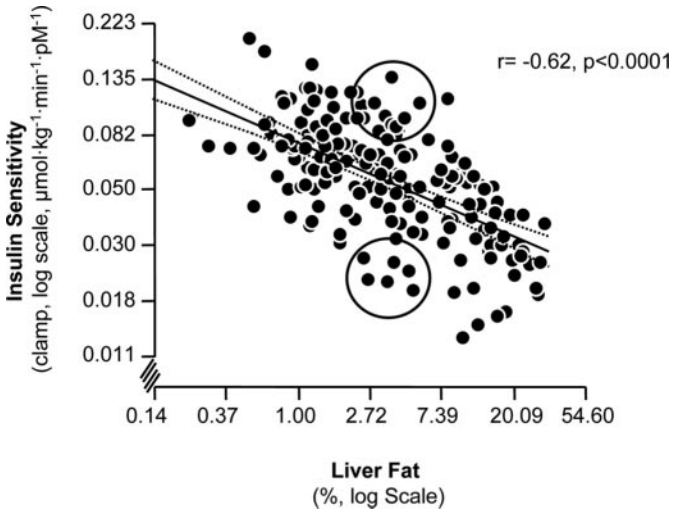

FIG. 4. Variability in the relationship between liver fat and insulin sensitivity in humans. This image depicts the strong, negative relationship between liver fat measured by ^{1}H-MRS and insulin sensitivity measured by the euglycemic- hyperinsulinemic clamp in 200 individuals without type 2 diabetes (regression line and 95% confidence interval). For a very similar amount of liver fat, individuals can be identified who are relatively insulin sensitive (*upper circle*) and insulin resistant (*lower circle*). Major determinants of insulin sensitivity such as age, gender, total and visceral body fat mass measured by MRT, and intramyocellular fat in the tibialis anterior muscle, measured by ^{1}H-MRS, cannot explain this difference in insulin sensitivity.

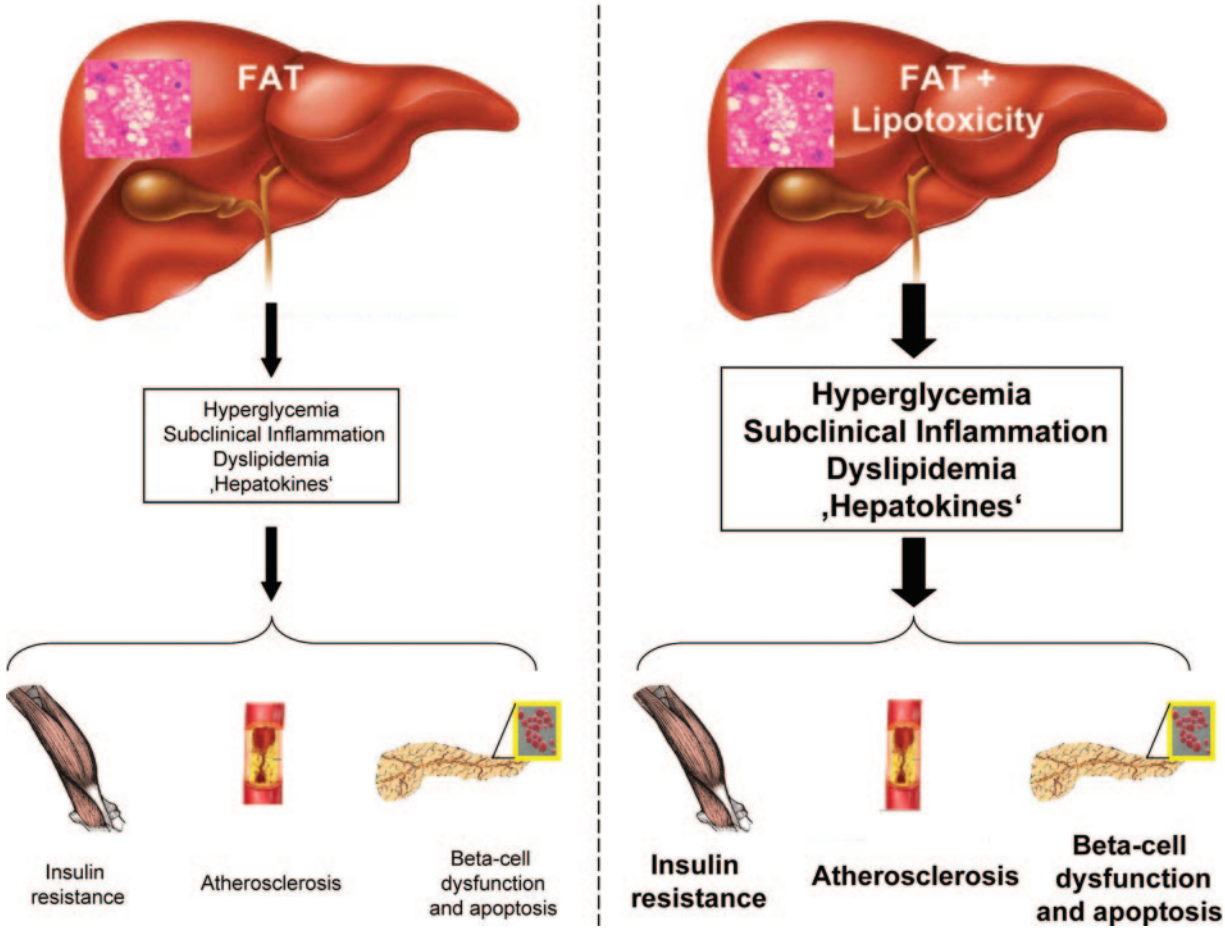

FIG. 5. Metabolic consequences of fatty liver. Fat accumulation in the liver induces hyperglycemia, subclinical inflammation dyslipidemia, and the secretion of parameters that can be referred to as "hepatokines" (*e.g.*, fetuin-A), thereby inducing insulin resistance, atherosclerosis, and possibly β-cell dysfunction and apoptosis. The degree of these conditions may be moderate [benign fatty liver (*left panel*)]. However, the same amount of hepatic fat accumulation may, by mechanisms that are yet not fully understood, be strongly associated with hepatic lipotoxicity, resulting in aggravation of hyperglycemia, subclinical inflammation, dyslipidemia, and an imbalance in hepatokine production as well as in their metabolic consequences. This state may be referred to as malign fatty liver (*right panel*).

Several pathways are thought to be operative in this process. Among them, activation of NF-κB and JNK pathways, as well as the Janus kinase-signal transducer and activator of transcription-3-SOCS-3 pathway, which are involved in insulin resistance (47, 223, 339), is critical. Cai *et al.* (59) elegantly showed that NF-κB transcriptional targets are activated in liver by obesity and a high-fat diet. This is associated with a chronic state of subacute inflammation and insulin resistance. Inhibition of NF-κB activation under a high-fat diet still results in hepatic steatosis; however, this intervention is not accompanied by insulin resistance (59). These findings indicate that fat accumulation in the liver leads to subacute hepatic inflammation through NF-κB activation. In addition, under conditions of inhibited NF-κB stimulation, fatty liver does not result in insulin resistance. In support of this hypothesis, liver-specific inactivation of the NF-κB essential modulator gene in mice under a high-fat diet results in hepatic steatosis, but not in insulin resistance (340). The susceptibility to inflammatory responses may modulate the dissociation of fatty liver and insulin resistance. In this aspect, carriers of the −1031C and −863A variants of the SNPs in the promoter region of the TNF-α gene (*TNF*) have high serum levels of the soluble TNF receptor 2, indicating elevated TNF-α production. Furthermore, they are insulin resistant and have steatohepatitis more frequently than simple steatosis (341). Similar results for other SNPs in *TNF* are reported elsewhere (342).

Another interesting animal model for the dissociation of fatty liver and insulin resistance is the liver-specific acyl: CoA:diacylglycerol acyltransferase 2 (DGAT2) transgene mouse (343). DGAT enzymes, among them particularly DGAT2, catalyze the final step of triacylglycerol biosynthesis (344). Liver-specific DGAT2 overexpressing mice develop hepatic steatosis with a 5-fold increase in liver triglyceride content compared with controls. However, this condition is not accompanied by whole-body or hepatic insulin resistance. In agreement with these novel findings, antisense oligonucleotide treatment targeting the DGAT2 gene reduces liver triglycerides in mice fed a high-fat diet, without improving insulin sensitivity or glucose tolerance (345). In another study, DGAT2 silencing also reduced hepatic steatosis, while insulin sensitivity improved as well. This finding,

however, may be attributable to an effect of DGAT2 silencing on decreasing body weight and epididymal fat pad mass (346). The mechanism for the dissociation of fatty liver and insulin resistance in this animal model is not fully understood. It may be that an increase in triglyceride synthesis protects from fatty acid-induced lipotoxicity. This hypothesis is supported by the finding that on a high-fat diet, activation of JNK and NF-κB in DGAT2 transgenic mice is not increased compared with controls. Alternatively, the increase in unsaturated fatty acids, which are found in the tissue of these animals and are considered to be less lipotoxic compared with saturated fatty acids, may generate the phenotype.

Support for the involvement of the fatty acid pattern in the dissociation of fatty liver and insulin resistance is provided by another recently described animal model. Mice deficient for the elongation of long-chain fatty acids (ELOVL) gene (*Elovl6*) develop obesity and hepatic steatosis, but not insulin resistance, hyperinsulinemia, or hyperglycemia under a high-fat diet (339). *Elovl6* encodes for the enzyme ELOVL, catalyzing the conversion of palmitate (C 16:0) to stearate (C 18:0) as well as palmitoleate (C 16:1n-7) to vaccinate (C 18:1n-7), thus regulating the tissue fatty acid composition (347, 348). Interestingly, amelioration of hepatic insulin resistance in these animals cannot be explained by changes in energy balance or proinflammatory signals. However, a suppression of elongation and degradation of fatty acids, resulting in moderately increased hepatic triglyceride content, as well as a decrease in the diacylglycerol-protein kinase Cε pathway occurs (339). This observation is important because hepatic protein kinase Cε is involved in the development of hepatic insulin resistance (349). Although these animal data provide novel and mechanistic evidence for the existence of a dissociation of fatty liver and insulin resistance, human studies have not specifically addressed this interesting point. Based on the aforementioned findings in animals, we studied the relationship of a SNP in *DGAT2*, which is associated with obesity (350), with liver fat and insulin resistance in humans. In 200 subjects, the SNP in *DGAT2* is associated with changes in liver fat, but not insulin sensitivity during a lifestyle intervention (our 184), supporting the hypothesis that DGAT2 may differentially affect liver fat and insulin sensitivity in humans, too.

