13 The Liver and Insulin Resistance: The Important Convergence of Endocrinology and Hepatology

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Introduction

Recognition of a link between insulin resistance (IR) and liver disease dates back at least 100 years to the term "hepatogenous diabetes," which describes the association between cirrhosis and development of diabetes [1], and more recently to the term "diabetic fatty liver," which antedated the now more common terms "nonalcoholic steatohepatitis" (NASH) and "nonalcoholic fatty liver disease" (NAFLD). These terms were introduced in the 1980s and 1990s, respectively. Since their introduction, the ever-rising prevalence of obesity has brought increased attention to these disorders as the hepatic manifestation of "metabolic" or "insulin resistance" syndrome. Indeed, IR appears to be the common link among metabolic syndrome, obesity, and nonalcoholic fatty liver. Metabolic alterations and hepatic steatosis can develop in the insulin-resistant state in the absence of and prior to diabetes mellitus. Moreover, it is now known that IR correlates with increasing fibrosis in other liver diseases including hepatitis C.

These pathological relationships have raised a now-common issue: "Does insulin resistance cause fatty liver or does fatty liver cause insulin resistance?" Below, we will discuss why the answer to this complicated "either – or" metabolic question is actually "yes." In other words, fatty liver both results from IR and contributes to the problem. In order to better understand the relationship between IR and fatty liver disease, it is best to consider them in light of the most basic actions of insulin and other co-variables important in energy homeostasis and, perhaps, to consider the most fundamental disturbance in pathological IR states—disturbed intracellular fatty acid metabolism that leads to "lipotoxicity" or cellular injury due to the excessive accumulation of triglycerides and fatty acids and their subsequent oxidation. By understanding the normal flux of glucose and lipid between the major targets of insulin (adipose, muscle, and liver) and how IR relates to fatty liver disease, we can hopefully identify possibilities for early therapeutic intervention. Moreover, integration of the hepatologist's knowledge of human hepatic pathology and pathophysiology coupled to the

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endocrinologist's knowledge of insulin signaling and the associated metabolism of glucose and fat is essential in managing the growing problem of liver disease associated with the IR syndrome.

Normal Glucose and Lipid Flux in the Fed and Fasting States

The liver plays a central role in maintaining energy homeostasis. It is the major source of glucose production through glycogenolysis and gluconeogenesis. Overall, glucose homeostasis occurs through a balance between energy supply and demands from key organs (muscle, adipose, brain, and liver) and differs in the fed versus fasting state. In the fasting state, rates of glucose production and utilization are equal. In this state, 50% of glucose disposal occurs in the brain, 25% occurs in the splanchnic area, and 25% occurs in muscles [2]. The liver meets its glucose demands through glycogenolysis and later through gluconeogenesis if fasting is prolonged beyond 10–18 h. While other organs are able to synthesize and hydrolyze glycogen, only the liver and kidney express glucose-6-phosphatase, the enzyme required for the release of glucose into the circulation.

Adipose tissue stores of triglycerides are an important source of energy during fasting through the release of stored fatty acids by hormone-sensitive lipase (which is normally inhibited in the fed state by insulin). Once cleaved from glycerol, albumin-bound fatty acids are delivered to other tissues via the fatty acid-binding protein (FABP), which facilitates movement of fatty acids into the cell. There they can then undergo oxidation to provide adenosine triphosphate (ATP) for cellular activity, while glycerol is either used to re-synthesize triglyceride or is converted to glucose through gluconeogenesis in the liver.

During periods of abundant calorie intake, excess glucose is converted to lipids, which are either stored as triglycerides or incorporated into lipoproteins (i.e., very low-density lipoproteins (VLDL)) to be exported out of the liver. De novo fatty acid synthesis from dietary carbohydrate occurs primarily in the liver, in lactating mammary glands, and to a lesser extent in the adipose tissue. In the fed state, triglycerides are synthesized within adipocytes through the action of lipoprotein lipase.

