Metabolic syndrome and nonalcoholic fatty liver disease: Is insulin resistance the link?

Asrih, Mohamed; Jornayvaz, François

How to cite

ASRIH, Mohamed, JORNAYVAZ, François. Metabolic syndrome and nonalcoholic fatty liver disease: Is insulin resistance the link? In: Molecular and Cellular Endocrinology, 2015, vol. 418, n° Pt 1, p. 55–65. doi: 10.1016/j.mce.2015.02.018

This publication URL: https://archive-ouverte.unige.ch//unige:96970
Publication DOI: 10.1016/j.mce.2015.02.018

Molecular and Cellular Endocrinology 418 (2015) 55–65

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Metabolic syndrome and nonalcoholic fatty liver disease: Is insulin resistance the link?

Mohamed Asrih, François R. Jornayvaz *

Service of Endocrinology, Diabetes and Metabolism, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, Lausanne 1011, Switzerland

ARTICLE INFO

Article history:
Received 19 November 2014
Received in revised form
2 February 2015
Accepted 17 February 2015
Available online 24 February 2015

Keywords:
Metabolic syndrome
NAFLD
Insulin resistance
Ectopic lipids
Inflammation

ABSTRACT

Metabolic syndrome (MetS) is a disease composed of different risk factors such as obesity, type 2 diabetes or dyslipidemia. The prevalence of this syndrome is increasing worldwide in parallel with the rise in obesity. Nonalcoholic fatty liver disease (NAFLD) is now the most frequent chronic liver disease in western countries, affecting more than 30% of the general population. NAFLD encompasses a spectrum of liver manifestations ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, which may ultimately progress to hepatocellular carcinoma. There is accumulating evidence supporting an association between NAFLD and MetS. Indeed, NAFLD is recognized as the liver manifestation of MetS. Insulin resistance is increasingly recognized as a key factor linking MetS and NAFLD. Insulin resistance is associated with excessive fat accumulation in ectopic tissues, such as the liver, and increased circulating free fatty acids, which can further promote inflammation and endoplasmic reticulum stress. This in turn aggravates and maintains the insulin resistant state, constituting a vicious cycle. Importantly, evidence shows that most of the patients developing NAFLD present at least one of the MetS traits. This review will define MetS and NAFLD, provide an overview of the common pathophysiological mechanisms linking MetS and NAFLD, and give a perspective regarding treatment of these ever growing metabolic diseases.

Contents

1. Introduction

Obesity is now a worldwide pandemic and is expected to affect 10% of the global population by 2030 if the current trend is maintained (Webber et al., 2014). In the United States, national surveys

* Corresponding author. Service of Endocrinology, Diabetes and Metabolism, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, 1011 Lausanne, Switzerland. Tel.: +41213140622; fax: +41213140630.
E-mail address: Francois.Jornayvaz@chuv.ch (F.R. Jornayvaz).

http://dx.doi.org/10.1016/j.mce.2015.02.018
0303-7207/

have observed a marked increase in the prevalence of obesity over time. For instance, ~20% of men and ~25% of women in the adult population and more than one-sixth of children are obese (Ogden et al., 2012). However, this increased prevalence of obesity is not confined to western countries. Notably, obesity is recognized as a major health problem in the United Arab Emirates (Hodge et al., 1995; Musaiger, 1996; Popkin, 1994). Moreover, obesity increases at an alarming rate in all Arabic-speaking countries with a prevalence of 2% to 55% in adult females and 1% to 30% in adult males (Badran and Laher, 2011). Other populations are also affected by this disorder, such as Indians, with a recent study reporting a prevalence of overweight and obesity in children up to 23% and 36%, respectively (Hoque et al., 2014). Obesity results from an imbalance between caloric intake and energy expenditure, leading to an excess of energy, which is stored as fat mainly in white adipose tissue (Chugh and Sharma, 2012; McKenney and Short, 2011). Importantly, obesity increases or exacerbates several health problems including cardiovascular diseases and type 2 diabetes (Kopelman, 2000). Metabolic alterations associated with obesity have been recognized and grouped to define the metabolic syndrome (MetS). MetS is a leading cause of mortality and morbidity in industrialized countries (Simons et al., 2011). It is characterized by the combination of multiple disorders including obesity, dyslipidemia, increased blood pressure, insulin resistance and a proinflammatory state (Reaven, 2002). The prevalence of MetS correlates with the global epidemic of obesity and is growing at an alarming rate, affecting more than 20% of the global adult population (Onat, 2011).

The rising epidemic of MetS and its related complications, such as cardiovascular diseases, has been accompanied by an increase in liver alterations including nonalcoholic fatty liver disease (NAFLD) (Angulo, 2002; Marchesini et al., 2003). In particular, it has been proposed that NAFLD may be the hepatic manifestation of MetS (Marchesini et al., 2003). NAFLD encompasses a wide spectrum of manifestations ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis (Tarantino et al., 2012). One of the major hallmarks of this disease is the consistent association with one of the characteristics of MetS, for instance type 2 diabetes mellitus, dyslipidemia or obesity (Vanni et al., 2010). Moreover, NAFLD is clearly associated with insulin resistance, which is a key risk factor for the development of type 2 diabetes (Jornayvaz and Shulman, 2012). Therefore, the aims of this review are 1) to discuss how MetS and NAFLD impact each other; 2) to describe the common mechanisms between these disorders; and 3) to provide an overview of the current diagnosis and treatment of both MetS and NAFLD.

2. Diagnosis and pathogenesis of MetS and NAFLD

MetS has received several definitions during the last decade. Therefore, it was important to find a consensus between different medical associations such as the World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), the National Cholesterol Education Program (NCEP), and finally the Third Adult Treatment Panel (ATPIII) (Alberti et al., 2006). The main aim of this consensus was to identify common criteria in order to use them in the clinical diagnosis of MetS worldwide. Using the ATPIII definition as a basis, the committee came with a new definition. Although insulin resistance is a critical feature of MetS, it remains difficult to measure in day-to-day clinical practice and thus was not included in the new definition. Central obesity, which is much easier to measure, was considered. Therefore, the new definition classified patients with MetS as subjects having central obesity and one of the following factors: raised triglycerides $\geq$1.7 mmol/l; reduced HDL-cholesterol $<$1.03 mmol/l in males and $<$1.29 mmol/l in females; raised systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg; raised fasting plasma glucose, with fasting plasma glucose $\geq$5.6 mmol/l or previously diagnosed type 2 diabetes (Alberti et al., 2006). The major characteristic of this definition is that central obesity is required to diagnose MetS. As insulin resistance is frequently associated with obesity, the consensus considered obesity as a surrogate marker of insulin resistance in the definition of MetS. However, this definition of MetS is still a matter of debate (Jornayvaz et al., 2010b).

NAFLD is a pathological entity encompassing a whole histological spectrum ranging from simple steatosis to steatohepatitis, with inflammation and fibrosis, to cirrhosis (Contos et al., 2004). Cirrhosis, which is irreversible, can further progress to hepatocellular carcinoma (Farazi and DePinho, 2006). The development of NAFLD is notably based on the concept of the “two hits” hypothesis (Day and James, 1998). The first hit is the accumulation of triglycerides, leading to hepatic steatosis, while the second hit is the production of free radicals and inflammatory mediators giving rise to NASH. However, more recently, it has been argued that multiple hits derive simultaneously from adipose tissue and gut to promote liver inflammation, suggesting that cellular inflammation and insulin resistance are acting at the same time (Tilg and Moschen, 2010). Others have proposed that hepatic insulin resistance may be at the origin of the development of NAFLD. Indeed, mice specifically lacking the insulin receptor in the liver (LIRKO mice) develop hepatic insulin resistance associated with hyperglycemia, suggesting that hepatic function is critical to control peripheral insulin responsiveness (Michael et al., 2000). Additionally, this insulin resistance leads to altered liver function. Thus, one could propose that hepatic insulin resistance is the first step in the development of peripheral insulin resistance and NAFLD. In accordance with this hypothesis, deletion of the insulin receptor in skeletal muscle (MIRKO mice) does not impair peripheral glucose levels (Bruning et al., 1998). In addition to insulin resistance, other aspects of MetS such as obesity have been related to NAFLD. For instance, 85% of the patients developing NAFLD present at least one of the MetS characteristics (Gariani et al., 2013).