V. Concluding Remarks

Although the roles of adipose tissue, and particularly VAT, in the pathophysiology of metabolic diseases such as type 2 diabetes, the metabolic syndrome, and atherosclerosis have been carefully studied, the impact of fatty liver in the natural history of these diseases has long been underestimated. With increasing evidence from transgenic and knockout animal models that hepatic steatosis is involved in several major pathways regulating glucose and lipid metabolism, fatty liver gained recognition in the metabolic field of research. This effect was accompanied by the identification of exciting novel targets to prevent and treat hepatic fat accumulation. Moreover, there is strong support indicating that different aspects of fatty liver exist and are associated with severe or merely moderate metabolic disturbances. Finally, similar to adipose tissue, liver under conditions of an increased lipid load may have important secretory functions, and in analogy to adipokines, hepatokines may become an interesting target for future research.

From a clinical aspect, prevention of ectopic fat deposition in liver, as well as in other insulin-sensitive tissues under conditions of a sedentary lifestyle, overnutrition, and disproportionate adipose tissue distribution, is the primary goal in the protection from obesity-induced insulin resistance. When such efforts are not very effective, targeting lipotoxicity, which appears to be the predominant mediator of metabolic consequences of fatty liver, seems to be an effective strategy to accomplish this mission.

Acknowledgments

We thank our colleagues in the Medical Department and the Department of Experimental Radiology at the University of Tübingen, as well as the Deutsche Forschungsgemeinschaft for their support.

Received February 13, 2008. Accepted August 11, 2008.

Address all correspondence and requests for reprints to: Hans-Ulrich Häring, M.D., Department of Internal Medicine, Otfried-Müller-Strasse 10, D-72076 Tübingen, Germany. E-mail: Hans-Ulrich.Haering@med.uni-tuebingen.de

This work was supported in part by a grant from the Deutsche Forschungsgemeinschaft (KFO 114). N.S. is currently supported by a Heisenberg Grant of the Deutsche Forschungsgemeinschaft.

Disclosure Statement: The authors have nothing to disclose.

References

1. **Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE** 2004 Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 351:2694–2703
2. **Shibata M, Kihara Y, Taguchi M, Tashiro M, Otsuki M** 2007 Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. Diabetes Care 30:2940–2944
3. **Targher G, Bertolini L, Poli F, Rodella S, Scala L, Tessari R, Zenari L, Falezza G** 2005 Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. Diabetes 54:3541–3546
4. **Kim HJ, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, Lim SK, Kim KR, Lee HC, Huh KB, Cha BS** 2004 Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med 164:2169–2175
5. **Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH** 2004 Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 40:1387–1395
6. **Angulo P** 2002 Nonalcoholic fatty liver disease. N Engl J Med 346:1221–1231
7. **Angulo P, Lindor KD** 2002 Non-alcoholic fatty liver disease. J Gastroenterol Hepatol 17 Suppl:S186–S190
8. **Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ** 1999 Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 29:664–669
9. **Lavine JE, Schwimmer JB** 2004 Nonalcoholic fatty liver disease in the pediatric population. Clin Liver Dis 8:549–555ix
10. **Nathan BM, Moran A** 2008 Metabolic complications of obesity in childhood and adolescence: more than just diabetes. Curr Opin Endocrinol Diabetes Obes 15:21–29
11. **Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S** 2007 The metabolic syndrome in children and adolescents: an IDF consensus report. Pediatr Diabetes 8:299–306

12. **Weiss R, Taksali SE, Caprio S** 2006 Development of type 2 diabetes in children and adolescents. Curr Diab Rep 6:182–187
13. **Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, Hobbs HH, Dobbins RL** 2005 Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 288:E462–E468
14. **Bellentani S, Saccoccio G, Masutti F, Croce LS, Brandi G, Sasso F, Cristanini G, Tiribelli C** 2000 Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 132:112–117
15. **Tolman KG, Fonseca V, Dalpiaz A, Tan MH** 2007 Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes Care 30:734–743
16. **Tominaga K, Kurata JH, Chen YK, Fujimoto E, Miyagawa S, Abe I, Kusano Y** 1995 Prevalence of fatty liver in Japanese children and relationship to obesity. An epidemiological ultrasonographic survey. Dig Dis Sci 40:2002–2009
17. **Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C** 2006 Prevalence of fatty liver in children and adolescents. Pediatrics 118:1388–1393
18. **Nadeau KJ, Klingensmith G, Zeitler P** 2005 Type 2 diabetes in children is frequently associated with elevated alanine aminotransferase. J Pediatr Gastroenterol Nutr 41:94–98
19. **Petersen KF, Dufour S, Feng J, Befroy D, Dziura J, Dalla MC, Cobelli C, Shulman GI** 2006 Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. Proc Natl Acad Sci USA 103:18273–18277
20. **Neuschwander-Tetri BA, Caldwell SH** 2003 Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology 37:1202–1219
21. **McCullough AJ** 2004 The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. Clin Liver Dis 8:521–533, viii
22. **Adams LA, Angulo P, Lindor KD** 2005 Nonalcoholic fatty liver disease. CMAJ 172:899–905
23. **Yano E, Tagawa K, Yamaoka K, Mori M** 2001 Test validity of periodic liver function tests in a population of Japanese male bank employees. J Clin Epidemiol 54:945–951
24. **Kotronen A, Westerbacka J, Bergholm R, Pietilainen KH, Yki-Jarvinen H** 2007 Liver fat in the metabolic syndrome. J Clin Endocrinol Metab 92:3490–3497
25. **Westerbacka J, Corner A, Tiikkainen M, Tamminen M, Vehkavaara S, Hakkinen AM, Fredriksson J, Yki-Jarvinen H** 2004 Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. Diabetologia 47:1360–1369
26. **Thamer C, Tschritter O, Haap M, Shirkavand F, Machann J, Fritsche A, Schick F, Haring H, Stumvoll M** 2005 Elevated serum GGT concentrations predict reduced insulin sensitivity and increased intrahepatic lipids. Horm Metab Res 37:246–251
27. **Wieckowska A, McCullough AJ, Feldstein AE** 2007 Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: present and future. Hepatology 46:582–589
28. **Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J** 1976 The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. N Engl J Med 294:739–745
29. **Flier JS, Kahn CR, Roth J** 1979 Receptors, antireceptor antibodies and mechanisms of insulin resistance. N Engl J Med 300:413–419
30. **Nanda K** 2004 Non-alcoholic steatohepatitis in children. Pediatr Transplant 8:613–618
31. **Harrison SA, Day CP** 2007 Benefits of lifestyle modification in NAFLD. Gut 56:1760–1769
32. **Tilg H, Kaser A** 2005 Treatment strategies in nonalcoholic fatty liver disease. Nat Clin Pract Gastroenterol Hepatol 2:148–155
33. **Bellentani S, Dalle GR, Suppini A, Marchesini G** 2008 Behavior therapy for nonalcoholic fatty liver disease: the need for a multidisciplinary approach. Hepatology 47:746–754
34. **Comar KM, Sterling RK** 2006 Review: drug therapy for non-alcoholic fatty liver disease. Aliment Pharmacol Ther 23:207–215
35. **Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K** 2006 A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 355:2297–2307
36. **Satapathy SK, Garg S, Chauhan R, Sakhuja P, Malhotra V, Sharma BC, Sarin SK** 2004 Beneficial effects of tumor necrosis factor-α inhibition by pentoxifylline on clinical, biochemical, and metabolic parameters of patients with nonalcoholic steatohepatitis. Am J Gastroenterol 99:1946–1952
37. **Adams LA, Zein CO, Angulo P, Lindor KD** 2004 A pilot trial of pentoxifylline in nonalcoholic steatohepatitis. Am J Gastroenterol 99:2365–2368
38. **Kotronen A, Juurinen L, Hakkarainen A, Westerbacka J, Corner A, Bergholm R, Yki-Jarvinen H** 2008 Liver fat is increased in type 2 diabetic patients and underestimated by serum alanine aminotransferase compared with equally obese nondiabetic subjects. Diabetes Care 31:165–169
39. **Church TS, Kuk JL, Ross R, Priest EL, Biltoft E, Blair SN** 2006 Association of cardiorespiratory fitness, body mass index, and waist circumference to nonalcoholic fatty liver disease. Gastroenterology 130:2023–2030
40. **Hsiao TJ, Chen JC, Wang JD** 2004 Insulin resistance and ferritin as major determinants of nonalcoholic fatty liver disease in apparently healthy obese patients. Int J Obes Relat Metab Disord 28:167–172
41. **Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC** 2003 Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. Am J Physiol Endocrinol Metab 285:E906–E916
42. **Thamer C, Machann J, Haap M, Stefan N, Heller E, Schnodt B, Stumvoll M, Claussen C, Fritsche A, Schick F, Haring H** 2004 Intrahepatic lipids are predicted by visceral adipose tissue mass in healthy subjects. Diabetes Care 27:2726–2729
43. **Kantartzis K, Rittig K, Balletshofer B, Machann J, Schick F, Porubska K, Fritsche A, Haring HU, Stefan N** 2006 The relationships of plasma adiponectin with a favorable lipid profile, decreased inflammation, and less ectopic fat accumulation depend on adiposity. Clin Chem 52:1934–1942
44. **Kotronen A, Yki-Jarvinen H** 2008 Fatty liver: a novel component of the metabolic syndrome. Arterioscler Thromb Vasc Biol 28:27–38
45. **Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW** 2003 Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112:1796–1808
46. **Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H** 2003 Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 112:1821–1830
47. **Hotamisligil GS** 2006 Inflammation and metabolic disorders. Nature 444:860–867
48. **Heilbronn L, Smith SR, Ravussin E** 2004 Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. Int J Obes Relat Metab Disord 28(Suppl 4):S12–S21
49. **Roden M** 2006 Mechanisms of disease: hepatic steatosis in type 2 diabetes—pathogenesis and clinical relevance. Nat Clin Pract Endocrinol Metab 2:335–348
50. **Montague CT, O'Rahilly S** 2000 The perils of portliness: causes and consequences of visceral adiposity. Diabetes 49:883–888
51. **Lebovitz HE, Banerji MA** 2005 Point: visceral adiposity is causally related to insulin resistance. Diabetes Care 28:2322–2325
52. **Morino K, Petersen KF, Shulman GI** 2006 Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. Diabetes 55(Suppl 2):S9–S15
53. **Wellen KE, Hotamisligil GS** 2005 Inflammation, stress, and diabetes. J Clin Invest 115:1111–1119
54. **Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS** 2006 TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 116:3015–3025
55. **Kim F, Pham M, Luttrell I, Bannerman DD, Tupper J, Thaler J, Hawn TR, Raines EW, Schwartz MW** 2007 Toll-like receptor-4 mediates vascular inflammation and insulin resistance in diet-induced obesity. Circ Res 100:1589–1596
56. **Kim JK** 2006 Fat uses a TOLL-road to connect inflammation and diabetes. Cell Metab 4:417–419
57. **Lin HZ, Yang SQ, Chuckaree C, Kuhajda F, Ronnet G, Diehl AM**