Hormonal Regulation: Insulin, Glucagon, and the Insulin Receptor Signaling Pathway

Under normal conditions, plasma glucose concentration is tightly maintained despite wide fluctuations in glucose supply and utilization during different states (fasting, fed, exercise, rest). Regulation is achieved through the competing hormones, insulin, glucagon, and epinephrine, and is heavily influenced by the activity of adipokines from adipose tissue and, more fundamentally, by the action of increased intracellular fatty acids that alter insulin signaling.

Insulin

Insulin is an anabolic hormone that regulates glucose homeostasis through actions on three integrated target tissues: liver, muscle, and adipose. It stimulates cell growth and differentiation, promotes storage of substrates in liver, fat, and muscle through lipogenesis as well as glycogen and protein synthesis, and inhibits lipolysis, glycogenolysis, and protein breakdown. Following a meal, one-third of the glucose is delivered to the liver, one-third to muscle and adipose, and one-third to non-insulin-dependent tissues (i.e., brain). A rise in plasma glucose concentration stimulates the release of insulin from pancreatic β(beta)-cells. The liver removes 60% of the insulin that enters through the portal vein. Peripheral insulin mediates glucose uptake, glycolysis, and conversion to glycogen in muscle and adipose tissue. Most of the glucose delivered to peripheral tissues is utilized by muscle (80–85%), whereas only a small amount (4–5%) is metabolized in adipose [2]. While glucose disposal in adipose tissue is relatively low compared to muscle, adipose tissue plays a key role in overall glucose homeostasis through the release of free fatty acids (FFAs) and expression of adipokines, as will be discussed below.

Insulin regulates glucose metabolism in the liver through both direct and indirect means. Direct effects on the liver result in decreased

glycogenolysis and gluconeogenesis by decreasing transcription and suppressing the activity of phosphoenolpyruvate carboxylase (PEPCK) and glucose-6-phosphatase (G-6-Pase), which are key enzymes involved in gluconeogenesis [3]. Indirect effects result from insulin's action on peripheral tissues. Insulin causes peripheral uptake of glucose in adipose and muscle tissue by stimulating translocation of the transporter GLUT 4 to the plasma membrane [4]. Insulin is anabolic in muscle by promoting glycogen and lipid synthesis while suppressing lipolysis and gluconeogenesis. Insulin promotes triglyceride storage and decreased FFA release in adipose tissue. The combined effects of insulin on muscle and adipose tissue result in decreased FFA influx into liver, which indirectly leads to less gluconeogenesis.

Glucagon and Epinephrine

Glucagon is a polypeptide secreted by α(alpha)-cells of the pancreas. Under physiologic conditions, it acts on the liver by activating glycogenolysis and has a relatively small role in gluconeogenesis. Glucagon favors partitioning of FFAs released by adipose tissue to oxidation in the liver to acetyl CoA, which can be used to form ketone bodies. Stress hormones including epinephrine, cortisol, and growth hormone increase glucose through stimulation of hepatic gluconeogenesis [5]. Epinephrine is also especially important in activating adenylate cyclase in the adipocyte membrane, which results in the formation of 3,5′-cyclic adenosine monophosphate (AMP) that leads to lipolysis through activation of hormone-sensitive lipase.

Insulin Receptor Signaling Pathway

The insulin receptor is a tetramer composed of 2 extracellular α(alpha)-units bound to 2 membrane-spanning β(beta)-units (Fig. 13.1). Activation begins with binding of insulin to the α(alpha)-subunit, which then triggers autophosphorylation of the β(beta)-subunit. Tyrosine kinase-mediated phosphorylation of the insulin receptor substrate (IRS) then triggers a cascade of pathways that differ depending upon the target tissue and the specific IRS type [6, 7]. Four