Clinically, NAFLD does not manifest with specific symptoms and is commonly silent. Currently, the diagnosis of NAFLD is based on exclusion criteria. For instance, causes such as alcohol consumption (more than 20 g/day for women and 30 g/day for men), autoimmune liver disease, viral hepatitis infection, hemochromatosis, Wilson’s disease, or drug consumption, must be excluded before considering NAFLD. Liver biopsy remains the gold standard to diagnose NAFLD, but this approach is associated with potential risks, such as bleeding. Therefore, patients need to be well selected before undergoing liver biopsy, although data are currently lacking regarding specific criteria. Alternative methods to assess NAFLD, such as non invasive imagery, are beyond the scope of this review and have been discussed elsewhere (Musso et al., 2011).

3. NAFLD: the liver manifestation of MetS

NAFLD is frequently associated with central obesity, insulin resistance and dyslipidemia, all of which are features of MetS. Therefore, NAFLD has been identified as the liver manifestation of MetS, with obesity as the main common component. Nevertheless, it should be noted that NAFLD also develops in non-obese patients, even though it is less common. For instance, several studies have shown that NAFLD could be detected in non-obese subjects with metabolic alterations (Kim et al., 2004; Musso et al., 2008; Sinn et al., 2012). Furthermore, these studies reported that NAFLD could be considered as an independent predictor of insulin resistance in non-obese patients (Kim et al., 2004; Musso et al., 2008;

Sinn et al., 2012). Although NAFLD is found in non-obese subjects, it remains closely related to central (or visceral) obesity. Indeed, Jeong and coworkers have reported a relationship between visceral fat and the prevalence of both NAFLD and MetS (Jeong et al., 2008). In their prospective study, they included 224 hospital workers and assessed the prevalence of NAFLD and MetS, as well as visceral fat thickness. MetS was diagnosed according to the ATP III guidelines, and NAFLD was diagnosed by ultrasonography. Altogether, their data revealed that 73.1% of the subjects with MetS had NAFLD, indicating a strong correlation between these two disorders. Additionally, visceral fat thickness, assessed by ultrasonography with a 3.5-MHz convex probe, was significantly increased by both MetS and the severity of NAFLD, indicating a direct association and suggesting that visceral fat could be considered as a common denominator of both MetS and NAFLD (Jeong et al., 2008). In line with these results, Kwon et al., studied a total of 29,994 adults who underwent routine comprehensive health evaluations, and found that NAFLD is associated with components of MetS such as insulin resistance or type 2 diabetes. Interestingly, this association was stronger in non-obese than in obese individuals (Kwon et al., 2012). Furthermore, Kwon et al., found that the differences in the amount of visceral fat between individuals with NAFLD and those without NAFLD may be greater in the non-obese group than in the obese group (Kwon et al., 2012). This suggests that visceral fat could be used as an important predictive factor for the development of NAFLD (Eguchi et al., 2006).

4. Common pathophysiological mechanisms involved in MetS and NAFLD

The increased prevalence of both MetS and NAFLD is mainly due to over-nutrition and a sedentary lifestyle. However, the contribution of MetS to NAFLD involves different factors among which insulin resistance, central obesity, inflammation, oxidative stress and genetic predispositions. Nevertheless, several controversies remain regarding which of these mechanisms comes first and how they drive each other to promote MetS and NAFLD. Therefore, this section will discuss studies highlighting these mechanisms.

4.1. Insulin resistance: a critical node between MetS and NAFLD

Insulin resistance, defined as the failure of insulin to stimulate glucose transport into its target cells, plays a central etiological role in MetS and is harmful for the liver since it likely promotes NAFLD (Bugianesi et al., 2005). Insulin is a pleiotropic hormone that regulates several cell functions among which stimulation of glucose transport, cell growth, energy balance and regulation of gene expression (de Luca and Olefsky, 2008). Insulin initiates its action through binding to the insulin receptor which results into dimerization and autophosphorylation of this insulin receptor. This in turn recruits and phosphorylates the insulin receptor substrate (IRS), IRS2 being the most represented isoform in the liver. Downstream, this actor modulates two different signaling pathways: the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (PKB/AKT) pathway, which promotes the metabolic actions of insulin, and the mitogen-activated protein kinase (MAPK) pathway, which regulates the expression of genes involved in cell growth and differentiation (Taniguchi et al., 2006). Alteration of these signaling pathways by various factors could therefore lead to insulin resistance. Among these, free fatty acids are recognized as a significant risk factor contributing to the development of insulin resistance in several organs. Notably, hepatic insulin resistance correlates with increased liver fat content, the latter mainly originating from plasma free fatty acids (Donnelly et al., 2005). Plasma free fatty acids are largely released by white adipose tissue when insulin resistance develops. Indeed, insulin resistance in this tissue results in increased lipolysis, which leads to high levels of circulating fatty acids (Fig. 1) (Eguchi et al., 2006). Altogether, hepatic fat accumulation causes NAFLD, subsequently leading to hepatic insulin resistance. Therefore, insulin resistance could be considered as the missing link between MetS and NAFLD, even in the absence of obesity. However, the mechanisms of hepatic insulin resistance remain poorly characterized in NAFLD. Several hypotheses regarding the development of hepatic insulin resistance in NAFLD can be considered and will be further discussed, such as ectopic fat accumulation, inflammation, endoplasmic reticulum (ER) stress and gut microbiota.

4.1.1. Ectopic fat accumulation promotes hepatic insulin resistance

As previously discussed, insulin resistance, a key feature of MetS, plays a critical role in the development of NAFLD. Indeed, numerous studies in animal models of NAFLD reveal a clear link between NAFLD and hepatic insulin resistance (Birkenfeld et al., 2011b, Camporez et al., 2013a, 2013b; Cantley et al., 2013; Jornayvaz et al., 2010a, 2011, 2012; Lee et al., 2011). Notably, evidence suggests that certain lipid intermediates, such as diacylglycerols, activate novel protein kinase Cε (PKCε) (Fig. 2), which further inhibits the insulin receptor and its downstream signaling (Samuel et al., 2004). Moreover, in obese non diabetic humans with NAFLD, Kumashiro et al., could show that hepatic diacylglycerol content was the best predictor of insulin resistance, when assessed by the HOMA index (Kumashiro et al., 2011). However, whether insulin resistance promotes hepatic lipid accumulation or whether NAFLD initiates insulin resistance remains unclear to date. Nevertheless, it appears that skeletal muscle insulin resistance can cause insulin resistance in other tissues (Jornayvaz and Shulman, 2012; Perry et al., 2014). For instance, deletion of the muscle insulin receptor in mice (MIRKO mice) results in the development of insulin resistance in other organs, possibly through substrates redistribution toward adipose tissue (Kim et al., 2000b). Similarly, mice lacking the insulin-responsive glucose transporter 4 (GLUT4) in skeletal muscle exhibit altered insulin sensitivity with redistribution of substrates to the liver, which promotes liver steatosis (Kotani et al., 2004). These results in animals were translated to humans, where skeletal muscle insulin resistance diverts ingested glucose away from muscle glycogen storage toward hepatic *de novo* lipogenesis, thus predisposing to the development of NAFLD (Petersen et al., 2007). Altogether, these findings suggest that peripheral insulin resistance leads to altered lipid metabolism, which may exacerbate liver steatosis. Interestingly, NAFLD and hepatic insulin resistance can develop in a very short time. Notably, Samuel and coworkers showed that hepatic insulin resistance as well as steatosis can occur in high fat fed rodents within three days (Samuel et al., 2004). In this model, hepatic insulin resistance was secondary to increased diacylglycerols synthesis, known to activate PKCε (Fig. 2). Supporting these findings, inhibition of PKCε using an antisense oligonucleotide prevented hepatic insulin resistance despite hepatic lipid accumulation (Samuel et al., 2007). Together, these studies showed that the regulation of hepatic lipid accumulation plays a major role in the development of NAFLD and associated hepatic insulin resistance.