2000 Metformin reverses fatty liver disease in obese, leptin-deficient mice. Nat Med 6:998–1003
58. **Memon RA, Grunfeld C, Feingold KR** 2001 TNF-α is not the cause of fatty liver disease in obese diabetic mice. Nat Med 7:2–3
59. **Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE** 2005 Local and systemic insulin resistance resulting from hepatic activation of IKK-β and NF-κB. Nat Med 11:183–190
60. **Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD** 2004 Splanchnic lipolysis in human obesity. J Clin Invest 113:1582–1588
61. **Koutsari C, Jensen MD** 2006 Thematic review series: patient-oriented research. Free fatty acid metabolism in human obesity. J Lipid Res 47:1643–1650
62. **Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ** 2005 Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 115:1343–1351
63. **Parks EJ, Hellerstein MK** 2006 Thematic review series: patient-oriented research. Recent advances in liver triacylglycerol and fatty acid metabolism using stable isotope labeling techniques. J Lipid Res 47:1651–1660
64. **Trujillo ME, Scherer PE** 2006 Adipose tissue-derived factors: impact on health and disease. Endocr Rev 27:762–778
65. **Kadowaki T, Yamauchi T** 2005 Adiponectin and adiponectin receptors. Endocr Rev 26:439–451
66. **Kershaw EE, Flier JS** 2004 Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 89:2548–2556
67. **Fernandez-Real JM, Ricart W** 2003 Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocr Rev 24:278–301
68. **Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G** 2001 Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 280:E745–E751
69. **Sopasakis VR, Sandqvist M, Gustafson B, Hammarstedt A, Schmelz M, Yang X, Jansson PA, Smith U** 2004 High local concentrations and effects on differentiation implicate interleukin-6 as a paracrine regulator. Obes Res 12:454–460
70. **Bugianesi E, Pagotto U, Manini R, Vanni E, Gastaldelli A, de Iasio R, Gentilcore E, Natale S, Cassader M, Rizzetto M, Pasquali R, Marchesini G** 2005 Plasma adiponectin in nonalcoholic fatty liver is related to hepatic insulin resistance and hepatic fat content, not to liver disease severity. J Clin Endocrinol Metab 90:3498–3504
71. **Stefan N, Machicao F, Staiger H, Machann J, Schick F, Tschritter O, Spieth C, Weigert C, Fritsche A, Stumvoll M, Haring HU** 2005 Polymorphisms in the gene encoding adiponectin receptor 1 are associated with insulin resistance and high liver fat. Diabetologia 48:2282–2291
72. **Tomas E, Tsao TS, Saha AK, Murrey HE, Zhang CC, Itani SI, Lodish HF, Ruderman NB** 2002 Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc Natl Acad Sci USA 99:16309–16313
73. **Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T** 2002 Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 8:1288–1295
74. **Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ** 2003 The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. J Clin Invest 112:91–100
75. **Unger RH** 2003 Minireview: weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. Endocrinology 144:5159–5165
76. **Reitman ML, Arioglu E, Gavrilova O, Taylor SI** 2000 Lipoatrophy revisited. Trends Endocrinol Metab 11:410–416
77. **Despres JP, Lemieux I** 2006 Abdominal obesity and metabolic syndrome. Nature 444:881–887
78. **Taskinen MR** 2003 Diabetic dyslipidaemia: from basic research to clinical practice. Diabetologia 46:733–749
79. **Lavoie JM, Gauthier MS** 2006 Regulation of fat metabolism in the liver: link to non-alcoholic hepatic steatosis and impact of physical exercise. Cell Mol Life Sci 63:1393–1409
80. **Utzschneider KM, Kahn SE** 2006 Review: the role of insulin resistance in nonalcoholic fatty liver disease. J Clin Endocrinol Metab 91:4753–4761
81. **Shimomura I, Bashmakov Y, Horton JD** 1999 Increased levels of nuclear SREBP-1c associated with fatty livers in two mouse models of diabetes mellitus. J Biol Chem 274:30028–30032
82. **Browning JD, Horton JD** 2004 Molecular mediators of hepatic steatosis and liver injury. J Clin Invest 114:147–152
83. **Pessayre D, Fromenty B** 2005 NASH: a mitochondrial disease. J Hepatol 42:928–940
84. **Wolfrum C, Asilmaz E, Luca E, Friedman JM, Stoffel M** 2004 Foxa2 regulates lipid metabolism and ketogenesis in the liver during fasting and in diabetes. Nature 432:1027–1032
85. **Montminy M, Koo SH** 2004 Diabetes: outfoxing insulin resistance? Nature 432:958–959
86. **Biddinger SB, Hernandez-Ono A, Rask-Madsen C, Haas JT, Aleman JO, Suzuki R, Scapa EF, Agarwal C, Carey MC, Stephanopoulos G, Cohen DE, King GL, Ginsberg HN, Kahn CR** 2008 Hepatic insulin resistance is sufficient to produce dyslipidemia and susceptibility to atherosclerosis. Cell Metab 7:125–134
87. **Iizuka K, Bruick RK, Liang G, Horton JD, Uyeda K** 2004 Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis. Proc Natl Acad Sci USA 101:7281–7286
88. **Biddinger SB, Almind K, Miyazaki M, Kokkotou E, Ntambi JM, Kahn CR** 2005 Effects of diet and genetic background on sterol regulatory element-binding protein-1c, stearoyl-CoA desaturase 1, and the development of the metabolic syndrome. Diabetes 54:1314–1323
89. **Yamashita H, Takenoshita M, Sakurai M, Bruick RK, Henzel WJ, Shillinglaw W, Arnot D, Uyeda K** 2001 A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. Proc Natl Acad Sci USA 98:9116–9121
90. **Dentin R, Benhamed F, Hainault I, Fauveau V, Foufelle F, Dyck JR, Girard J, Postic C** 2006 Liver-specific inhibition of ChREBP improves hepatic steatosis and insulin resistance in ob/ob mice. Diabetes 55:2159–2170
91. **Juurinen L, Tiikkainen M, Hakkinen AM, Hakkarainen A, Yki-Jarvinen H** 2007 Effects of insulin therapy on liver fat content and hepatic insulin sensitivity in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 292:E829–E835
92. **Schwarz JM, Linfoot P, Dare D, Aghajanian K** 2003 Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenergetic diets. Am J Clin Nutr 77:43–50
93. **Parks EJ** 2002 Dietary carbohydrate's effects on lipogenesis and the relationship of lipogenesis to blood insulin and glucose concentrations. Br J Nutr 87(Suppl 2):S247–S253
94. **Diraison F, Moulin P, Beylot M** 2003 Contribution of hepatic de novo lipogenesis and reesterification of plasma nonesterified fatty acids to plasma triglyceride synthesis during non-alcoholic fatty liver disease. Diabetes Metab 29:478–485
95. **Storlien LH, Higgins JA, Thomas TC, Brown MA, Wang HQ, Huang XF, Else PL** 2000 Diet composition and insulin action in animal models. Br J Nutr 83(Suppl 1):S85–S90
96. **Clarke SD** 2001 Nonalcoholic steatosis and steatohepatitis. I. Molecular mechanism for polyunsaturated fatty acid regulation of gene transcription. Am J Physiol Gastrointest Liver Physiol 281:G865–G869
97. **Sekiya M, Yahagi N, Matsuzaka T, Najima Y, Nakakuki M, Nagai R, Ishibashi S, Osuga J, Yamada N, Shimano H** 2003 Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression. Hepatology 38:1529–1539
98. **Hussein O, Grosovski M, Lasri E, Svalb S, Ravid U, Assy N** 2007 Monounsaturated fat decreases hepatic lipid content in non-alcoholic fatty liver disease in rats. World J Gastroenterol 13:361–368
99. **Capristo E, Miele L, Forgione A, Vero V, Farnetti S, Mingrone G, Greco AV, Gasbarrini G, Grieco A** 2005 Nutritional aspects in patients with non-alcoholic steatohepatitis (NASH). Eur Rev Med Pharmacol Sci 9:265–268
100. **Musso G, Gambino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, Faga E, Silli B, Pagano G** 2003 Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology 37:909–916