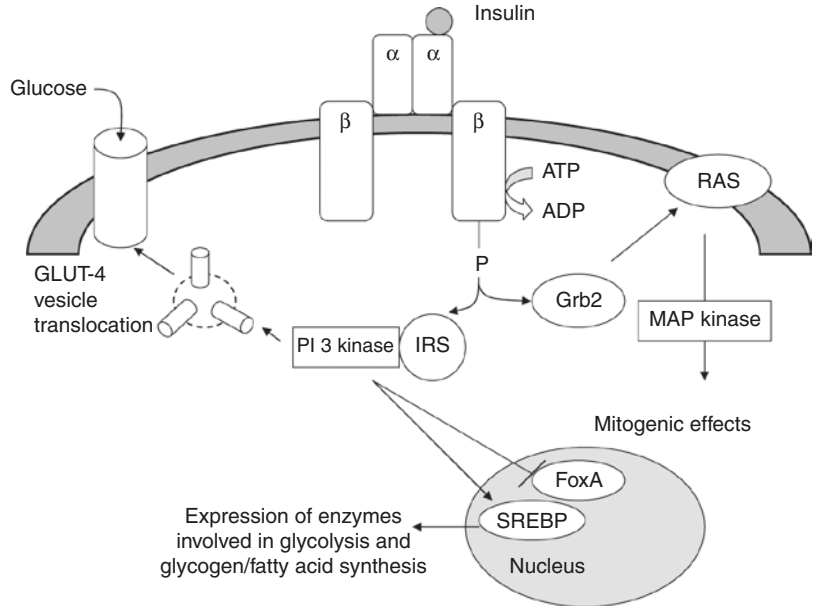

Fig. 13.1 Insulin receptor signaling pathway. Insulin binds to a four-subunit membrane-spanning receptor, triggering tyrosine phosphorylation of the beta subunit, which results in a signaling cascade with combined endpoints: (a) translocation of the GLUT-4 glucose transporter; (b) metabolic effects mediated through steroid regulatory element-binding protein (SREBP); and (c) mitogenic effects (growth, cell differentiation) through activation of the mitogen-activated protein kinase (MAPK) pathway

different types of IRS proteins have been identified: IRS 1 (skeletal muscle), IRS 2 (liver), IRS 3 (adipose, β[beta]-cells, liver), and IRS 4 (thymus, brain, kidney) [8]. Binding of insulin to IRS proteins in muscle and adipose activates phosphatidylinositol 3-kinase (PI3K), which leads to translocation of GLUT 4 glucose transporter proteins to the cell membrane, resulting in an increase in transport of glucose into cells.

Unlike in muscle and adipose tissue, glucose transport in the liver occurs through the GLUT 2 transporter, which is not affected by insulin. This is an important distinction, as failure of insulin to suppress endogenous glucose production by the hepatocyte constitutes one of the pillars of the insulin-resistant state. This nondependence of the hepatocyte on insulin for glucose uptake may in fact allow the liver to function as something of a sink for excess glucose. Insulin signaling by PI3K in the liver appears to be important in activation of downstream expression of genes encoding enzymes involved in glycolysis, glycogen synthesis, and lipid synthesis through steroid regulatory element-binding protein (SREBP)-1c. Gluconeogenesis is inhibited by altering gene expression by the forkhead family of transcriptional factors (FoxA), while growth and cell differentiation effects of insulin are mediated through activation of the mitogen-activated protein kinase (MAPK) pathway via growth factor receptor-binding protein 2 (Grb2).

The Insulin-Resistant State

Insulin Resistance and Insulin Resistance Syndrome Defined

IR is defined as impaired response to normal or elevated insulin levels [9]. While it is often quantified through the euglycemic clamp model [10] and homeostasis model assessment (HOMA) [11] or quantitative insulin sensitivity check index (QUICKI) assessments [12, 13], it is important to note that these only address the role of insulin in glucose metabolism. Using a modification of the fasting insulin and glucose-derived QUICKI, efforts have been made to incorporate fasting fatty acid levels to improve the measurement of IR [14]. However, all these tests have some inherent limitations, although they remain clinically and experimentally very useful [15].