Hepatic lipid uptake and oxidation also play an important role in the development of NAFLD. Notably, specific hepatic overexpression of lipoprotein lipase (LPL) in mice promoted hepatic lipid accumulation and hepatic insulin resistance (Kim et al., 2001). Impaired lipid oxidation may also lead to an imbalance leading to increased hepatic lipid content. Indeed, Fullerton et al., have shown that mutations in both acetyl-CoA carboxylase 1 and 2 (ACC 1, ACC2) promote lipogenesis and decrease lipid oxidation. These mutations led to the inability of AMPK-activated protein kinase

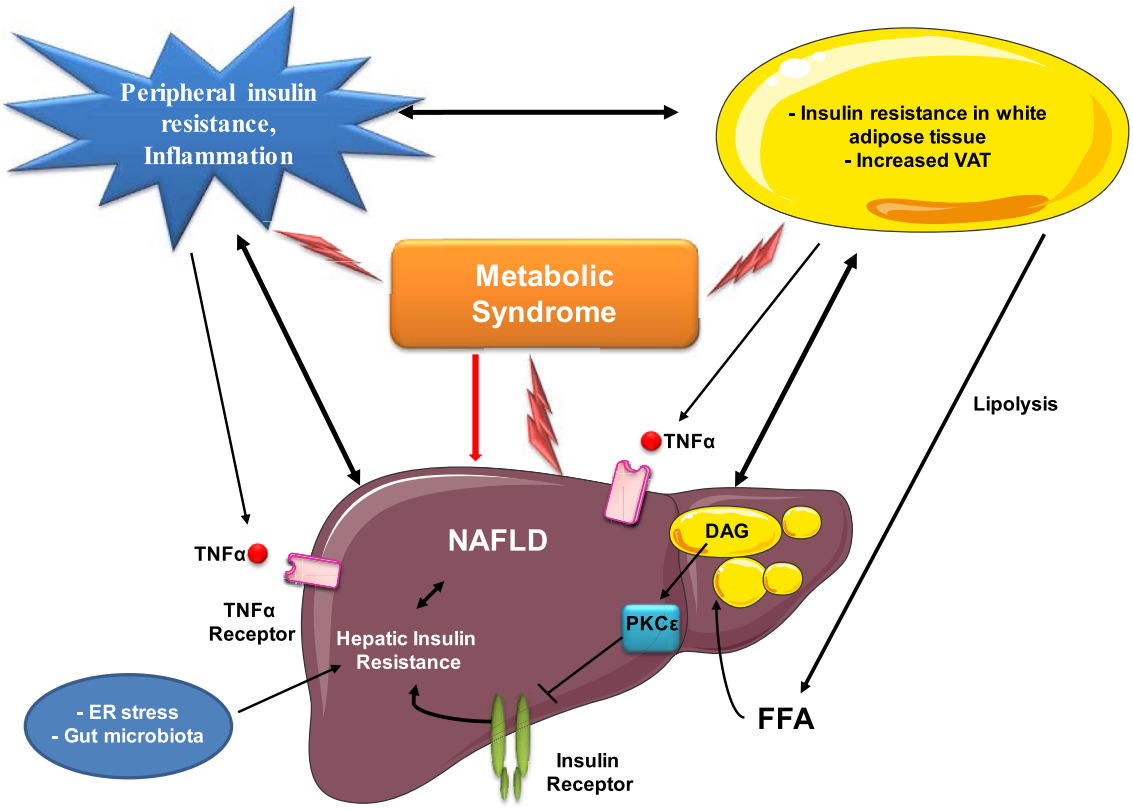

Fig. 1. Role of white adipose tissue and liver in the development of MetS and NAFLD.
Obesity, one of the central features of MetS, is associated with increased visceral adipose tissue (VAT) release of proinflammatory cytokines such as tumor necrosis factor α (TNFα) and free fatty acids (FFA), which promote hepatic diacylglycerols (DAG) accumulation and activation of inflammatory pathways. DAG in turn activate protein kinase ε (PKCε), which inhibits insulin signaling, leading to hepatic insulin resistance. These processes in turn play a major role in the development of MetS and its hepatic manifestation, known as NAFLD. Other factors such as peripheral insulin resistance, inflammation, endoplasmic reticulum (ER) stress and gut microbiota also play a role in the development of NAFLD and hepatic insulin resistance.

(AMPK) to phosphorylate ACC1 and 2 and thus inactivate these enzymes (Fullerton et al., 2013). Therefore, in this case, impaired lipid oxidation led to increased hepatic lipid content and hepatic insulin resistance. In contrast, in another mouse model, increased AMPK activity promoted inactivation of ACC1 and ACC2, leading to increased lipid oxidation, lower hepatic diacylglycerol content and decreased PKCε activity, leading to a protection from diet-induced hepatic insulin resistance (Birkenfeld et al., 2011a).

Importantly, fatty acids that promote hepatic insulin resistance and NAFLD mainly originate from white adipose tissue lipolysis. Lipolysis increases with total fat mass content (Mittendorfer et al., 2009; Pardina et al., 2009). However, the relationship between lipolysis and insulin responsiveness seems to be independent of body mass. For instance, insulin resistant obese adolescents present higher visceral fat content than their weight-matched, insulin sensitive counterparts (Weiss et al., 2005). Similarly, in rodents, obese mice lacking fatty-acid-binding protein (FABP) in adipocytes are more insulin sensitive than their wild-type littermates (Cao et al., 2006). Therefore, it seems that the increase in white adipose tissue lipolysis provides substrates for ectopic lipid accumulation and plays a facilitative role in the induction of hepatic insulin resistance. The importance of adipose tissue in the development of insulin resistance and NAFLD has been revealed by lipodystrophic models. Indeed, despite the absence of peripheral or visceral fat expansion in lipodystrophy, fatty acids accumulate in the liver and skeletal muscle, which leads to the development of insulin resistance. For instance, in a genetic mouse model expressing the dominant negative protein A-ZIP/F-1 ("fatless" mice) in adipose tissue, there is a lack of visceral and peripheral fat, but an ectopic accumulation of fat in liver and skeletal muscle, leading to severe insulin resistance in these tissues (Kim et al., 2000a). Interestingly, transplantation of white adipose tissue from wild-type mice to these lipodystrophic mice leads to an improvement in insulin sensitivity (Kim et al., 2000a). Similar results are observed with leptin administration (Shimomura et al., 1999). In line with these studies, investigations in humans with lipodystrophia revealed that although visceral or peripheral fat were almost absent, these patients developed NAFLD and hepatic insulin resistance (Petersen et al., 2002; Savage et al., 2005). Leptin treatment of these subjects decreased hepatic lipid content and improved hepatic insulin sensitivity (Petersen et al., 2002). Altogether, these studies emphasize the important role of ectopic lipid accumulation in the development of insulin resistance. Notably, fatty acids derived from white adipose tissue play a critical role in the induction of NAFLD and hepatic insulin resistance. Further, reversion of hepatic seatosis in these models of lipodystrophia restores hepatic insulin sensitivity.

In addition to lipodystophia, another important model exemplifying the major role of white adipose tissue in the development of liver steatosis and insulin resistance is ageing. Indeed, the prevalence of NAFLD and MetS in the general population increases with age (Choi and Diehl, 2008; Kagansky et al., 2004; Reynolds and Wildman, 2009). Moreover, body fat distribution shifts from subcutaneous adipose tissue to visceral adipose tissue (VAT) in elder subjects, leading to deleterious metabolic consequences such as the development of insulin resistance (Petta et al., 2010; Tran et al.,