101. **Cortez-Pinto H, Jesus L, Barros H, Lopes C, Moura MC, Camilo ME** 2006 How different is the dietary pattern in non-alcoholic steatohepatitis patients? Clin Nutr 25:816–823
102. **Drenick EJ, Simmons F, Murphy JF** 1970 Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small-bowel bypass. N Engl J Med 282:829–834
103. **Palmer M, Schaffner F** 1990 Effect of weight reduction on hepatic abnormalities in overweight patients. Gastroenterology 99:1408–1413
104. **Huang MA, Greenson JK, Chao C, Anderson L, Peterman D, Jacobson J, Emick D, Lok AS, Conjeevaram HS** 2005 One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. Am J Gastroenterol 100:1072–1081
105. **Westerbacka J, Lammi K, Hakkinen AM, Rissanen A, Salminen I, Aro A, Yki-Jarvinen H** 2005 Dietary fat content modifies liver fat in overweight nondiabetic subjects. J Clin Endocrinol Metab 90: 2804–2809
106. **Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI** 2005 Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes 54:603–608
107. **Tiikkainen M, Bergholm R, Vehkavaara S, Rissanen A, Hakkinen AM, Tamminen M, Teramo K, Yki-Jarvinen H** 2003 Effects of identical weight loss on body composition and features of insulin resistance in obese women with high and low liver fat content. Diabetes 52:701–707
108. **Larson-Meyer DE, Heilbronn LK, Redman LM, Newcomer BR, Frisard MI, Anton S, Smith SR, Alfonso A, Ravussin E** 2006 Effect of calorie restriction with or without exercise on insulin sensitivity, β-cell function, fat cell size, and ectopic lipid in overweight subjects. Diabetes Care 29:1337–1344
109. **Tamura Y, Tanaka Y, Sato F, Choi JB, Watada H, Niwa M, Kinoshita J, Ooka A, Kumashiro N, Igarashi Y, Kyogoku S, Maehara T, Kawasumi M, Hirose T, Kawamori R** 2005 Effects of diet and exercise on muscle and liver intracellular lipid contents and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 90:3191–3196
110. **Luyckx FH, Lefebvre PJ, Scheen AJ** 2000 Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. Diabetes Metab 26:98–106
111. **Kang H, Greenson JK, Omo JT, Chao C, Peterman D, Anderson L, Foess-Wood L, Sherbondy MA, Conjeevaram HS** 2006 Metabolic syndrome is associated with greater histologic severity, higher carbohydrate, and lower fat diet in patients with NAFLD. Am J Gastroenterol 101:2247–2253
112. **Solga S, Alkhuraishe AR, Clark JM, Torbenson M, Greenwald A, Diehl AM, Magnuson T** 2004 Dietary composition and nonalcoholic fatty liver disease. Dig Dis Sci 49:1578–1583
113. **Yancy Jr WS, Olsen MK, Guyton JR, Bakst RP, Westman EC** 2004 A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 140:769–777
114. **Minehira K, Vega N, Vidal H, Acheson K, Tappy L** 2004 Effect of carbohydrate overfeeding on whole body macronutrient metabolism and expression of lipogenic enzymes in adipose tissue of lean and overweight humans. Int J Obes Relat Metab Disord 28:1291–1298
115. **Le KA, Tappy L** 2006 Metabolic effects of fructose. Curr Opin Clin Nutr Metab Care 9:469–475
116. **Faeh D, Minehira K, Schwarz JM, Periasamy R, Park S, Tappy L** 2005 Effect of fructose overfeeding and fish oil administration on hepatic de novo lipogenesis and insulin sensitivity in healthy men. Diabetes 54:1907–1913
117. **Le KA, Faeh D, Stettler R, Ith M, Kreis R, Vermathen P, Boesch C, Ravussin E, Tappy L** 2006 A 4-wk high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. Am J Clin Nutr 84:1374–1379
118. **Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ** 2002 Fructose, weight gain, and the insulin resistance syndrome. Am J Clin Nutr 76:911–922
119. **Sanyal AJ, Mofrad PS, Contos MJ, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, Shiffman ML, Clore J, Mills AS** 2004 A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2:1107–1115
120. **Dufour JF, Oneta CM, Gonvers JJ, Bihl F, Cerny A, Cereda JM, Zala JF, Helbling B, Steuerwald M, Zimmermann A** 2006 Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin E in nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 4:1537–1543
121. **Claudel T, Staels B, Kuipers F** 2005 The Farnesoid X receptor: a molecular link between bile acid and lipid and glucose metabolism. Arterioscler Thromb Vasc Biol 25:2020–2030
122. **Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, Messaddeq N, Harney JW, Ezaki O, Kodama T, Schoonjans K, Bianco AC, Auwerx J** 2006 Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature 439:484–489
123. **Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf DJ, Shan B** 1999 Identification of a nuclear receptor for bile acids. Science 284:1362–1365
124. **Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel JB, Willson TM, Zavacki AM, Moore DD, Lehmann JM** 1999 Bile acids: natural ligands for an orphan nuclear receptor. Science 284:1365–1368
125. **Rader DJ** 2007 Liver X receptor and farnesoid X receptor as therapeutic targets. Am J Cardiol 100:n15–n19
126. **Goodwin B, Jones SA, Price RR, Watson MA, McKee DD, Moore LB, Galardi C, Wilson JG, Lewis MC, Roth ME, Maloney PR, Willson TM, Kliewer SA** 2000 A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell 6:517–526
127. **Houten SM, Watanabe M, Auwerx J** 2006 Endocrine functions of bile acids. EMBO J 25:1419–1425
128. **Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, Luo G, Jones SA, Goodwin B, Richardson JA, Gerard RD, Repa JJ, Mangelsdorf DJ, Kliewer SA** 2005 Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell Metab 2:217–225
129. **Lundasen T, Galman C, Angelin B, Rudling M** 2006 Circulating intestinal fibroblast growth factor 19 has a pronounced diurnal variation and modulates hepatic bile acid synthesis in man. J Intern Med 260:530–536
130. **Kuipers F, Stroeve JH, Caron S, Staels B** 2007 Bile acids, farnesoid X receptor, atherosclerosis and metabolic control. Curr Opin Lipidol 18:289–297
131. **Gupta S, Stravitz RT, Dent P, Hylemon PB** 2001 Down-regulation of cholesterol 7α-hydroxylase (CYP7A1) gene expression by bile acids in primary rat hepatocytes is mediated by the c-Jun N-terminal kinase pathway. J Biol Chem 276:15816–15822
132. **Miller NE, Nestel PJ** 1974 Triglyceride-lowering effect of chenodeoxycholic acid in patients with endogenous hypertriglyceridaemia. Lancet 2:929–931
133. **Bilz S, Samuel V, Morino K, Savage D, Choi CS, Shulman GI** 2006 Activation of the farnesoid X receptor improves lipid metabolism in combined hyperlipidemic hamsters. Am J Physiol Endocrinol Metab 290:E716–E722
134. **Zhang Y, Lee FY, Barrera G, Lee H, Vales C, Gonzalez FJ, Willson TM, Edwards PA** 2006 Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. Proc Natl Acad Sci USA 103:1006–1011
135. **Watanabe M, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, Moore DD, Auwerx J** 2004 Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SREBP-1c. J Clin Invest 113:1408–1418
136. **Tomlinson E, Fu L, John L, Hultgren B, Huang X, Renz M, Stephan JP, Tsai SP, Powell-Braxton L, French D, Stewart TA** 2002 Transgenic mice expressing human fibroblast growth factor-19 display increased metabolic rate and decreased adiposity. Endocrinology 143:1741–1747
137. **Kast HR, Nguyen CM, Sinal CJ, Jones SA, Laffitte BA, Reue K, Gonzalez FJ, Willson TM, Edwards PA** 2001 Farnesoid X-activated receptor induces apolipoprotein C-II transcription: a molecular mechanism linking plasma triglyceride levels to bile acids. Mol Endocrinol 15:1720–1728

138. **Ma K, Saha PK, Chan L, Moore DD** 2006 Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 116: 1102–1109
139. **Fiorucci S, Rizzo G, Donini A, Distrutti E, Santucci L** 2007 Targeting farnesoid X receptor for liver and metabolic disorders. Trends Mol Med 13:298–309
140. **Urizar NL, Liverman AB, Dodds DT, Silva FV, Ordentlich P, Yan Y, Gonzalez FJ, Heyman RA, Mangelsdorf DJ, Moore DD** 2002 A natural product that lowers cholesterol as an antagonist ligand for FXR. Science 296:1703–1706
141. **Urizar NL, Dowhan DH, Moore DD** 2000 The farnesoid X-activated receptor mediates bile acid activation of phospholipid transfer protein gene expression. J Biol Chem 275:39313–39317
142. **Claudel T, Sturm E, Duez H, Torra IP, Sirvent A, Kosykh V, Fruchart JC, Dallongeville J, Hum DW, Kuipers F, Staels B** 2002 Bile acid-activated nuclear receptor FXR suppresses apolipoprotein A-I transcription via a negative FXR response element. J Clin Invest 109:961–971
143. **Ueno T, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, Torimura T, Inuzuka S, Sata M, Tanikawa K** 1997 Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. J Hepatol 27:103–107
144. **Sreenivasa BC, Alexander G, Kalyani B, Pandey R, Rastogi S, Pandey A, Choudhuri G** 2006 Effect of exercise and dietary modification on serum aminotransferase levels in patients with nonalcoholic steatohepatitis. J Gastroenterol Hepatol 21:191–198
145. **Lawlor DA, Sattar N, Smith GD, Ebrahim S** 2005 The associations of physical activity and adiposity with alanine aminotransferase and α-glutamyltransferase. Am J Epidemiol 161:1081–1088
146. **Perseghin G, Lattuada G, De Cobelli F, Ragogna F, Ntali G, Esposito A, Belloni E, Canu T, Terruzzi I, Scifo P, Del Maschio A, Luzi L** 2007 Habitual physical activity is associated with intrahepatic fat content in humans. Diabetes Care 30:683–688
147. **Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, Goto T, Westerbacka J, Sovijarvi A, Halavaara J, Yki-Jarvinen H** 2002 Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab 87: 3023–3028
148. **Nguyen-Duy TB, Nichaman MZ, Church TS, Blair SN, Ross R** 2003 Visceral fat and liver fat are independent predictors of metabolic risk factors in men. Am J Physiol Endocrinol Metab 284: E1065–E1071
149. **Kantartzis K, Thamer C, Peter A, Machann J, Schick F, Niess A, Fritsche A, Haring H, Stefan N,** High cardiorespiratory fitness independently predicts decrease in liver fat during a lifestyle intervention in humans. Gut (in press)
150. **Sui X, LaMonte MJ, Laditka JN, Hardin JW, Chase N, Hooker SP, Blair SN** 2007 Cardiorespiratory fitness and adiposity as mortality predictors in older adults. JAMA 298:2507–2516
151. **Stefan N, Kantartzis K, Haring HU** 2008 Cardiorespiratory fitness, adiposity, and mortality. JAMA 299:1013–1014
152. **Rankinen T, Bouchard C** 2007 Invited commentary: physical activity, mortality, and genetics. Am J Epidemiol 166:260–262
153. **Stefan N, Thamer C, Staiger H, Machicao F, Machann J, Schick F, Venter C, Niess A, Laakso M, Fritsche A, Haring HU** 2007 Genetic variations in PPARD and PPARGC1A determine mitochondrial function and change in aerobic physical fitness and insulin sensitivity during lifestyle intervention. J Clin Endocrinol Metab 92:1827–1833
154. **Wang YX, Lee CH, Tiep S, Yu RT, Ham J, Kang H, Evans RM** 2003 Peroxisome-proliferator-activated receptor δ activates fat metabolism to prevent obesity. Cell 113:159–170
155. **Goodpaster BH, Katsiaras A, Kelley DE** 2003 Enhanced fat oxidation through physical activity is associated with improvements in insulin sensitivity in obesity. Diabetes 52:2191–2197
156. **Church TS, Earnest CP, Skinner JS, Blair SN** 2007 Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA 297:2081–2091
157. **Toledo FG, Watkins S, Kelley DE** 2006 Changes induced by physical activity and weight loss in the morphology of intermyofibrillar mitochondria in obese men and women. J Clin Endocrinol Metab 91:3224–3227
158. **Thamer C, Machann J, Stefan N, Schafer SA, Machicao F, Staiger H, Laakso M, Bottcher M, Claussen C, Schick F, Fritsche A, Haring HU** 2008 Variations in PPARD determine the change in body composition during lifestyle intervention: a whole-body magnetic resonance study. J Clin Endocrinol Metab 93:1497–1500
159. **Wei Y, Rector RS, Thyfault JP, Ibdah JA** 2008 Nonalcoholic fatty liver disease and mitochondrial dysfunction. World J Gastroenterol 14:193–199
160. **Ibdah JA, Perlegas P, Zhao Y, Angdisen J, Borgerink H, Shadoan MK, Wagner JD, Matern D, Rinaldo P, Cline JM** 2005 Mice heterozygous for a defect in mitochondrial trifunctional protein develop hepatic steatosis and insulin resistance. Gastroenterology 128:1381–1390
161. **Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN** 2001 Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 120:1183–1192
162. **Gesta S, Tseng YH, Kahn CR** 2007 Developmental origin of fat: tracking obesity to its source. Cell 131:242–256
163. **Pietilainen KH, Rissanen A, Kaprio J, Makimattila S, Hakkinen AM, Westerbacka J, Sutinen J, Vehkavaara S, Yki-Jarvinen H** 2005 Acquired obesity is associated with increased liver fat, intra-abdominal fat, and insulin resistance in young adult monozygotic twins. Am J Physiol Endocrinol Metab 288:E768–E774
164. **Kohjima M, Enjoji M, Higuchi N, Kato M, Kotoh K, Yoshimoto T, Fujino T, Yada M, Yada R, Harada N, Takayanagi R, Nakamuta M** 2007 Re-evaluation of fatty acid metabolism-related gene expression in nonalcoholic fatty liver disease. Int J Mol Med 20: 351–358
165. **Westerbacka J, Kolak M, Kiviluoto T, Arkkila P, Siren J, Hamsten A, Fisher RM, Yki-Jarvinen H** 2007 Genes involved in fatty acid partitioning and binding, lipolysis, monocyte/macrophage recruitment, and inflammation are overexpressed in the human fatty liver of insulin-resistant subjects. Diabetes 56:2759–2765
166. **Rubio A, Guruceaga E, Vazquez-Chantada M, Sandoval J, Martinez-Cruz LA, Segura V, Sevilla JL, Podhorski A, Corrales FJ, Torres L, Rodriguez M, Aillet F, Ariz U, Arrieta FM, Caballeria J, Martin-Duce A, Lu SC, Martinez-Chantar ML, Mato JM** 2007 Identification of a gene-pathway associated with non-alcoholic steatohepatitis. J Hepatol 46:708–718
167. **Chiappini F, Barrier A, Saffroy R, Domart MC, Dagues N, Azoulay D, Sebagh M, Franc B, Chevalier S, Debuire B, Dudoit S, Lemoine A** 2006 Exploration of global gene expression in human liver steatosis by high-density oligonucleotide microarray. Lab Invest 86:154–165
168. **Day CP** 2006 Genes or environment to determine alcoholic liver disease and non-alcoholic fatty liver disease. Liver Int 26:1021–1028
169. **Motomura W, Inoue M, Ohtake T, Takahashi N, Nagamine M, Tanno S, Kohgo Y, Okumura T** 2006 Up-regulation of ADRP in fatty liver in human and liver steatosis in mice fed with high fat diet. Biochem Biophys Res Commun 340:1111–1118
170. **Younossi ZM, Baranova A, Ziegler K, Del Giacco L, Schlauch K, Born TL, Elariny H, Gorreta F, VanMeter A, Younoszai A, Ong JP, Goodman Z, Chandhoke V** 2005 A genomic and proteomic study of the spectrum of nonalcoholic fatty liver disease. Hepatology 42:665–674
171. **Bernard S, Touzet S, Personne I, Lapras V, Bondon PJ, Berthezene F, Moulin P** 2000 Association between microsomal triglyceride transfer protein gene polymorphism and the biological features of liver steatosis in patients with type II diabetes. Diabetologia 43: 995–999
172. **Wang H, Zhang H, Jia Y, Zhang Z, Craig R, Wang X, Elbein SC** 2004 Adiponectin receptor 1 gene (ADIPOR1) as a candidate for type 2 diabetes and insulin resistance. Diabetes 53:2132–2136
173. **Damcott CM, Ott SH, Pollin TI, Reinhart LJ, Wang J, O'Connell JR, Mitchell BD, Shuldiner AR** 2005 Genetic variation in adiponectin receptor 1 and adiponectin receptor 2 is associated with type 2 diabetes in the Old Order Amish. Diabetes 54:2245–2250
174. **Hara K, Horikoshi M, Kitazato H, Yamauchi T, Ito C, Noda M, Ohashi J, Froguel P, Tokunaga K, Nagai R, Kadowaki T** 2005 Absence of an association between the polymorphisms in the genes