Insulin resistance syndrome has been defined by Reaven to encompass the multiple sequelae that result from the compensatory hyperinsulinemic state associated with IR. This includes dyslipidemia, endothelial dysfunction, and alterations in procoagulant factors and markers of inflammation [16]. Clinical manifestations include diabetes mellitus, cardiovascular disease, hypertension, polycystic ovary syndrome, and NAFLD.

Target Organ Alterations in IR

With the exception of specific genetic defects in the insulin receptor (leprechaunism, Rabson–Mendenhall syndrome, type A syndrome of IR), IR results from the typical combination of predisposing genetic and environmental factors (e.g., excessive calorie intake for the level of physical activity). In the early stages of IR, compensatory hyperinsulinemia maintains euglycemia. Progression to impaired glucose tolerance and later diabetes mellitus occurs when β(beta)-cells of the pancreas are no longer able to provide adequate insulin production. Thus, the development of overt diabetes in insulin resistance syndrome depends on the vitality, or lack thereof, of the islet cells, and other target organ damage resulting from hyperinsulinemia may occur in the absence of diabetes mellitus.

Phenotypic manifestations of insulin resistance syndrome are characterized by alterations in all 3 target tissues. In skeletal muscle, IR is associated with decreased glucose uptake (due to impaired translocation of GLUT4), decreased glycogen synthesis, and increased triglyceride accumulation [17]. In adipocytes, the major effect of IR is increased lipolysis with uncontrolled release of FFAs [18]. Excess FFAs released by adipose tissue plays a role in mediating hepatic IR both directly by interfering with insulin receptor signaling [6], or indirectly by promoting increased hepatic triglyceride accumulation

and subsequent hepatic steatosis. Hepatic IR, defined as impaired ability of insulin to suppress hepatic glucose output, can be viewed as a result of impaired response to insulin resulting from mediators released by peripheral tissue (FFAs and adipokines) or from causes within the liver itself (hepatic steatosis). The association of hepatic steatosis with IR may be bidirectional; products released by IR in the peripheral tissue (FFAs) contribute to hepatic steatosis; however, hepatic steatosis itself also contributes to IR.

Hepatic Steatosis: Is Fatty Liver a Cause, a Result, or Simply a Part of IR?

Epidemiologic studies support a direct association between IR and NAFLD [19–21]. In nondiabetic individuals, hepatic steatosis correlates directly with IR as measured by HOMA-IR [22]. A direct effect of hyperinsulinemia on hepatic steatosis is supported by the observation of a rim of subcapsular hepatic steatosis when insulin is added to peritoneal dialysate [23] and observation of hepatic steatosis following successful intraportal islet transplantation [24]. This provides evidence of a direct effect of hyperinsulinemia on lipogenesis and is supported by the evidence of increased de novo lipogenesis in individuals with NAFLD [25]. Insulin promotes lipogenesis through the activation of sterol response element-binding protein (SREBP)—a major transcription factor that activates genes involved in lipogenesis [26]. Hepatic steatosis associated with IR also results from excess FFAs released by peripheral lipolysis [25, 27].

Whereas there is a clear association between hepatic steatosis and IR, evidence suggesting that hepatic steatosis may itself cause IR is less clear. Evidence in rats with fatty liver in the absence of peripheral IR suggests a direct correlation between hepatic fat accumulation and hepatic IR through stimulation of gluconeogenesis and impaired activation of glycogen synthase [28]. In humans, increased liver fat is associated with impairment of insulin-induced suppression of hepatic glucose output, independent of obesity and fat distribution [29]. However, hepatic steatosis is not invariably associated with IR. For example, individuals with hepatic steatosis in the setting of familial heterozygous hypobetalipoproteinemia (FHBL) have normal HOMA-IR. In addition, patients with exposure to petrochemicals have been clearly shown to develop fatty liver independent of IR, as measured by HOMA [30].