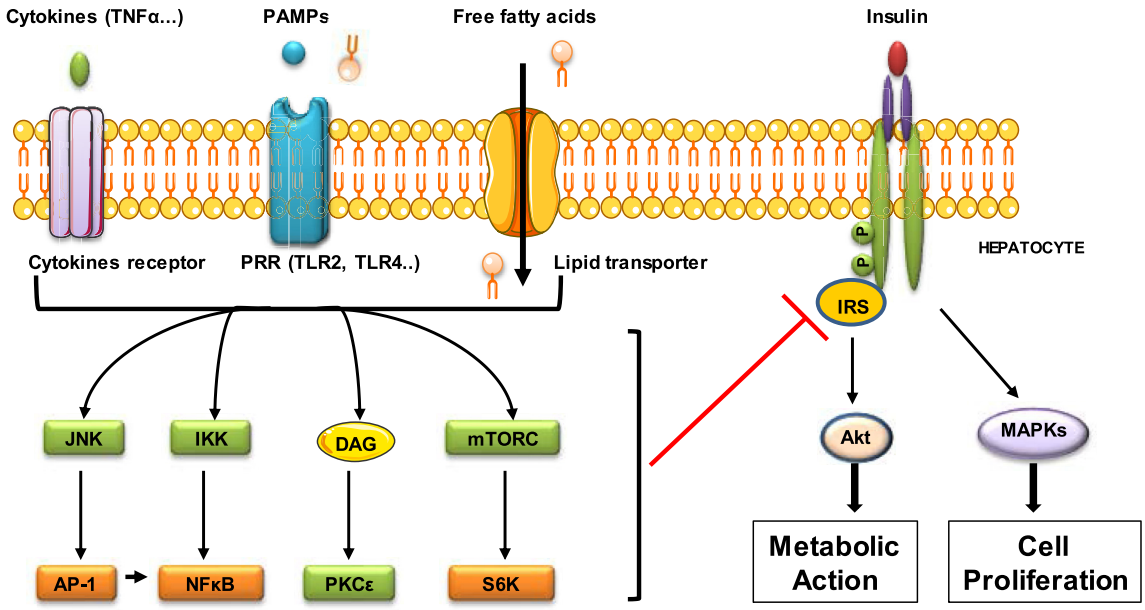

Fig. 2. Inhibition of insulin signaling pathways associated with both MetS and NAFLD.
Insulin receptor substrate (IRS) phosphorylation can be inhibited by various processes, in particular inflammatory or kinases proteins as well as lipid derived sub-products. For instance, inflammatory proteins such as cytokines (notably TNFα), and others such as PAMPs, bind to their receptor and activate downstream inflammatory signaling pathways including IKK, mTORC or JNK. In turn, these effectors recruit downstream molecules, respectively NFκB, S6K and AP-1, which target the inhibition of IRS phosphorylation, thus leading to hepatic insulin resistance. Moreover, accumulation of toxic lipid metabolites in the liver such as diacylglycerols (DAG) can activate kinases such as protein kinase Cε (PKCε), which is known to inhibit IRS phosphorylation, subsequently leading to hepatic insulin resistance. Therefore, multiple ways can induce insulin resistance in the liver.

2008). Expansion of VAT notably promotes the production of deleterious cytokines such as tumor necrosis factor α (TNFα). TNFα binds to its receptor and activates downstream inflammatory signaling pathways including IKK, mTORC or JNK. In turn, these effectors recruit downstream molecules, respectively nuclear factor-kappa B (NFκB), S6 kinase (S6K) and activator protein-1 (AP-1), which inhibit IRS phosphorylation, subsequently impairing insulin signaling in the liver (Kamada et al., 2008; Lumeng et al., 2008; Ozes et al., 2001) (Fig. 2). Evidence is accumulating that ageing is associated with mitochondrial dysfunction, which leads to accumulation of ectopic lipids and finally insulin resistance (Petersen et al., 2003).

In addition to ectopic fat accumulation, NAFLD can also be associated with genetic predisposition. This hypothesis originates from the fact that NAFLD also develops in healthy subjects without criteria of MetS. For instance, healthy Indian and Asian men are more prone to develop hepatic steatosis and hepatic insulin resistance than other populations because of specific polymorphisms in the insulin-response element for the apolipoprotein C3 gene (Petersen et al., 2006, 2010). Confirming the role of the genome in the pathogenesis of NAFLD, another study revealed that Hispanic adults and children are at high risk for the development of NAFLD due to a missense mutation found in the Patatin-like phospholipase domain-containing protein 3 gene (*PNPLA3*), which is more present in this ethnic group compared to the general population (Romeo et al., 2008). Interestingly, however, patients with variants of the *PNPLA3* gene did not develop insulin resistance, suggesting that in this case NAFLD could be dissociated from insulin resistance (Kantartzis et al., 2009). However, in these studies on variants of the *PNPLA3* gene, control subjects were obese and probably had already some degree of insulin resistance, making it difficult to specifically assess insulin resistance in subjects with NAFLD-associated *PNPLA3* gene variants. Moreover, treatment of high-fat fed rats with specific antisense oligonucleotides reducing *PNPLA3* expression protected them from the development of NAFLD and hepatic insulin resistance (Kumashiro et al., 2013).

4.1.2. *Inflammation and ER stress induce insulin resistance in MetS and NAFLD*

Inflammation is present in both MetS and NAFLD. For instance, several systemic inflammatory markers such as TNFα, interleukin-6 (IL-6) and C-reactive protein (CRP) are increased in MetS (Haffner, 2003). Moreover, high plasma levels of CRP have been used as a predictor for the development of NAFLD because patients with NASH are more insulin resistant and have remarkably higher plasma CRP concentrations than overweight nonsteatotic patients with similar visceral adipose tissue mass (Targher et al., 2008). In Addition to elevated pro-inflammatory cytokines, it was observed that metabolic dysfunctions such as insulin resistance are associated with reduced protective adipokines (such as adiponectin (Hotta et al., 2000)), and increased macrophage accumulation in the liver and adipose tissue (Lanthier et al., 2010). In particular, CD4 (+) and CD8 (+) T cells infiltration increases in the liver (Gadd et al., 2013). Nevertheless, the mechanisms of the inflammatory response related to MetS are far from been completely elucidated.

Pattern Recognition Receptors (PRRs) are a family of receptors that plays a critical role in innate immune systems and are well known for their ability to sense pathogen associated molecular patters (PAMPs). Of these PRRs, Toll like receptors (TLRs) received a particular attention. Several TLRs isoforms were identified but only TLR2 and TLR4 were involved in obesity and insulin resistance, two features of MetS (Fresno et al., 2011; Konner and Bruning, 2011). Moreover, most of the studies focused on TLR4 isoform because of its ability to bind to free fatty acids and initiate the proinflammatory signaling pathway NFκB (Fig. 2) (Fessler et al., 2009). In line with these results, mice knockout for the *TLR4* gene is protected from obesity-induced inflammation and lipid infusion-induced insulin resistance (Shi et al., 2006). These results in animals were also confirmed in humans. Notably, obese patients and patients with type 2 diabetes have elevated TLR4 muscle

expression, which positively correlates with insulin resistance (Konner and Bruning, 2011). In addition to its role in obesity, TLR4 was identified as a critical effector in the development of NAFLD (Miura et al., 2010). Therefore, TLR4 could be considered as one of the critical nodes between obesity, which represents the central feature of MetS, and NAFLD.

In addition to the NFκB pathway that can be activated through cytokine receptor or TLR, JNKs are other inflammation sensing proteins that are activated in obese patients (Solinas and Karin, 2010). These kinases appear to play an important role in the development of NAFLD and insulin resistance (Czaja, 2010; Donath and Shoelson, 2011). Although both JNK1 and JNK2 contribute to metabolic disorders, distinct functions for these proteins have been identified (Sabapathy et al., 2004). Indeed, JNKs were found to be increased in diet-induced and genetic models of obesity (Hirosumi et al., 2002). However, JNK1 plays a more prominent role in obesity and insulin responsiveness than JNK2. For instance, mice lacking JNK1, but not mice lacking JNK2, display a decreased weight gain, decreased glucose and insulin levels, and improved hepatic insulin sensitivity (Aguirre et al., 2000; Hirosumi et al., 2002). Based on these studies, one could suppose that JNK2 is not involved in metabolic alterations. Therefore, in order to address the question of the role of JNK2 in metabolism, Tuncman and coworkers generated *jnk2* null mice with one *jnk1* allele and found that these mice were protected from high-fat diet-induced obesity (Tuncman et al., 2006). These studies indicate that JNK1 and JNK2 are both involved in metabolic disorders such as obesity, and that JNK1 is able to compensate a loss of function of JNK2. Among metabolic alterations known in obesity, abnormal high levels of circulating cytokines activate the JNK pathway, which is considered as the molecular link between obesity and metabolic alterations (Solinas and Karin, 2010). For instance, IL-6 and TNFα, two proinflammatory cytokines present at high levels in obese patients (Asrih and Jornayvaz, 2013), have been shown to activate the JNK signaling pathway, leading to the development of insulin resistance (Hotamisligil et al., 1993; Spranger et al., 2003). Altogether, these studies suggest that the JNK pathway plays a major role in the development of MetS in obesity.

In addition to its function in obesity and insulin resistance, JNK has been shown to play a major role in the development of NAFLD (Schattenberg et al., 2006; Singh et al., 2009). For instance, Schattenberg et al., using a methionine- and choline-deficient (MCD) diet, induced the development of steatohepatitis in mice. In this case, the development of NAFLD was driven by an activation of the JNK-cJun-AP1 signaling pathway (Schattenberg et al., 2006). In line with this study and the one showing that *jnk1* plays a more prominent role in the development of insulin resistance than *jnk2*, Singh et al., revealed that *jnk1* but not *jnk2* null mice are protected from high-fat diet-induced steatosis and liver injury (Singh et al., 2009). Together, these data reveal that JNK1 plays a major role in the development of insulin resistance and NAFLD, but the exact mechanisms remain unclear. Moreover, JNK2 is likely involved in the development of NAFLD, although its exact function is still unresolved.