encoding adiponectin receptors and type 2 diabetes. Diabetologia 48:1307–1314
175. **Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y** 2002 Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 8:731–737
176. **Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, Yano W, Froguel P, Nagai R, Kimura S, Kadowaki T, Noda T** 2002 Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 277:25863–25866
177. **Kantartzis K, Fritsche A, Tschritter O, Thamer C, Haap M, Schafer S, Stumvoll M, Haring HU, Stefan N** 2005 The association between plasma adiponectin and insulin sensitivity in humans depends on obesity. Obes Res 13:1683–1691
178. **Martin LJ, Woo JG, Daniels SR, Goodman E, Dolan LM** 2005 The relationships of adiponectin with insulin and lipids are strengthened with increasing adiposity. J Clin Endocrinol Metab 90:4255–4259
179. **Kantartzis K, Fritsche A, Machicao F, Haring HU, Stefan N** 2006 The −8503 G/A polymorphism of the adiponectin receptor 1 gene is associated with insulin sensitivity dependent on adiposity. Diabetes Care 29:464
180. **Lowell BB, Shulman GI** 2005 Mitochondrial dysfunction and type 2 diabetes. Science 307:384–387
181. **Lin J, Handschin C, Spiegelman BM** 2005 Metabolic control through the PGC-1 family of transcription coactivators. Cell Metab 1:361–370
182. **Finck BN, Kelly DP** 2006 PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. J Clin Invest 116:615–622
183. **Yoon JC, Puigserver P, Chen G, Donovan J, Wu Z, Rhee J, Adelmant G, Stafford J, Kahn CR, Granner DK, Newgard CB, Spiegelman BM** 2001 Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1. Nature 413:131–138
184. **Kantartzis K, Machicao F, Machann J, Schick F, Fritsche A, Häring HU, Stefan N**, The DGAT2 gene is a candidate for dissociation between fatty liver and insulin resistance in humans. Clin Sci (Lond), in press
185. **Hirota Y, Ohara T, Zenibayashi M, Kuno S, Fukuyama K, Teranishi T, Kouyama K, Miyake K, Maeda E, Kasuga M** 2007 Lack of association of CPT1A polymorphisms or haplotypes on hepatic lipid content or insulin resistance in Japanese individuals with type 2 diabetes mellitus. Metabolism 56:656–661
186. **Deeb SS, Zambon A, Carr MC, Ayyobi AF, Brunzell JD** 2003 Hepatic lipase and dyslipidemia: interactions among genetic variants, obesity, gender, and diet. J Lipid Res 44:1279–1286
187. **Deeb SS, Peng R** 2000 The C-514T polymorphism in the human hepatic lipase gene promoter diminishes its activity. J Lipid Res 41:155–158
188. **Zambon A, Deeb SS, Hokanson JE, Brown BG, Brunzell JD** 1998 Common variants in the promoter of the hepatic lipase gene are associated with lower levels of hepatic lipase activity, buoyant LDL, and higher HDL2 cholesterol. Arterioscler Thromb Vasc Biol 18:1723–1729
189. **Tahvanainen E, Syvanne M, Frick MH, Murtomaki-Repo S, Antikainen M, Kesaniemi YA, Kauma H, Pasternak A, Taskinen MR, Ehnholm C** 1998 Association of variation in hepatic lipase activity with promoter variation in the hepatic lipase gene. The LOCAT Study Investigators. J Clin Invest 101:956–960
190. **Stefan N, Schafer S, Machicao F, Machann J, Schick F, Claussen CD, Stumvoll M, Haring HU, Fritsche A** 2005 Liver fat and insulin resistance are independently associated with the −514C>T polymorphism of the hepatic lipase gene. J Clin Endocrinol Metab 90:4238–4243
191. **Stumvoll M, Haring H** 2002 The peroxisome proliferator-activated receptor-γ2 Pro12Ala polymorphism. Diabetes 51:2341–2347
192. **Kantartzis K, Fritsche A, Machicao F, Stumvoll M, Machann J, Schick F, Haring HU, Stefan N** 2007 Upstream transcription factor 1 gene polymorphisms are associated with high antilipolytic insulin sensitivity and show gene-gene interactions. J Mol Med 85: 55–61
193. **Pajukanta P, Lilja HE, Sinsheimer JS, Cantor RM, Lusis AJ, Gentile M, Duan XJ, Soro-Paavonen A, Naukkarinen J, Saarela J, Laakso M, Ehnholm C, Taskinen MR, Peltonen L** 2004 Familial combined hyperlipidemia is associated with upstream transcription factor 1 (USF1). Nat Genet 36:371–376
194. **Coon H, Xin Y, Hopkins PN, Cawthon RM, Hasstedt SJ, Hunt SC** 2005 Upstream stimulatory factor 1 associated with familial combined hyperlipidemia, LDL cholesterol, and triglycerides. Hum Genet 117:444–451
195. **Sookoian S, Castano G, Gemma C, Gianotti TF, Pirola CJ** 2007 Common genetic variations in CLOCK transcription factor are associated with nonalcoholic fatty liver disease. World J Gastroenterol 13:4242–4248
196. **Vance DE, Walkey CJ, Cui Z** 1997 Phosphatidylethanolamine N-methyltransferase from liver. Biochim Biophys Acta 1348:142–150
197. **Walkey CJ, Yu L, Agellon LB, Vance DE** 1998 Biochemical and evolutionary significance of phospholipid methylation. J Biol Chem 273:27043–27046
198. **Song J, da Costa KA, Fischer LM, Kohlmeier M, Kwock L, Wang S, Zeisel SH** 2005 Polymorphism of the PEMT gene and susceptibility to nonalcoholic fatty liver disease (NAFLD). FASEB J 19: 1266–1271
199. **Frayling TM** 2007 Genome-wide association studies provide new insights into type 2 diabetes aetiology. Nat Rev Genet 8:657–662
200. **Chen Y, Rollins J, Paigen B, Wang X** 2007 Genetic and genomic insights into the molecular basis of atherosclerosis. Cell Metab 6:164–179
201. **Villanova N, Moscatiello S, Ramilli S, Bugianesi E, Magalotti D, Vanni E, Zoli M, Marchesini G** 2005 Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. Hepatology 42:473–480
202. **Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, Cigolini M, Falezza G, Arcaro G** 2006 Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 29:1325–1330
203. **Brea A, Mosquera D, Martin E, Arizti A, Cordero JL, Ros E** 2005 Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. Arterioscler Thromb Vasc Biol 25: 1045–1050
204. **Targher G** 2007 Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. Diabet Med 24:1–6
205. **Ginsberg HN, Zhang YL, Hernandez-Ono A** 2006 Metabolic syndrome: focus on dyslipidemia. Obesity (Silver Spring) 14(Suppl 1): 41S–49S
206. **Toledo FG, Sniderman AD, Kelley DE** 2006 Influence of hepatic steatosis (fatty liver) on severity and composition of dyslipidemia in type 2 diabetes. Diabetes Care 29:1845–1850
207. **Adiels M, Taskinen MR, Packard C, Caslake MJ, Soro-Paavonen A, Westerbacka J, Vehkavaara S, Hakkinen A, Olofsson SO, Yki-Jarvinen H, Boren J** 2006 Overproduction of large VLDL particles is driven by increased liver fat content in man. Diabetologia 49:755–765
208. **Cali AM, Zern TL, Taksali SE, de Oliveira AM, Dufour S, Otvos JD, Caprio S** 2007 Intrahepatic fat accumulation and alterations in lipoprotein composition in obese adolescents: a perfect proatherogenic state. Diabetes Care 30:3093–3098
209. **Adeli K, Taghibiglou C, Van Iderstine SC, Lewis GF** 2001 Mechanisms of hepatic very low-density lipoprotein overproduction in insulin resistance. Trends Cardiovasc Med 11:170–176
210. **Taghibiglou C, Rashid-Kolvear F, Van Iderstine SC, Le Tien H, Fantus IG, Lewis GF, Adeli K** 2002 Hepatic very low density lipoprotein-apoB overproduction is associated with attenuated hepatic insulin signaling and overexpression of protein-tyrosine phosphatase 1B in a fructose-fed hamster model of insulin resistance. J Biol Chem 277:793–803
211. **Nikkila EA, Huttunen JK, Ehnholm C** 1977 Postheparin plasma lipoprotein lipase and hepatic lipase in diabetes mellitus. Relationship to plasma triglyceride metabolism. Diabetes 26:11–21
212. **Howard BV, Abbott WG, Beltz WF, Harper IT, Fields RM, Grundy SM, Taskinen MR** 1987 Integrated study of low density