Insulin Resistance in Disease States

Nonalcoholic Fatty Liver Disease

NAFLD is common among individuals with obesity and IR [31, 32], and its prevalence in the general population is expected to increase with rising obesity [33]. Pediatric cases of NAFLD are now being increasingly recognized and are an important public health concern [34]. The term NAFLD is used to include both simple hepatic steatosis without inflammation and NASH. The latter is defined by histologic findings of hepatic steatosis, inflammation, hepatocyte ballooning, and fibrosis [35], in conjunction with clinical and historical features, notably the absence of significant (>20 g daily) alcohol intake. Steatosis without inflammation is generally felt to carry a benign prognosis [36], whereas individuals with NASH can progress to cirrhosis and hepatocellular carcinoma [37]. IR and its metabolic consequences are the fundamental mechanisms leading to hepatic fat accumulation in NAFLD. However, only a subset of individuals with NAFLD has NASH. A “two-hit” hypothesis has been proposed as a pathophysiologic model to account for cellular injury, inflammation, and fibrosis beyond the simple hepatic steatosis observed in the subset of individuals with NASH [38].

Fat accumulation associated with IR is the “first hit” in NASH and results from a derangement in the physiologic mechanisms designed to maintain energy homeostasis. There is preferential activation of cellular pathways characteristic of calorie/macronutrient deficiency despite being in a state of excess. The liver, skeletal muscles, and adipose tissue all play roles in hepatic steatogenesis and promotion of IR. The resistance

of visceral adipocytes to insulin's anti-lipolysis effects drives excess FFA accumulation. Additionally, escalated hepatic de novo lipid synthesis, reduced fatty acid β(beta)-oxidation by hepatocyte mitochondria, and impaired hepatic VLDL export, promote FFA accumulation [39]. The cellular mechanisms by which these paradoxical and maladaptive events occur involve a complex interplay between the insulin/glucagon ratio and the cytokine milieu. These factors together modulate the transcription of the relevant genes and activity of their target enzymes. The sterol regulatory element-binding protein 1c (SREBP 1c), carbohydrate-responsive element-binding protein (ChREBP), and peroxisome proliferator-activated receptors (PPAR) are three such transcription factors. PPARs promote lipid oxidation via increasing uptake of long-chain fatty acids in skeletal muscle and liver and promoting their β(beta)-oxidation in mitochondria. Hepatic lipogenesis is enhanced via SREBP 1c and ChREBP, which are stimulated by insulin and glucose, respectively [40]. The biology of SREBP 1c provides a relevant example of the interrelationship between diet, cytokines, and the pathogenesis of NAFLD. Glucose, sterol, and saturated fat consumption upregulates SREBP 1c synthesis, whereas intake of polyunsaturated fats has the opposite effect [41]. These nuclear transcription factors are also impacted by cytokines released from adipose tissue, the so-called "adipokines." Adiponectin is an insulin-sensitizing adipokine, and animal models have demonstrated an inverse correlation between adiponectin and SREBP 1c levels [42]. The role of adipokines in NAFLD will be discussed in detail below in the context of obesity and IR.

The evolution of simple hepatic steatosis to NASH is characterized histologically by the appearance of cytologic ballooning, necroinflammation, and pericellular fibrosis. The two-hit hypothesis accounts for this transition by proposing additional insults that result in more severe hepatic manifestations of the metabolic syndrome. The inflammatory component of NASH is partially due to macrophage accumulation in visceral adipose tissue. These macrophages secrete pro-inflammatory cytokines, which further promote IR, and contribute to trafficking of inflammatory cells to the steatotic liver [43]. The ensuing hepatocyte apoptosis results from oxidative stress related to reactive oxygen species (ROS) accumulation and immune-mediated cytotoxicity. Mitochondrial dysfunction promotes ROS formation, resulting in both cellular necrosis and a self-propagating feedback cycle from ROS stimulation of tumor necrosis factor-alpha (TNF-α[alpha]) synthesis. TNF-α(alpha) and other pro-inflammatory cytokines potentiate mitochondrial dysfunction and promote the lymphocyte infiltration typical of NASH [40].