As previously discussed, different kinases including JNK-cJun could be activated by cytokines as well as by ER stress. This stress arises from an impaired synthesis capacity of the ER, which activates the unfolded protein response (UPR) (Xu et al., 2005). ER stress has been associated with obesity and was found to develop in liver and adipose tissue in genetic and diet-induced obese rodent models (Ozcan et al., 2004). In the latter study, the authors focused on a specific transcription factor named X-Box binding protein 1 (XBP1) known to modulate the ER stress response. They demonstrated that when deleted in mice, this leads to the development of insulin resistance through an activation of the JNK-cJun signaling pathway (Ozcan et al., 2004), suggesting a role of XBP1 in the development of insulin resistance. Additionally, mice with liver-specific deletion of XBP1 have improved hepatosteatosis, liver damage, and hypercholesterolemia (So et al., 2012). Because these mice displayed lower plasma triglycerides compared to their wild-type littermates, insulin sensitivity was expected to be improved. However, insulin resistance was not investigated in this study (So et al., 2012). In contrast, Jurczak et al., challenged XBP1 liver depleted mice with a fructose diet to assess the respective roles of ER stress and liver lipids in the development of hepatic insulin resistance (Jurczak et al., 2012). They found that despite increased ER stress, XBP1 depleted mice showed increased hepatic insulin sensitivity along with decreased lipid accumulation in the liver (Jurczak et al., 2012). Therefore, these studies revealed controversies regarding the role of XBP1 in the development of NAFLD and insulin resistance, warranting further investigations to elucidate its exact functions. Finally, fibroblast growth factor 21 (FGF21), a major regulator of lipid and glucose homeostasis found to be upregulated in patients with obesity and NAFLD, has been shown to be regulated by XBP1 (Jiang et al., 2014). Indeed, increased XBP1 expression, along with the simultaneous elevation of FGF21 expression, were associated with the occurrence of NAFLD and type 2 diabetes in humans (Jiang et al., 2014). Therefore, it will be worthy to understand how XBP1 affects the development of obesity, insulin resistance and NAFLD in humans. Importantly, XBP1 is not the only factor involved in ER stress. Nevertheless, it is a central regulator of ER adaptive responses (Gregor et al., 2013).

4.1.3. Role of gut microbiota in the development of insulin resistance

In addition to ectopic fat accumulation, inflammation and ER stress, recent research findings revealed that gut microbiota plays an important role in the development of obesity and insulin resistance (Lee and Mazmanian, 2010; Ley et al., 2005; Palermo et al., 2014). Indeed, by comparing microbiota from lean and obese patients, Ley and coworkers found that gut microbiota differs in composition (Ley et al., 2006). In this study, the authors quantified *Bacteroidetes* and *Firmicutes* and showed that the relative proportion of *Bacteroidetes*, one of the major beneficial bacteria in human gut, was decreased in obese people compared to lean people (Ley et al., 2006). These results are corroborated by rodent studies revealing an increase of *Firmicutes* and decrease of *Bacteroidetes* in genetic obese mouse models compared to wild-type mice (Ley et al., 2005). However, although these results are promising, they are still a matter of debate (Arumugam et al., 2011; Schwiertz et al., 2010). Controversies about these results could be due to dietary variations in the different regions of the globe.

The beneficial effects of the microbiome in energy balance were further demonstrated in clinical studies (Kootte et al., 2012; Smits et al., 2013; Vrieze et al., 2012). For instance, insulin resistant male subjects with MetS receiving either feces infusion from lean donors exhibited improved peripheral insulin responsiveness (Vrieze et al., 2012). This was associated with increased butyrate-producing bacteria (mainly *Roseburia* and *Eubacterium halii*) in feces. This study was supported by others investigations that observed decreased butyrate-producing bacteria in the gut microbiota of diabetic patients (Karlsson et al., 2013; Qin et al., 2012). Butyrate is a short-chain fatty acids produced by the intestinal bacteria through a fermentation process (Cummings, 1981). Interestingly, oral administration of butyrate to mice improved insulin sensitivity and increased energy expenditure (Gao et al., 2009). Whether butyrate promotes similar effects in human is still under investigation. However, as insulin resistance is associated with NAFLD, one could propose that butyrate may improve NAFLD. Indeed, Mattace Raso and coworkers showed that sodium butyrate

Table 1
Potential treatments for nonalcoholic fatty liver disease (NAFLD).

Treatment	Results of the study	Relevance for NAFLD	Reference
Weight loss, lifestyle changes, adjuvant appetite suppressants	Reduction of waist circumference, systolic and diastolic blood pressure, triglycerides, total cholesterol, LDL-cholesterol, uric acid, fasting insulin, and HOMA index	Could lead to a reduction of hepatic lipid content and improve NAFLD	Park et al., 2004
Orlistat (lipase inhibitor)	Significant decrease in body weight, HbA1c, ALT and AST	A 10% reduction in body weight improved steatosis and fibrosis as well as HbA1c levels in the majority of patients	Harrison et al., 2004
Metformin	Improvements in liver histology and ALT levels in 30% of patients with NASH	Appears to be beneficial for NAFLD patients but not for non-obese patients developing NAFLD	Loomba et al., 2009
Pioglitazone (insulin sensitizing agent)	Improvement in biochemical and histological features of NASH	Could be used as a treatment for NAFLD	Promrat et al., 2004
Pioglitazone (insulin sensitizing agent)	Improvement of insulin resistance but not in hepatic fibrosis and ALT levels	Not adapted to treat NAFLD	Sanyal et al., 2010
Atorvostatin (statin, lipid lowering agent)	74.2% of patients normalized transaminases levels. Increased adiponectin and decreased TNFα levels. Decreased fatty acids. Steatosis and NAFLD were improved. However, 4 patients had progression of fibrosis. Thus, these results require further investigations	May represent a therapeutic approach but further investigations are required	Hyogo et al., 2008
Lifestyle advices and treatment for hypertension (mainly inhibitors of the renin-angiotensin system), impaired fasting glucose (metformin), obesity (orlistat) and dyslipidaemia (atorvastatin, fenofibrate)	At the end of treatment, 67% of patients on atorvastatin, 42% on fenofibrate and 70% on combination treatment had no longer evidence of NAFLD	Represents a multifactorial therapeutic approach	Athyros et al., 2006
PPARα agonists	Prevented the development of liver fibrosis in mice	Potential to delay progression to NASH in humans	Pawlak et al., 2014
Salsalate (inflammation inhibitor)	Improvement in glucose levels, lipid homeostasis and NAFLD	Because inflammation is part of NAFLD, salsalate may represent a new therapeutic approach	Goldfine et al., 2008; Jung et al., 2013
Etanercept (TNFα inhibitor)	Improves β-cell function	Could be considered as a treatment for NAFLD but studies enclosing larger cohorts for an extended period are required to confirm the results	Dominguez et al., 2005 Campanati et al., 2013
4-Phenyl butyric acid and taurine-conjugated ursodeoxycholic acid (Chaperone proteins)	Normalization of hyperglycemia, restoration of systemic insulin sensitivity, resolution of fatty liver disease, and enhancement of insulin action in liver, muscle, and adipose tissue in diabetic mouse models	As ER stress is involved in NAFLD development, chaperones could represent an interesting option to treat NAFLD in human	Ozcan et al., 2006
FGF21 analogs	Decreased fasting plasma insulin and improved cholesterol panel, decreased body weight (humans). Improved hepatic steatosis (animal models)	Could be considered as a treatment for NAFLD, but requires further investigations in humans	Gaich et al., 2013, Huang et al., 2013
Low-fat or low-carbohydrate low-calorie diet	Increased beneficial gut bacteria such as *Bacteroidetes* and restored insulin sensitivity	Since insulin resistance is a major risk for NAFLD, these diets may improve NAFLD	Ley et al., 2006 Cotillard et al., 2013; Wu et al., 2011b

Fibroblast growth factor 21 (FGF21), endothelial reticulum stress (ER stress), glycated hemoglobin (HbA1c), alanine and aspartate transaminase (ALT, AST), Low density lipoprotein (LDL) cholesterol.

protected high-fat fed rats from NAFLD (Mattace Raso et al., 2013). Altogether, these studies reveal a potentially important role of gut microbiota in the development of MetS, NAFLD and insulin resistance.