lipoprotein metabolism and very low density lipoprotein metabolism in non-insulin-dependent diabetes. Metabolism 36:870–877
213. **Goldberg IJ** 2001 Clinical review 124: diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab 86:965–971
214. **Julius U** 2003 Influence of plasma free fatty acids on lipoprotein synthesis and diabetic dyslipidemia. Exp Clin Endocrinol Diabetes 111:246–250
215. **Lewis GF** 1997 Fatty acid regulation of very low density lipoprotein production. Curr Opin Lipidol 8:146–153
216. **Navab M, Anantharamaiah GM, Reddy ST, Van Lenten BJ, Ansell BJ, Fogelman AM** 2006 Mechanisms of disease: proatherogenic HDL—an evolving field. Nat Clin Pract Endocrinol Metab 2:504–511
217. **Rader DJ** 2006 Molecular regulation of HDL metabolism and function: implications for novel therapies. J Clin Invest 116:3090–3100
218. **Kontush A, Chapman MJ** 2006 Antiatherogenic small, dense HDL—guardian angel of the arterial wall? Nat Clin Pract Cardiovasc Med 3:144–153
219. **Groop PH, Thomas MC, Rosengard-Barlund M, Mills V, Ronnback M, Thomas S, Forsblom C, Taskinen MR, Viberti G** 2007 HDL composition predicts new-onset cardiovascular disease in patients with type 1 diabetes. Diabetes Care 30:2706–2707
220. **Lamarche B, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Despres JP** 1997 Associations of HDL2 and HDL3 subfractions with ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. Arterioscler Thromb Vasc Biol 17:1098–1105
221. **Soedamah-Muthu SS, Chang YF, Otvos J, Evans RW, Orchard TJ** 2003 Lipoprotein subclass measurements by nuclear magnetic resonance spectroscopy improve the prediction of coronary artery disease in type 1 diabetes. A prospective report from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetologia 46: 674–682
222. **Kantartzis K, Rittig K, Cegan A, Machann J, Schick F, Balletshofer B, Fritsche A, Schleicher E, Haring HU, Stefan N** 2008 Fatty liver is independently associated with alterations in circulating HDL2 and HDL3 subfractions. Diabetes Care 31:366–368
223. **Shoelson SE, Lee J, Goldfine AB** 2006 Inflammation and insulin resistance. J Clin Invest 116:1793–1801
224. **Racanelli V, Rehermann B** 2006 The liver as an immunological organ. Hepatology 43:S54–S62
225. **Shoelson SE, Herrero L, Naaz A** 2007 Obesity, inflammation, and insulin resistance. Gastroenterology 132:2169–2180
226. **Mackay IR** 2002 Hepatoimmunology: a perspective. Immunol Cell Biol 80:36–44
227. **Gale RP, Sparkes RS, Golde DW** 1978 Bone marrow origin of hepatic macrophages (Kupffer cells) in humans. Science 201: 937–938
228. **Keitel V, Donner M, Winandy S, Kubitz R, Haussinger D** 2008 Expression and function of the bile acid receptor TGR5 in Kupffer cells. Biochem Biophys Res Commun 372:78–84
229. **Lauwerys BR, Garot N, Renauld JC, Houssiau FA** 2000 Cytokine production and killer activity of NK/T-NK cells derived with IL-2, IL-15, or the combination of IL-12 and IL-18. J Immunol 165:1847–1853
230. **Gregory SH, Wing EJ** 1998 Neutrophil-Kupffer-cell interaction in host defenses to systemic infections. Immunol Today 19:507–510
231. **Yoshimoto T, Bendelac A, Watson C, Hu-Li J, Paul WE** 1995 Role of NK1.1+ T cells in a TH2 response and in immunoglobulin E production. Science 270:1845–1847
232. **Tilg H, Hotamisligil GS** 2006 Nonalcoholic fatty liver disease: cytokine-adipokine interplay and regulation of insulin resistance. Gastroenterology 131:934–945
233. **Medina J, Fernandez-Salazar LI, Garcia-Buey L, Moreno-Otero R** 2004 Approach to the pathogenesis and treatment of nonalcoholic steatohepatitis. Diabetes Care 27:2057–2066
234. **Lichtman SN, Sartor RB, Keku J, Schwab JH** 1990 Hepatic inflammation in rats with experimental small intestinal bacterial overgrowth. Gastroenterology 98:414–423
235. **Drenick EJ, Fisler J, Johnson D** 1982 Hepatic steatosis after intestinal bypass—prevention and reversal by metronidazole, irrespective of protein-calorie malnutrition. Gastroenterology 82:535–548
236. **Hocking MP, Davis GL, Franzini DA, Woodward ER** 1998 Long-term consequences after jejunoileal bypass for morbid obesity. Dig Dis Sci 43:2493–2499
237. **Wigg AJ, Roberts-Thomson IC, Dymock RB, McCarthy PJ, Grose RH, Cummins AG** 2001 The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor α in the pathogenesis of non-alcoholic steatohepatitis. Gut 48:206–211
238. **Bengmark S** 1998 Ecological control of the gastrointestinal tract. The role of probiotic flora. Gut 42:2–7
239. **Cope K, Risby T, Diehl AM** 2000 Increased gastrointestinal ethanol production in obese mice: implications for fatty liver disease pathogenesis. Gastroenterology 119:1340–1347
240. **Mezey E, Imbembo AL, Potter JJ, Rent KC, Lombardo R, Holt PR** 1975 Endogenous ethanol production and hepatic disease following jejunoileal bypass for morbid obesity. Am J Clin Nutr 28:1277–1283
241. **Spinucci G, Guidetti M, Lanzoni E, Pironi L** 2006 Endogenous ethanol production in a patient with chronic intestinal pseudoobstruction and small intestinal bacterial overgrowth. Eur J Gastroenterol Hepatol 18:799–802
242. **Nair S, Cope K, Risby TH, Diehl AM** 2001 Obesity and female gender increase breath ethanol concentration: potential implications for the pathogenesis of nonalcoholic steatohepatitis. Am J Gastroenterol 96:1200–1204
243. **Billiar TR, Maddaus MA, West MA, Curran RD, Wells CA, Simmons RL** 1988 Intestinal gram-negative bacterial overgrowth in vivo augments the in vitro response of Kupffer cells to endotoxin. Ann Surg 208:532–540
244. **Solga SF, Diehl AM** 2003 Non-alcoholic fatty liver disease: lumen-liver interactions and possible role for probiotics. J Hepatol 38: 681–687
245. **Lichtman SN, Keku J, Schwab JH, Sartor RB** 1991 Hepatic injury associated with small bowel bacterial overgrowth in rats is prevented by metronidazole and tetracycline. Gastroenterology 100: 513–519
246. **Li Z, Yang S, Lin H, Huang J, Watkins PA, Moser AB, Desimone C, Song XY, Diehl AM** 2003 Probiotics and antibodies to TNF inhibit inflammatory activity and improve nonalcoholic fatty liver disease. Hepatology 37:343–350
247. **Loguercio C, Federico A, Tuccillo C, Terracciano F, D'Auria MV, De Simone C, Del Vecchio BC** 2005 Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. J Clin Gastroenterol 39:540–543
248. **Muoio DM, Newgard CB** 2004 Biomedicine. Insulin resistance takes a trip through the ER. Science 306:425–426
249. **Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, Tuncman G, Gorgun C, Glimcher LH, Hotamisligil GS** 2004 Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science 306:457–461
250. **Zhang K, Shen X, Wu J, Sakaki K, Saunders T, Rutkowski DT, Back SH, Kaufman RJ** 2006 Endoplasmic reticulum stress activates cleavage of CREBH to induce a systemic inflammatory response. Cell 124:587–599
251. **Cullinan SB, Diehl JA** 2006 Coordination of ER and oxidative stress signaling: the PERK/Nrf2 signaling pathway. Int J Biochem Cell Biol 38:317–332
252. **Hensley K, Kotake Y, Sang H, Pye QN, Wallis GL, Kolker LM, Tabatabaie T, Stewart CA, Konishi Y, Nakae D, Floyd RA** 2000 Dietary choline restriction causes complex I dysfunction and increased H(2)O(2) generation in liver mitochondria. Carcinogenesis 21:983–989
253. **Yang S, Zhu H, Li Y, Lin H, Gabrielson K, Trush MA, Diehl AM** 2000 Mitochondrial adaptations to obesity-related oxidant stress. Arch Biochem Biophys 378:259–268
254. **Seki S, Kitada T, Yamada T, Sakaguchi H, Nakatani K, Wakasa K** 2002 In situ detection of lipid peroxidation and oxidative DNA damage in non-alcoholic fatty liver diseases. J Hepatol 37:56–62
255. **Eizirik DL, Cardozo AK, Cnop M** 2008 The role for endoplasmic reticulum stress in diabetes mellitus. Endocr Rev 29:42–61
256. **Zambon A, Gervois P, Pauletto P, Fruchart JC, Staels B** 2006 Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-α activators: clinical and experimental evidence. Arterioscler Thromb Vasc Biol 26:977–986