The Role of Obesity in IR and NAFLD

While obesity is not essential for the development of IR and NAFLD, the strong association among these three conditions may provide some understanding of how the liver, adipose tissue, and other sites of insulin action are related in the development of clinical manifestations observed in the insulin-resistant state. Epidemiologic studies clearly demonstrate a positive correlation between increasing body mass index (BMI) and IR [44, 45]. Similarly, a positive association between obesity and NAFLD exists [46, 47]. Central to the understanding of how obesity plays a role in IR and NAFLD is the concept that adipose tissue is not only an energy store but also serves a role as an endocrine organ through the release of circulating FFAs and adipokines. One might even go so far as to think of these circulating factors as part of a "vicious cycle" whereby they are both a contributor to, and a result of, IR.

Obesity is associated with elevated circulating FFA levels [48, 49] due to increased adipose mass as well as increased lipolysis due to IR. Increased FFA contributes to peripheral IR [50] via impairment of GLUT-4-mediated glucose transport [51, 52] and hepatic IR through competitive inhibition of IRS 2 signaling by diacylglycerol [53]. In vitro, FFAs promote hepatic IR by stimulating PEPCK and pyruvate carboxylase [54], key enzymes in gluconeogenesis, and by increasing the activity of glucose-6-phosphatase, the enzyme responsible for the release of glucose from the liver [55]. In vivo, increased serum FFA levels are associated with increased hepatic gluconeogenesis and

decreased glycogenolysis [54, 56, 57]. Increased FFAs associated with obesity and IR result in hepatic steatosis through increased triglyceride formation, increased de novo lipogenesis, and decreased secretion of apolipoprotein B, which results in decreased export of triglycerides out of the hepatocyte as VLDL [39].

Altered expression of adipokines (leptin, adiponectin, resistin, TNF-α[alpha]) by adipose tissue in obesity also contributes to IR and hepatic steatosis. Adiponectin is a protein with insulin-sensitizing effects that is expressed exclusively by adipocytes in response to PPAR-γ(gamma) activation. Receptors for adiponectin have been identified in skeletal muscle and liver [58] and are downregulated in obesity-linked IR and diabetes [59]. Serum adiponectin levels correlate inversely with BMI [60, 61] and liver fat content [62–64], suggesting an inhibitory role in obesity and hepatic steatosis. Recombinant adiponectin improves IR in mouse models of obesity and type 2 diabetes [65]. Insulin-sensitizing effects may occur through increased fatty acid oxidation in muscle and decreased fatty acid transport into the liver, resulting in a net decrease in triglyceride accumulation in both muscle and liver [65]. Leptin is a protein expressed by mature adipocytes that acts on the hypothalamus to serve as a signal of energy sufficiency. It is produced in proportion to adipose tissue mass and improves IR and hepatic steatosis in patients with severe lipodystrophy [66]. Serum leptin levels are increased in NASH [67]; however, its role in NASH is debated [68].

Unlike leptin and adiponectin, which are produced exclusively by adipocytes, other adipokines such as TNF-α(alpha) are derived mostly from macrophages in adipose tissue. Increased TNF-α(alpha) levels are found in obese individuals owing to increased macrophage infiltration in adipose tissue [69–71] and overexpression of TNF-α(alpha) by enlarged adipocytes [72]. Levels are elevated in individuals with NAFLD compared to controls matched for age, BMI, and sex [73]. TNF-α(alpha) impairs insulin signaling through serine phosphorylation of IRS-1 [74].