5. Treatment of MetS and NAFLD

There is no specific therapy for MetS or NAFLD. However, due to their potential common trigger, insulin resistance, some therapies notably studied in NAFLD may be relevant for MetS as well. As MetS is also characterized by other cardiovascular risk factors, it is important to treat separately these associated diseases, such as hypertension and dyslipidemia. To date, there is no established therapy for NAFLD either. Weight loss, physical activity and lifestyle changes remain the most effective approaches to improve NAFLD (Asrih and Jornayvaz, 2014; Park et al., 2004). To achieve weight loss, the simplest solution is to change dietary habits. Also, dietary modifications have been shown to be beneficial for gut microbiota (Wu et al., 2011b). For instance, patients under a low-fat or low-carbohydrate low-calorie diet present an increase in beneficial gut bacteria such as *Bacteroidetes* and a decrease in deleterious bacteria such as *Firmicutes* (Ley et al., 2006). These data are in accordance with other studies showing that diet-induced weight loss reduces systemic inflammation in obese patients and enriches intestinal microbial diversity (Cotillard et al., 2013; Wu et al., 2011b). Together, these studies show that dietary interventions stimulate the growth of beneficial gut bacteria, which may in part contribute to reverse NAFLD and hepatic insulin resistance.

Because of the association between MetS and NAFLD, several therapeutic agents used in obesity and insulin resistance have been considered for NAFLD (Table 1). Notably, orlistat, which inhibits pancreatic lipases, prevents fat absorption in the digestive tract, leading to weight loss. Indeed, Harrison and coworkers found that orlistat was effective in reducing body weight, subsequently significantly improving aminotransferases levels and haemoglobin A1C in the majority of patients. These data suggest that orlistat could be used as a therapeutic drug against NAFLD (Harrison et al., 2004).

Most of current pharmacological approaches aimed at treating NAFLD consist in inhibiting either 1) fat absorption; 2) inflammation; 3) the endocannabinoid system; or 4) modulating the central nervous system (Carter et al., 2012). Notably, metformin was shown to improve liver injury, but this medication used in type 2 diabetes could not prevent fibrosis in patients with steatosis (Loomba et al., 2009). Also, glitazones, which are peroxisome proliferator-activated receptor γ (PPARγ) agonists, were found to be efficient in managing NAFLD, by notably decreasing liver fibrosis (Promrat et al., 2004). In contrast, another study revealed that pioglitazone does not promote beneficial effects on liver fibrosis, although it diminished inflammation and steatosis (Sanyal et al., 2010). Therefore, further studies are required to elucidate these contradictory results.

In addition to PPARγ agonists, several studies have investigated the role of PPARα activation in NAFLD since it is involved in lipid and glucose metabolism (Auboeuf et al., 1997; Cariou et al., 2013; Fruchart, 2013; Shiri-Sverdlov et al., 2006). Recently, Pawlak et al., using a pharmacological approach, showed that activation of PPARα inhibited hepatic inflammation and the transition from steatosis toward NASH through a direct, anti-inflammatory mechanism independent of its lipid handling properties (Pawlak et al., 2014). These findings highlight the potential of novel therapeutic strategies to limit the progression of chronic inflammatory liver diseases initiated by metabolic perturbations.

Atorvastatin, a lipid lowering agent of the statins class, led to improved liver steatosis and NAFLD score (Eslami et al., 2013; Foster et al., 2011; Hyogo et al., 2008). Another study including a larger cohort of patients revealed similar results with atorvastatin treatment (Athyros et al., 2006). Also, salsalate, a potential anti-diabetic drug under development, has been shown to improve glycemia in diabetic patients through a downregulation of the proinflammatory IKKβ/NFκB pathway (Goldfine et al., 2008). Additionally, this agent is likely improving NAFLD through an induction of adiponectin (Jung et al., 2013).

Further pharmacological agents inhibiting inflammatory signaling such as etanercept, which inhibits TNFα, and chaperone proteins, which inhibit ER stress, were used in obese patients with insulin resistance and resulted in metabolic benefits (Dominguez et al., 2005; Ozcan et al., 2006). However, Dominguez and coworkers revealed only benefit on β-cell function with etanercept treatment, suggesting that it may not be a valuable treatment for NAFLD. However, others found that etanercept reduced the risk of developing hepatic fibrosis in patients with MetS (Campanati et al., 2013). In this study, patients with psoriasis, which are at risk of developing NAFLD and MetS probably because of underlying insulin resistance, were treated with etanercept and compared to patients treated with UVA. The group receiving etanercept showed significant reductions in transaminases, CRP and fasting insulin levels, and improved HOMA index, indicating that etanercept may be efficacious in reducing the development of NAFLD and MetS in patients with psoriasis. However, there were some limitations in this study, such as the diagnosis of NAFLD, which was done by ultrasonography (Campanati et al., 2013).

Most Recently, FGF21, a potent metabolic regulator, has been proposed as a therapeutic agent for obesity and type 2 diabetes. Notably, FGF21 has been shown to reverse hepatic steatosis in animal models of NAFLD and insulin resistance (Camporez et al., 2013b; Xu et al., 2009). In particular, Camporez et al. showed that these improvements were associated with reduced hepatocellular triglyceride and diacylglycerol contents, decreased activation of PKCε in the liver, as well as improved insulin signaling (Camporez et al., 2013b). Interestingly, in humans, FGF21 plasma levels increase in situations of insulin resistance such as obesity, type 2 diabetes and NAFLD (Chavez et al., 2009; Dushay et al., 2010; Li et al., 2010; Zhang et al., 2008). This increase in FGF21 plasma levels may reflect a state of FGF21 resistance. Nevertheless, FGF21 action was investigated in obese human subjects with type 2 diabetes by the use of an analog, LY2405319 (Gaich et al., 2013). In this clinical trial, the FGF21 analog produced significant improvements in dyslipidemia, body weight and fasting plasma insulin decreased, but only at higher concentrations of the analog. Surprisingly, plasma glucose only modestly decreased, and this was not significant. This may be due to the short duration of the trial (28 days), but may also reflect FGF21 resistance (Fisher et al., 2010). Importantly, other FGF21 mimetic molecules are in development (Foltz et al., 2012; Huang et al., 2013; Veniant et al., 2012; Wu et al., 2011a). It would be of interest to investigate whether FGF21 analogs are able to reverse or stop the development of NAFLD in humans as they do in animals. If so, this may lead to a novel therapeutic approach targeting MetS and NAFLD.

6. Conclusions

MetS and NAFLD are always more prevalent in western countries, but are also increasing in emerging countries, making these diseases public health problems. The association between MetS and NAFLD is becoming increasingly clear, although the exact mechanisms linking these diseases remain only partly known. To date, many questions remain without answers. Notably, it is not clear whether MetS precedes NAFLD or if it the opposite. Also, why are some patients with MetS more susceptible to develop NAFLD than others? Are there unknown genetic susceptibilities to unravel? These questions require further investigations. Nevertheless, it appears that hepatic insulin resistance, which is notably due to ectopic lipid accumulation and inflammation, may be a central player in the development of both MetS and NAFLD. Current therapies for these metabolic diseases are currently disappointing and mainly rely on lifestyle measures and weight loss. These interventions may stimulate the growth or activity of beneficial bacterial species such as *Bacteroidetes*, thus modifying gut microbiota, potentially leading to improved hepatic insulin responsiveness and decreased NAFLD. Nevertheless, further research is warranted to better understand the pathophysiology of both MetS and NAFLD in order to better identify potential therapeutic targets in these ever growing diseases.

Acknowledgments

This work was supported by the Helmut Horten Foundation and SwissLife.

References

Aguirre, V., Uchida, T., Yenush, L., Davis, R., White, M.F., 2000. The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307). J. Biol. Chem 275, 9047–9054.

Alberti, K.G., Zimmet, P., Shaw, J., 2006. Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet. Med 23, 469–480.