257. **Pepys MB, Hirschfield GM** 2003 C-reactive protein: a critical update. J Clin Invest 111:1805–1812
258. **Anty R, Bekri S, Luciani N, Saint-Paul MC, Dahman M, Iannelli A, Amor IB, Staccini-Myx A, Huet PM, Gugenheim J, Sadoul JL, Marchand-Brustel Y, Tran A, Gual P** 2006 The inflammatory C-reactive protein is increased in both liver and adipose tissue in severely obese patients independently from metabolic syndrome, type 2 diabetes, and NASH. Am J Gastroenterol 101:1824–1833
259. **Park SH, Kim BI, Yun JW, Kim JW, Park DI, Cho YK, Sung IK, Park CY, Sohn CI, Jeon WK, Kim H, Rhee EJ, Lee WY, Kim SW** 2004 Insulin resistance and C-reactive protein as independent risk factors for non-alcoholic fatty liver disease in non-obese Asian men. J Gastroenterol Hepatol 19:694–698
260. **Iwasaki T, Nakajima A, Yoneda M, Terauchi Y** 2006 Relationship between the serum concentrations of C-reactive protein and parameters of adiposity and insulin resistance in patients with type 2 diabetes mellitus. Endocr J 53:345–356
261. **Targher G, Arcaro G** 2007 Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. Atherosclerosis 191: 235–240
262. **Yoneda M, Mawatari H, Fujita K, Iida H, Yonemitsu K, Kato S, Takahashi H, Kirikoshi H, Inamori M, Nozaki Y, Abe Y, Kubota K, Saito S, Iwasaki T, Terauchi Y, Togo S, Maeyama S, Nakajima A** 2007 High-sensitivity C-reactive protein is an independent clinical feature of nonalcoholic steatohepatitis (NASH) and also of the severity of fibrosis in NASH. J Gastroenterol 42:573–582
263. **Kahn BB, Flier JS** 2000 Obesity and insulin resistance. J Clin Invest 106:473–481
264. **Kahn SE, Hull RL, Utzschneider KM** 2006 Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 444: 840–846
265. **Matthaei S, Stumvoll M, Kellerer M, Haring HU** 2000 Pathophysiology and pharmacological treatment of insulin resistance. Endocr Rev 21:585–618
266. **Stumvoll M, Goldstein BJ, van Haeften TW** 2005 Type 2 diabetes: principles of pathogenesis and therapy. Lancet 365:1333–1346
267. **Muniyappa R, Montagnani M, Koh KK, Quon MJ** 2007 Cardiovascular actions of insulin. Endocr Rev 28:463–491
268. **Bloomgarden ZT** 2007 Insulin resistance, dyslipidemia, and cardiovascular disease. Diabetes Care 30:2164–2170
269. **Nigro J, Osman N, Dart AM, Little PJ** 2006 Insulin resistance and atherosclerosis. Endocr Rev 27:242–259
270. **Van Gaal LF, Mertens IL, De Block CE** 2006 Mechanisms linking obesity with cardiovascular disease. Nature 444:875–880
271. **Shulman GI** 2000 Cellular mechanisms of insulin resistance. J Clin Invest 106:171–176
272. **Samuel VT, Liu ZX, Qu X, Elder BD, Bilz S, Befroy D, Romanelli AJ, Shulman GI** 2004 Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. J Biol Chem 279:32345–32353
273. **Willner IR, Waters B, Patil SR, Reuben A, Morelli J, Riely CA** 2001 Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. Am J Gastroenterol 96:2957–2961
274. **Tiikkainen M, Tamminen M, Hakkinen AM, Bergholm R, Vehkavaara S, Halavaara J, Teramo K, Rissanen A, Yki-Jarvinen H** 2002 Liver-fat accumulation and insulin resistance in obese women with previous gestational diabetes. Obes Res 10:859–867
275. **Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, Karim R, Lin R, Samarasinghe D, Liddle C, Weltman M, George J** 2002 NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology 35:373–379
276. **Chalasani N, Deeg MA, Persohn S, Crabb DW** 2003 Metabolic and anthropometric evaluation of insulin resistance in nondiabetic patients with nonalcoholic steatohepatitis. Am J Gastroenterol 98: 1849–1855
277. **Cassader M, Gambino R, Musso G, Depetris N, Mecca F, Cavallo-Perin P, Pacini G, Rizzetto M, Pagano G** 2001 Postprandial triglyceride-rich lipoprotein metabolism and insulin sensitivity in nonalcoholic steatohepatitis patients. Lipids 36:1117–1124
278. **Perseghin G, Bonfanti R, Magni S, Lattuada G, De Cobelli F, Canu T, Esposito A, Scifo P, Ntali G, Costantino F, Bosio L, Ragogna F, Del Maschio A, Chiumello G, Luzi L** 2006 Insulin resistance and whole body energy homeostasis in obese adolescents with fatty liver disease. Am J Physiol Endocrinol Metab 291:E697–E703
279. **Perseghin G, Lattuada G, De Cobelli F, Ntali G, Esposito A, Burska A, Belloni E, Canu T, Ragogna F, Scifo P, Del Maschio A, Luzi L** 2006 Serum resistin and hepatic fat content in nondiabetic individuals. J Clin Endocrinol Metab 91:5122–5125
280. **Bajaj M, Suraamornkul S, Hardies LJ, Pratipanawatr T, DeFronzo RA** 2004 Plasma resistin concentration, hepatic fat content, and hepatic and peripheral insulin resistance in pioglitazone-treated type II diabetic patients. Int J Obes Relat Metab Disord 28:783–789
281. **Stefan N, Hennige AM, Staiger H, Machann J, Schick F, Krober SM, Machicao F, Fritsche A, Haring HU** 2006 α2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. Diabetes Care 29: 853–857
282. **Liska D, Dufour S, Zern TL, Taksali S, Cali AM, Dziura J, Shulman GI, Pierpont BM, Caprio S** 2007 Interethnic differences in muscle, liver and abdominal fat partitioning in obese adolescents. PLoS ONE 2:e569
283. **Teranishi T, Ohara T, Maeda K, Zenibayashi M, Kouyama K, Hirota Y, Kawamitsu H, Fujii M, Sugimura K, Kasuga M** 2007 Effects of pioglitazone and metformin on intracellular lipid content in liver and skeletal muscle of individuals with type 2 diabetes mellitus. Metabolism 56:1418–1424
284. **Koska J, Stefan N, Permana PA, Weyer C, Sonoda M, Bogardus C, Smith SR, Joanisse DR, Funahashi T, Krakoff J, Bunt JC** 2008 Increased fat accumulation in liver may link insulin resistance with subcutaneous abdominal adipocyte enlargement, visceral adiposity, and hypoadiponectinemia in obese individuals. Am J Clin Nutr 87:295–302
285. **Stefan N, Machann J, Schick F, Claussen CD, Thamer C, Fritsche A, Haring HU** 2005 New imaging techniques of fat, muscle and liver within the context of determining insulin sensitivity. Horm Res 64(Suppl 3):38–44
286. **Thamer C, Machann J, Stefan N, Haap M, Schafer S, Brenner S, Kantartzis K, Claussen C, Schick F, Haring H, Fritsche A** 2007 High visceral fat mass and high liver fat are associated with resistance to lifestyle intervention. Obesity (Silver Spring) 15:531–538
287. **Wajchenberg BL** 2000 Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 21:697–738
288. **Ryysy L, Hakkinen AM, Goto T, Vehkavaara S, Westerbacka J, Halavaara J, Yki-Jarvinen H** 2000 Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients. Diabetes 49:749–758
289. **Hwang JH, Stein DT, Barzilai N, Cui MH, Tonelli J, Kishore P, Hawkins M** 2007 Increased intrahepatic triglyceride is associated with peripheral insulin resistance: in vivo MR imaging and spectroscopy studies. Am J Physiol Endocrinol Metab 293:E1663–E1669
290. **Lautamaki R, Borra R, Iozzo P, Komu M, Lehtimaki T, Salmi M, Jalkanen S, Airaksinen KE, Knuuti J, Parkkola R, Nuutila P** 2006 Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 291:E282–E290
291. **Bugianesi E** 2008 Nonalcoholic fatty liver disease (NAFLD) and cardiac lipotoxicity: another piece of the puzzle. Hepatology 47:2–4
292. **Perseghin G, Lattuada G, De Cobelli F, Esposito A, Belloni E, Ntali G, Ragogna F, Canu T, Scifo P, Del Maschio A, Luzi L** 2008 Increased mediastinal fat and impaired left ventricular energy metabolism in young men with newly found fatty liver. Hepatology 47:51–58
293. **Ueki K, Kondo T, Tseng YH, Kahn CR** 2004 Central role of suppressors of cytokine signaling proteins in hepatic steatosis, insulin resistance, and the metabolic syndrome in the mouse. Proc Natl Acad Sci USA 101:10422–10427
294. **Emanuelli B, Peraldi P, Filloux C, Sawka-Verhelle D, Hilton D, Van Obberghen E** 2000 SOCS-3 is an insulin-induced negative regulator of insulin signaling. J Biol Chem 275:15985–15991
295. **Emanuelli B, Peraldi P, Filloux C, Chavey C, Freidinger K, Hilton DJ, Hotamisligil GS, Van Obberghen E** 2001 SOCS-3 inhibits insulin signaling and is up-regulated in response to tumor necrosis