Lipodystrophy Syndromes

Paradoxically, loss of adipose tissue, as seen in patients with lipodystrophy, is also associated with IR. Lipodystrophies are disorders characterized by selective and variable loss of subcutaneous adipose tissue. They are clinically heterogeneous, and the affected patients are predisposed to IR, hypertriglyceridemia, hepatic steatosis, polycystic ovary syndrome, and type 2 diabetes. Lipodystrophies can be either acquired or inherited (familial).

Acquired lipodystrophies are much more common than the inherited forms. The most common form of acquired lipodystrophy is that seen in patients with human immunodeficiency virus (HIV) infection who are receiving treatment with highly active protease inhibitors. Patients typically present with loss of subcutaneous fat in the face, arms, and legs [75], with or without concomitant fat accumulation in the neck and trunk [76]. Patients may develop IR, hypertriglyceridemia, hepatic steatosis, low serum levels of high-density lipoprotein (HDL) cholesterol, and hyperglycemia [77–79]. Possible mechanisms by which protease inhibitors cause lipodystrophy include impaired pre-adipocyte differentiation [80], increased apoptosis of subcutaneous adipocytes [81], and reduced mRNA expression of sterol regulatory element-binding protein 1c (SREBP1c) and peroxisome proliferator-activated receptor γ (gamma) (PPARγ[gamma])—two key transcription factors involved in adipogenesis [82]. In addition, protease inhibitors may directly induce IR by reducing the intrinsic transport activity of glucose transporter 4 [83].

Other forms of acquired lipodystrophies are rare [84]. Patients with acquired generalized lipodystrophy present with clinical features of loss of subcutaneous fat, muscular prominence, acanthosis nigricans, hepatic steatosis, autoimmune hepatitis, and cirrhosis. Patients with acquired partial lipodystrophy have fat loss affecting the face, neck, arms, thorax, and upper abdomen. In contrast, excess fat may be deposited in the hips and legs. Both acquired generalized and partial lipodystrophies occur during child-

hood and adolescence and occur approximately 3–4 times more often in women. Localized lipodystrophies refer to loss of subcutaneous adipose tissue in small areas and may be caused by local injection of medicines such as insulin and corticosteroids, recurrent pressure, trauma, inflammation, or other unknown mechanisms.

Inherited lipodystrophies are extremely rare and are caused by various genetic mutations [84]. Congenital generalized lipodystrophy is an autosomal recessive disorder characterized by near-complete lack of adipose tissue since birth, with clinical features including acanthosis nigricans, hepatic steatosis, cirrhosis, splenomegaly, and umbilical hernia. Patients usually have severe IR/hyperinsulinemia, hypertriglyceridemia, and type 2 diabetes. Familial partial lipodystrophies are characterized by partial loss of subcutaneous fat in various parts of the body with distinct clinical features due to different genetic mutations. Patients may develop hypertriglyceridemia, fatty liver, and type 2 diabetes.

Metabolic complications such as IR, hypertriglyceridemia, hepatic steatosis, and type 2 diabetes increase in frequency and severity with the extent of fat loss. Patients initially develop compensatory hyperinsulinemia and later overt hyperglycemia and type 2 diabetes owing to gradual loss of β(beta)-cell function resulting from islet amyloidosis and cell atrophy [85]. Though the underlying mechanisms remain unclear, it appears that ectopic accumulation of triglycerides may be the major culprit. Indeed, a major function of subcutaneous adipose depot is to store triglycerides during energy excess; and in patients with lipodystrophies the storage capacity decreases or even disappears, leading to the accumulation of excess triglycerides in the liver, intra-abdominal fat depot, and skeletal muscles [86–88].

A large body of evidence has confirmed that accumulation of fat in these sites leads to IR [89–92]. Mice with congenital lipodystrophy manifest with severe IR in the liver and muscle, and hyperglycemia [93]. These mice have higher intracellular fatty acyl-CoA content in both muscle and liver than wild-type mice, and have defects in the insulin activation of IRS-1 and IRS-2 associated PI 3-kinase activity in muscle and liver [94]. The importance of having subcutaneous fat depots is further demonstrated by the observation that transplanting adipose tissue from wild-type mice into the subcutaneous space in lipodystrophic mice reduces liver and muscle lipid contents and reverses IR as manifested by increased muscle glucose uptake and suppressed hepatic glucose production in response to insulin [94].