Angulo, P., 2002. Nonalcoholic fatty liver disease. N. Engl. J. Med 346, 1221–1231.
Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D.R., et al., 2011. Enterotypes of the human gut microbiome. Nature 473, 174–180.
Asrih, M., Jornayvaz, F.R., 2013. Inflammation as a potential link between nonalcoholic fatty liver disease and insulin resistance. J. Endocrinol 218, R25–R36.
Asrih, M., Jornayvaz, F.R., 2014. Diets and nonalcoholic fatty liver disease: the good and the bad. Clin. Nutr 33, 186–190.
Athyros, V.G., Mikhailidis, D.P., Didangelos, T.P., Giouleme, O.I., Liberopoulos, E.N., Karagiannis, A., et al., 2006. Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. Curr. Med. Res. Opin 22, 873–883.
Auboeuf, D., Rieusset, J., Fajas, L., Vallier, P., Frering, V., Riou, J.P., et al., 1997. Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator-activated receptors and liver X receptor-alpha in humans: no alteration in adipose tissue of obese and NIDDM patients. Diabetes 46, 1319–1327.
Badran, M., Laher, I., 2011. Obesity in Arabic-speaking countries. J. Obes 2011, 686430.
Birkenfeld, A.L., Lee, H.Y., Guebre-Egziabher, F., Alves, T.C., Jurczak, M.J., Jornayvaz, F.R., et al., 2011. Deletion of the mammalian INDY homolog mimics aspects of dietary restriction and protects against adiposity and insulin resistance in mice. Cell Metab 14, 184–195.
Birkenfeld, A.L., Lee, H.Y., Majumdar, S., Jurczak, M.J., Camporez, J.P., Jornayvaz, F.R., et al., 2011. Influence of the hepatic Eukaryotic Initiation Factor 2 alpha (eIF2 alpha) Endoplasmic Reticulum (ER) stress response pathway on insulin-mediated ER stress and hepatic and peripheral glucose metabolism. J. Biol. Chem 286, 36163–36170.
Bruning, J.C., Michael, M.D., Winnay, J.N., Hayashi, T., Horsch, D., Accili, D., et al., 1998. A muscle-specific insulin receptor knockout exhibits features of the metabolic syndrome of NIDDM without altering glucose tolerance. Mol. Cell 2, 559–569.
Bugianesi, E., McCullough, A.J., Marchesini, G., 2005. Insulin resistance: a metabolic pathway to chronic liver disease. Hepatology 42, 987–1000.
Campanati, A., Ganzetti, G., Di Sario, A., Damiani, A., Sandroni, L., Rosa, L., et al., 2013. The effect of etanercept on hepatic fibrosis risk in patients with non-alcoholic fatty liver disease, metabolic syndrome, and psoriasis. J. Gastroenterol 48, 839–846.
Camporez, J.P., Jornayvaz, F.R., Lee, H.Y., Kanda, S., Guigni, B.A., Kahn, M., et al., 2013. Cellular mechanism by which estradiol protects female ovariectomized mice from high-fat diet-induced hepatic and muscle insulin resistance. Endocrinology 154, 1021–1028.
Camporez, J.P., Jornayvaz, F.R., Petersen, M.C., Pesta, D., Guigni, B.A., Serr, J., et al., 2013. Cellular mechanisms by which FGF21 improves insulin sensitivity in male mice. Endocrinology 154, 3099–3109.
Cantley, J.L., Yoshimura, T., Camporez, J.P., Zhang, D., Jornayvaz, F.R., Kumashiro, N., et al., 2013. CGI-58 knockdown sequesters diacylglycerols in lipid droplets/ER-preventing diacylglycerol-mediated hepatic insulin resistance. Proc. Natl. Acad. Sci. U.S.A. 110, 1869–1874.
Cao, H., Maeda, K., Gorgun, C.Z., Kim, H.J., Park, S.Y., Shulman, G.I., et al., 2006. Regulation of metabolic responses by adipocyte/macrophage Fatty Acid-binding proteins in leptin-deficient mice. Diabetes 55, 1915–1922.
Cariou, B., Hanf, R., Lambert-Porcheron, S., Zair, Y., Sauvinet, V., Noel, B., et al., 2013. Dual peroxisome proliferator-activated receptor alpha/delta agonist GFT505 improves hepatic and peripheral insulin sensitivity in abdominally obese subjects. Diabetes Care 36, 2923–2930.
Carter, R., Mouralidarane, A., Ray, S., Soeda, J., Oben, J., 2012. Recent advancements in drug treatment of obesity. Clin. Med. (Northfield Il) 12, 456–460.
Chavez, A.O., Molina-Carrion, M., Abdul-Ghani, M.A., Folli, F., Defronzo, R.A., Tripathy, D., 2009. Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. Diabetes Care 32, 1542–1546.
Choi, S.S., Diehl, A.M., 2008. Hepatic triglyceride synthesis and nonalcoholic fatty liver disease. Curr. Opin. Lipidol 19, 295–300.
Chugh, P.K., Sharma, S., 2012. Recent advances in the pathophysiology and pharmacological treatment of obesity. J. Clin. Pharm. Ther 37, 525–535.
Contos, M.J., Choudhury, J., Mills, A.S., Sanyal, A.J., 2004. The histologic spectrum of nonalcoholic fatty liver disease. Clin. Liver Dis 8, 481–500 vii.
Cotillard, A., Kennedy, S.P., Kong, L.C., Prifti, E., Pons, N., Le Chatelier, E., et al., 2013. Dietary intervention impact on gut microbial gene richness. Nature 500, 585–588.
Cummings, J.H., 1981. Short chain fatty acids in the human colon. Gut 22, 763–779.
Czaja, M.J., 2010. JNK regulation of hepatic manifestations of the metabolic syndrome. Trends Endocrinol. Metab 21, 707–713.
de Luca, C., Olefsky, J.M., 2008. Inflammation and insulin resistance. FEBS Lett 582, 97–105.
Day, C.P., James, O.F., 1998. Steatohepatitis: a tale of two "hits"? Gastroenterology 114, 842–845.
Dominguez, H., Storgaard, H., Rask-Madsen, C., Steffen Hermann, T., Ihlemann, N., Baunbjerg Nielsen, D., et al., 2005. Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. J. Vasc. Res 42, 517–525.
Donath, M.Y., Shoelson, S.E., 2011. Type 2 diabetes as an inflammatory disease. Nat. Rev. Immunol 11, 98–107.
Donnelly, K.L., Smith, C.I., Schwarzenberg, S.J., Jessurun, J., Boldt, M.D., Parks, E.J., 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.
Dushay, J., Chui, P.C., Gopalakrishnan, G.S., Varela-Rey, M., Crawley, M., Fisher, F.M., et al., 2010. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. Gastroenterology 139, 456–463.
Eguchi, Y., Eguchi, T., Mizuta, T., Ide, Y., Yasutake, T., Iwakiri, R., et al., 2006. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. J. Gastroenterol 41, 462–469.
Eslami, L., Merat, S., Malekzadeh, R., Nasseri-Moghaddam, S., Aramin, H., 2013. Statins for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Cochrane Database Syst. Rev (12). CD008623.
Farazi, P.A., DePinho, R.A., 2006. Hepatocellular carcinoma pathogenesis: from genes to environment. Nat. Rev. Cancer 6, 674–687.
Fessler, M.B., Rudel, L.L., Brown, J.M., 2009. Toll-like receptor signaling links dietary fatty acids to the metabolic syndrome. Curr. Opin. Lipidol 20, 379–385.
Fisher, F.M., Chui, P.C., Antonellis, P.J., Bina, H.A., Kharitonenkov, A., Flier, J.S., et al., 2010. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes 59, 2781–2789.
Foltz, I.N., Hu, S., King, C., Wu, X., Yang, C., Wang, W., et al., 2012. Treating diabetes and obesity with an FGF21-mimetic antibody activating the betaKlotho/FGFR1c receptor complex. Sci. Transl. Med 4, 162ra153.
Foster, T., Budoff, M.J., Saab, S., Ahmadi, N., Gordon, C., Guerci, A.D., 2011. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. Am. J. Gastroenterol 106, 71–77.
Fresno, M., Alvarez, R., Cuesta, N., 2011. Toll-like receptors, inflammation, metabolism and obesity. Arch. Physiol. Biochem 117, 151–164.
Fruchart, J.C., 2013. Selective peroxisome proliferator-activated receptor alpha modulators (SPPARMalpha): the next generation of peroxisome proliferator-activated receptor alpha-agonists. Cardiovasc. Diabetol 12, 82.
Fullerton, M.D., Galic, S., Marcinko, K., Sikkema, S., Pulinilkunnil, T., Chen, Z.P., et al., 2013. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. Nat. Med 19, 1649–1654.
Gadd, V.L., Melino, M., Roy, S., Horsfall, L., O'Rourke, P., Williams, M.R., et al., 2013. Portal, but not lobular, macrophages express matrix metalloproteinase-9: association with the ductular reaction and fibrosis in chronic hepatitis C. Liver Int 33, 569–579.
Gaich, G., Chien, J.Y., Fu, H., Glass, L.C., Deeg, M.A., Holland, W.L., et al., 2013. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. Cell Metab 18, 333–340.
Gao, Z., Yin, J., Zhang, J., Ward, R.E., Martin, R.J., Lefevre, M., et al., 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 58, 1509–1517.
Gariani, K., Philippe, J., Jornayvaz, F.R., 2013. Non-alcoholic fatty liver disease and insulin resistance: from bench to bedside. Diabetes Metab 39, 16–26.
Goldfine, A.B., Silver, R., Aldhahi, W., Cai, D., Tatro, E., Lee, J., et al., 2008. Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. Clin. Transl. Sci 1, 36–43.
Gregor, M.F., Misch, E.S., Yang, L., Hummasti, S., Inouye, K.E., Lee, A.H., et al., 2013. The role of adipocyte XBP1 in metabolic regulation during lactation. Cell Rep 3, 1430–1439.
Haffner, S.M., 2003. Insulin resistance, inflammation, and the prediabetic state. Am. J. Cardiol 92, 18J–26J.
Harrison, S.A., Fincke, C., Helinski, D., Torgerson, S., Hayashi, P., 2004. A pilot study of orlistat treatment in obese, non-alcoholic steatohepatitis patients. Aliment. Pharmacol. Ther 20, 623–628.
Hirosumi, J., Tuncman, G., Chang, L., Gorgun, C.Z., Uysal, K.T., Maeda, K., et al., 2002. A central role for JNK in obesity and insulin resistance. Nature 420, 333–336.
Hodge, A.M., Dowse, G.K., Zimmet, P.Z., Collins, V.R., 1995. Prevalence and secular trends in obesity in Pacific and Indian Ocean island populations. Obes. Res 3 (Suppl. 2), 77s–87s.
Hoque, M.E., Doi, S.A.R., Mannan, M., Long, K., Niessen, L.W., Mamun, A.A., 2014. Prevalence of overweight and obesity among children and adolescents of the Indian subcontinent: a meta-analysis. Nutr. Rev 72, 541–550.
Hotamisligil, G.S., Shargill, N.S., Spiegelman, B.M., 1993. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 259, 87–91.
Hotta, K., Funahashi, T., Arita, Y., Takahashi, M., Matsuda, M., Okamoto, Y., et al., 2000. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler. Thromb. Vasc. Biol 20, 1595–1599.
Huang, J., Ishino, T., Chen, G., Rolzin, P., Osothprarop, T.F., Retting, K., et al., 2013. Development of a novel long-acting antidiabetic FGF21 mimetic by targeted conjugation to a scaffold antibody. J. Pharmacol. Exp. Ther 346, 270–280.
Hyogo, H., Tazuma, S., Arihiro, K., Iwamoto, K., Nabeshima, Y., Inoue, M., et al., 2008. Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia. Metabolism 57, 1711–1718.
Jeong, S.K., Kim, Y.K., Park, J.W., Shin, Y.J., Kim, D.S., 2008. Impact of visceral fat on the metabolic syndrome and nonalcoholic fatty liver disease. J. Korean Med. Sci 23, 789–795.
Jiang, S., Yan, C., Fang, Q.C., Shao, M.L., Zhang, Y.L., Liu, Y., et al., 2014. Fibroblast growth factor 21 is regulated by the IRE1alpha-XBP1 branch of the unfolded protein response and counteracts endoplasmic reticulum stress-induced hepatic steatosis. J. Biol. Chem 289, 29751–29765.
Jornayvaz, F.R., Shulman, G.I., 2012. Diacylglycerol activation of protein kinase Cepsilon and hepatic insulin resistance. Cell Metab 15, 574–584.
Jornayvaz, F.R., Jurczak, M.J., Lee, H.Y., Birkenfeld, A.L., Frederick, D.W., Zhang, D.Y., et al., 2010. A high-fat, ketogenic diet causes hepatic insulin resistance in mice,