factor-α in the adipose tissue of obese mice. J Biol Chem 276:47944–47949
296. **Ueki K, Kondo T, Kahn CR** 2004 Suppressor of cytokine signaling 1 (SOCS-1) and SOCS-3 cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receptor substrate proteins by discrete mechanisms. Mol Cell Biol 24:5434–5446
297. **Ueki K, Kadowaki T, Kahn CR** 2005 Role of suppressors of cytokine signaling SOCS-1 and SOCS-3 in hepatic steatosis and the metabolic syndrome. Hepatol Res 33:185–192
298. **Farrell GC** 2005 Signalling links in the liver: knitting SOCS with fat and inflammation. J Hepatol 43:193–196
299. **Fryer LG, Parbu-Patel A, Carling D** 2002 The anti-diabetic drugs rosiglitazone and metformin stimulate AMP-activated protein kinase through distinct signaling pathways. J Biol Chem 277:25226–25232
300. **Tiikkainen M, Hakkinen AM, Korsheninnikova E, Nyman T, Makimattila S, Yki-Jarvinen H** 2004 Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes 53:2169–2176
301. **Kintscher U, Law RE** 2005 PPARγ-mediated insulin sensitization: the importance of fat versus muscle. Am J Physiol Endocrinol Metab 288:E287–E291
302. **Lautt WW** 1999 The HISS story overview: a novel hepatic neurohumoral regulation of peripheral insulin sensitivity in health and diabetes. Can J Physiol Pharmacol 77:553–562
303. **Petersen KF, Tygstrup N** 1994 A liver factor increasing glucose uptake in rat hindquarters. J Hepatol 20:461–465
304. **An J, Muoio DM, Shiota M, Fujimoto Y, Cline GW, Shulman GI, Koves TR, Stevens R, Millington D, Newgard CB** 2004 Hepatic expression of malonyl-CoA decarboxylase reverses muscle, liver and whole-animal insulin resistance. Nat Med 10:268–274
305. **Denecke B, Graber S, Schafer C, Heiss A, Woltje M, Jahnen-Dechent W** 2003 Tissue distribution and activity testing suggest a similar but not identical function of fetuin-B and fetuin-A. Biochem J 376:135–145
306. **Auberger P, Falquerho L, Contreres JO, Pages G, Le Cam G, Rossi B, Le Cam A** 1989 Characterization of a natural inhibitor of the insulin receptor tyrosine kinase: cDNA cloning, purification, and anti-mitogenic activity. Cell 58:631–640
307. **Rauth G, Poschke O, Fink E, Eulitz M, Tippmer S, Kellerer M, Haring HU, Nawratil P, Haasemann M, Jahnen-Dechent W**1992 The nucleotide and partial amino acid sequences of rat fetuin. Identity with the natural tyrosine kinase inhibitor of the rat insulin receptor. Eur J Biochem 204:523–529
308. **Srinivas PR, Wagner AS, Reddy LV, Deutsch DD, Leon MA, Goustin AS, Grunberger G** 1993 Serum α 2-HS-glycoprotein is an inhibitor of the human insulin receptor at the tyrosine kinase level. Mol Endocrinol 7:1445–1455
309. **Mathews ST, Srinivas PR, Leon MA, Grunberger G** 1997 Bovine fetuin is an inhibitor of insulin receptor tyrosine kinase. Life Sci 61:1583–1592
310. **Mathews ST, Chellam N, Srinivas PR, Cintron VJ, Leon MA, Goustin AS, Grunberger G** 2000 α2-HSG, a specific inhibitor of insulin receptor autophosphorylation, interacts with the insulin receptor. Mol Cell Endocrinol 164:87–98
311. **Mathews ST, Singh GP, Ranalletta M, Cintron VJ, Qiang X, Goustin AS, Jen KL, Charron MJ, Jahnen-Dechent W, Grunberger G** 2002 Improved insulin sensitivity and resistance to weight gain in mice null for the Ahsg gene. Diabetes 51:2450–2458
312. **Siddiq A, Lepretre F, Hercberg S, Froguel P, Gibson F** 2005 A synonymous coding polymorphism in the α2-Heremans-Schmid glycoprotein gene is associated with type 2 diabetes in French Caucasians. Diabetes 54:2477–2481
313. **Kalabay L, Jakab L, Prohaszka Z, Fust G, Benko Z, Telegdy L, Lorincz Z, Zavodszky P, Arnaud P, Fekete B** 2002 Human fetuin/α2HS-glycoprotein level as a novel indicator of liver cell function and short-term mortality in patients with liver cirrhosis and liver cancer. Eur J Gastroenterol Hepatol 14:389–394
314. **Lin X, Braymer HD, Bray GA, York DA** 1998 Differential expression of insulin receptor tyrosine kinase inhibitor (fetuin) gene in a model of diet-induced obesity. Life Sci 63:145–153
315. **Mori K, Emoto M, Yokoyama H, Araki T, Teramura M, Koyama H, Shoji T, Inaba M, Nishizawa Y** 2006 Association of serum fetuin-A with insulin resistance in type 2 diabetic and nondiabetic subjects. Diabetes Care 29:468
316. **Stefan N, Fritsche A, Weikert C, Boeing H, Joost HG, Häring HU, Schulze MB** 2008 Plasma fetuin-A levels and the risk of type 2 diabetes. Diabetes 57:2762–2767
317. **Ix JH, Wassel CL, Kanaya AM, Vittinghoff E, Johnson KC, Koster A, Cauley JA, Harris TB, Cummings SR, Shlipak MG; Health ABC Study** 2008 Fetuin-A and incident diabetes mellitus in older persons. JAMA 300:182–188
318. **Nishimura T, Nakatake Y, Konishi M, Itoh N** 2000 Identification of a novel FGF, FGF-21, preferentially expressed in the liver. Biochim Biophys Acta 1492:203–206
319. **Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, Sandusky GE, Hammond LJ, Moyers JS, Owens RA, Gromada J, Brozinick JT, Hawkins ED, Wroblewski VJ, Li DS, Mehrbod F, Jaskunas SR, Shanafelt AB** 2005 FGF-21 as a novel metabolic regulator. J Clin Invest 115:1627–1635
320. **Kharitonenkov A, Wroblewski VJ, Koester A, Chen YF, Clutinger CK, Tigno XT, Hansen BC, Shanafelt AB, Etgen GJ** 2007 The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. Endocrinology 148:774–781
321. **Wente W, Efanov AM, Brenner M, Kharitonenkov A, Koster A, Sandusky GE, Sewing S, Treinies I, Zitzer H, Gromada J** 2006 Fibroblast growth factor-21 improves pancreatic β-cell function and survival by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways. Diabetes 55:2470–2478
322. **Moyers JS, Shiyanova TL, Mehrbod F, Dunbar JD, Noblitt TW, Otto KA, Reifel-Miller A, Kharitonenkov A** 2007 Molecular determinants of FGF-21 activity-synergy and cross-talk with PPARγ signaling. J Cell Physiol 210:1–6
323. **Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E** 2007 Hepatic fibroblast growth factor 21 is regulated by PPARα and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab 5:426–437
324. **Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y, Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC, Hammer RE, Mangelsdorf DJ, Kliewer SA** 2007 Endocrine regulation of the fasting response by PPARα-mediated induction of fibroblast growth factor 21. Cell Metab 5:415–425
325. **Moore DD** 2007 Physiology. Sister act. Science 316:1436–1438
326. **Reitman ML** 2007 FGF21: a missing link in the biology of fasting. Cell Metab 5:405–407
327. **Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, Wong RL, Chow WS, Tso AW, Lam KS, Xu A** 2008 Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 57:1246–1253
328. **Blaner WS** 1989 Retinol-binding protein: the serum transport protein for vitamin A. Endocr Rev 10:308–316
329. **Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB** 2005 Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 436:356–362
330. **Abel ED, Peroni O, Kim JK, Kim YB, Boss O, Hadro E, Minnemann T, Shulman GI, Kahn BB** 2001 Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature 409:729–733
331. **Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, Wason CJ, Oberbach A, Jansson PA, Smith U, Kahn BB** 2006 Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med 354:2552–2563
332. **Kloting N, Graham TE, Berndt J, Kralisch S, Kovacs P, Wason CJ, Fasshauer M, Schon MR, Stumvoll M, Bluher M, Kahn BB** 2007 Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. Cell Metab 6:79–87
333. **Stefan N, Hennige AM, Staiger H, Machann J, Schick F, Schleicher E, Fritsche A, Haring HU** 2007 High circulating retinol-binding protein 4 is associated with elevated liver fat but not with total, subcutaneous, visceral, or intramyocellular fat in humans. Diabetes Care 30:1173–1178
334. **Balagopal P, Graham TE, Kahn BB, Altomare A, Funanage V, George D** 2007 Reduction of elevated serum retinol binding protein

in obese children by lifestyle intervention: association with subclinical inflammation. J Clin Endocrinol Metab 92:1971–1974
335. **Lee DC, Lee JW, Im JA** 2007 Association of serum retinol binding protein 4 and insulin resistance in apparently healthy adolescents. Metabolism 56:327–331
336. **Gavi S, Stuart LM, Kelly P, Melendez MM, Mynarcik DC, Gelato MC, McNurlan MA** 2007 Retinol-binding protein 4 is associated with insulin resistance and body fat distribution in nonobese subjects without type 2 diabetes. J Clin Endocrinol Metab 92:1886–1890
337. **Unger RH** 1995 Lipotoxicity in the pathogenesis of obesity-dependent NIDDM. Genetic and clinical implications. Diabetes 44:863–870
338. **Poitout V, Robertson RP** 2008 Glucolipotoxicity: fuel excess and β-cell dysfunction. Endocr Rev 29:351–366
339. **Matsuzaka T, Shimano H, Yahagi N, Kato T, Atsumi A, Yamamoto T, Inoue N, Ishikawa M, Okada S, Ishigaki N, Iwasaki H, Iwasaki Y, Karasawa T, Kumadaki S, Matsui T, Sekiya M, Ohashi K, Hasty AH, Nakagawa Y, Takahashi A, Suzuki H, Yatoh S, Sone H, Toyoshima H, Osuga J, Yamada N** 2007 Crucial role of a long-chain fatty acid elongase, Elovl6, in obesity-induced insulin resistance. Nat Med 13:1193–1202
340. **Wunderlich FT, Luedde T, Singer S, Schmidt-Supprian M, Baumgartl J, Schirmacher P, Pasparakis M, Bruning JC** 2008 Hepatic NF-κB essential modulator deficiency prevents obesity-induced insulin resistance but synergizes with high-fat feeding in tumorigenesis. Proc Natl Acad Sci USA 105:1297–1302
341. **Tokushige K, Takakura M, Tsuchiya-Matsushita N, Taniai M, Hashimoto E, Shiratori K** 2007 Influence of TNF gene polymorphisms in Japanese patients with NASH and simple steatosis. J Hepatol 46:1104–1110
342. **Valenti L, Fracanzani AL, Dongiovanni P, Santorelli G, Branchi A, Taioli E, Fiorelli G, Fargion S** 2002 Tumor necrosis factor α promoter polymorphisms and insulin resistance in nonalcoholic fatty liver disease. Gastroenterology 122:274–280
343. **Monetti M, Levin MC, Watt MJ, Sajan MP, Marmor S, Hubbard BK, Stevens RD, Bain JR, Newgard CB, Farese Sr RV, Hevener AL, Farese Jr RV** 2007 Dissociation of hepatic steatosis and insulin resistance in mice overexpressing DGAT in the liver. Cell Metab 6:69–78
344. **Buhman KK, Chen HC, Farese Jr RV**2001 The enzymes of neutral lipid synthesis. J Biol Chem 276:40369–40372
345. **Yu XX, Murray SF, Pandey SK, Booten SL, Bao D, Song XZ, Kelly S, Chen S, McKay R, Monia BP, Bhanot S** 2005 Antisense oligonucleotide reduction of DGAT2 expression improves hepatic steatosis and hyperlipidemia in obese mice. Hepatology 42:362–371
346. **Choi CS, Savage DB, Kulkarni A, Yu XX, Liu ZX, Morino K, Kim S, Distefano A, Samuel VT, Neschen S, Zhang D, Wang A, Zhang XM, Kahn M, Cline GW, Pandey SK, Geisler JG, Bhanot S, Monia BP, Shulman GI** 2007 Suppression of diacylglycerol acyltransferase-2 (DGAT2), but not DGAT1, with antisense oligonucleotides reverses diet-induced hepatic steatosis and insulin resistance. J Biol Chem 282:22678–22688
347. **Matsuzaka T, Shimano H, Yahagi N, Yoshikawa T, Amemiya-Kudo M, Hasty AH, Okazaki H, Tamura Y, Iizuka Y, Ohashi K, Osuga J, Takahashi A, Yato S, Sone H, Ishibashi S, Yamada N** 2002 Cloning and characterization of a mammalian fatty acyl-CoA elongase as a lipogenic enzyme regulated by SREBPs. J Lipid Res 43:911–920
348. **Moon YA, Shah NA, Mohapatra S, Warrington JA, Horton JD** 2001 Identification of a mammalian long chain fatty acyl elongase regulated by sterol regulatory element-binding proteins. J Biol Chem 276:45358–45366
349. **Samuel VT, Liu ZX, Wang A, Beddow SA, Geisler JG, Kahn M, Zhang XM, Monia BP, Bhanot S, Shulman GI** 2007 Inhibition of protein kinase Cε prevents hepatic insulin resistance in nonalcoholic fatty liver disease. J Clin Invest 117:739–745
350. **Friedel S, Reichwald K, Scherag A, Brumm H, Wermter AK, Fries HR, Koberwitz K, Wabitsch M, Meitinger T, Platzer M, Biebermann H, Hinney A, Hebebrand J** 2007 Mutation screen and association studies in the diacylglycerol O-acyltransferase homolog 2 gene (DGAT2), a positional candidate gene for early onset obesity on chromosome 11q13. BMC Genet 8:17

Endocrine Reviews **is published by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**