Patients with severe lipodystrophy have low plasma leptin levels. In mice with congenital lipodystrophy, chronic low-dose leptin treatment reverses IR and diabetes mellitus [95]. This suggests that leptin deficiency may play an important role in the pathogenesis of IR and type 2 diabetes in patients with lipodystrophies. Indeed, recent studies have shown that leptin replacement in these patients results in improved insulin sensitivity in both muscle and liver and better glycemic and lipemic control [66, 96, 97]. Reduced intramyocellular and liver fat contents and reduced appetite could be part of the mechanism [66, 96].

Hepatitis C

IR and the associated steatosis is an emerging aspect of chronic hepatitis C infection. Worsening IR affects chronic hepatitis C in several respects. For example, there appears to be an increased prevalence of type 2 diabetes in hepatitis C patients, especially with increasing age, even when adjusting for confounding variables such as weight [98], and an association between increased HOMA and chronic genotype 1 HCV infection has been observed [99]. The occurrence of IR and the development of steatosis have a significant impact on the risk of disease progression [100–102]. Finally, IR appears to have an impact on the response to interferon-based antiviral therapy, although this aspect remains somewhat uncertain, as it is unclear whether this represents the effects of obesity on drug delivery [103] or direct effects of IR itself. Moreover, more recent studies have failed to confirm results of earlier reports regarding the impact of steatosis and BMI on response, although the association with more

advanced histology seems consistent among studies [104]. It is possible and even likely that some of these relationships are obscured by the tendency of NASH to become decreasingly steatotic as the disease progresses and that fibrosis stage, which appears to be accelerated by steatosis in HCV, is also a predictor of sustained virological response. This may explain why another recent study revealed an association between steatosis and stage-3 fibrosis, but not stage-4 (cirrhosis) fibrosis [105].

Steatosis when present in HCV is, indeed, often associated with typical findings of NASH in these patients and with increased activation of the hepatic stellate cells [106]. The mechanisms by which an HCV-infected liver accumulates excessive triglyceride stores are related to both host and viral factors. Not surprisingly, many such patients have independent risk factors for metabolic syndrome and therefore for NAFLD. However, there are also direct viral replication factors related especially to the metabolism of the nucleocapsid core protein and related to (but not restricted to) certain genotypes of the virus. For example, the prevalence of steatosis in genotype 3 is almost 2 times that of other genotypes [107]. However, both in vitro and in vivo data have indicated that the core protein of other genotypes, including genotype 1, the most common genotype in the United States, alters intracellular fat metabolism [108]. These changes appear to involve significantly decreased levels of PPARα(alpha) and CPT-1, which therefore inhibit fatty acid oxidation. Other mechanisms may be simultaneously at work, including the indirect effects of increased TNFα(alpha) in HCV and HCV-mediated changes in IR phosphorylation [109, 110]. The potential role of insulin-sensitizing agents in conjunction with anti-HCV therapy and related concerns about lipid-lowering agents in HCV are areas in need of further investigation [111].

Summary and Conclusions

Insulin regulates energy homeostasis through its effects on key target organs: liver, adipose tissue, and muscle. Glucose and lipid metabolisms are closely linked via circulating FFAs and adipokines and their effects on insulin receptor signaling, glucose transport, and triglyceride accumulation within these organs. Paradoxically, IR is found in states associated with both adipose excess (obesity) and adipose loss (lipoatrophy). Adipokines released from both adipocytes and macrophages within adipose tissue play key roles in mediating IR and in inflammation. Further understanding of the complex interaction between key target organs and circulating mediators of IR may help guide therapy for NAFLD and other clinical manifestations of the insulin resistance syndrome.

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