despite increasing energy expenditure and preventing weight gain. Am. J. Physiol. Endocrinol. Metab 299, E808–E815.
Jornayvaz, F.R., Samuel, V.T., Shulman, G.I., 2010. The role of muscle insulin resistance in the pathogenesis of atherogenic dyslipidemia and nonalcoholic fatty liver disease associated with the metabolic syndrome. Annu. Rev. Nutr 30, 273–290.
Jornayvaz, F.R., Birkenfeld, A.L., Jurczak, M.J., Kanda, S., Guigni, B.A., Jiang, D.C., et al., 2011. Hepatic insulin resistance in mice with hepatic overexpression of diacylglycerol acyltransferase 2. Proc. Natl. Acad. Sci. U.S.A. 108, 5748–5752.
Jornayvaz, F.R., Lee, H.Y., Jurczak, M.J., Alves, T.C., Guebre-Egziabher, F., Guigni, B.A., et al., 2012. Thyroid hormone receptor-alpha gene knockout mice are protected from diet-induced hepatic insulin resistance. Endocrinology 153, 583–591.
Jung, T.W., Choi, H.Y., Lee, S.Y., Hong, H.C., Yang, S.J., Yoo, H.J., et al., 2013. Salsalate and adiponectin improve palmitate-induced insulin resistance via inhibition of selenoprotein P through the AMPK-FOXO1alpha pathway. PLoS ONE 8, e66529.
Jurczak, M.J., Lee, A.H., Jornayvaz, F.R., Lee, H.Y., Birkenfeld, A.L., Guigni, B.A., et al., 2012. Dissociation of inositol-requiring enzyme (IRE1alpha)-mediated c-Jun N-terminal kinase activation from hepatic insulin resistance in conditional X-box-binding protein-1 (XBP1) knock-out mice. J. Biol. Chem 287, 2558–2567.
Kagansky, N., Levy, S., Keter, D., Rimon, E., Taiba, Z., Fridman, Z., et al., 2004. Non-alcoholic fatty liver disease—a common and benign finding in octogenarian patients. Liver Int 24, 588–594.
Kamada, Y., Takehara, T., Hayashi, N., 2008. Adipocytokines and liver disease. J. Gastroenterol 43, 811–822.
Kantartzis, K., Peter, A., Machicao, F., Machann, J., Wagner, S., Konigsrainer, I., et al., 2009. Dissociation between fatty liver and insulin resistance in humans carrying a variant of the patatin-like phospholipase 3 gene. Diabetes 58, 2616–2623.
Karlsson, F.H., Tremaroli, V., Nookaew, I., Bergstrom, G., Behre, C.J., Fagerberg, B., et al., 2013. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature 498, 99–103.
Kim, H.J., Kim, H.J., Lee, K.E., Kim, D.J., Kim, S.K., Ahn, C.W., et al., 2004. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch. Intern. Med 164, 2169–2175.
Kim, J.K., Gavrilova, O., Chen, Y., Reitman, M.L., Shulman, G.I., 2000. Mechanism of insulin resistance in A-ZIP/F-1 fatless mice. J. Biol. Chem 275, 8456–8460.
Kim, J.K., Michael, M.D., Previs, S.F., Peroni, O.D., Mauvais-Jarvis, F., Neschen, S., et al., 2000. Redistribution of substrates to adipose tissue promotes obesity in mice with selective insulin resistance in muscle. J. Clin. Invest 105, 1791–1797.
Kim, J.K., Fillmore, J.J., Chen, Y., Yu, C., Moore, I.K., Pypaert, M., et al., 2001. Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. Proc. Natl. Acad. Sci. U.S.A. 98, 7522–7527.
Konner, A.C., Bruning, J.C., 2011. Toll-like receptors: linking inflammation to metabolism. Trends Endocrinol. Metab 22, 16–23.
Kootte, R.S., Vrieze, A., Holleman, F., Dallinga-Thie, G.M., Zoetendal, E.G., de Vos, W.M., et al., 2012. The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. Diabetes Obes. Metab 14, 112–120.
Kopelman, P.G., 2000. Obesity as a medical problem. Nature 404, 635–643.
Kotani, K., Peroni, O.D., Minokoshi, Y., Boss, O., Kahn, B.B., 2004. GLUT4 glucose transporter deficiency increases hepatic lipid production and peripheral lipid utilization. J. Clin. Invest 114, 1666–1675.
Kumashiro, N., Erion, D.M., Zhang, D., Kahn, M., Beddow, S.A., Chu, X., et al., 2011. Cellular mechanism of insulin resistance in nonalcoholic fatty liver disease. Proc. Natl. Acad. Sci. U.S.A. 108, 16381–16385.
Kumashiro, N., Yoshimura, T., Cantley, J.L., Majumdar, S.K., Guebre-Egziabher, F., Kursawe, R., et al., 2013. Role of patatin-like phospholipase domain-containing 3 on lipid-induced hepatic steatosis and insulin resistance in rats. Hepatology 57, 1763–1772.
Kwon, Y.M., Oh, S.W., Hwang, S.S., Lee, C., Kwon, H., Chung, G.E., 2012. Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in Korean adults. Am. J. Gastroenterol 107, 1852–1858.
Lanthier, N., Molendi-Coste, O., Horsmans, Y., van Rooijen, N., Cani, P.D., Leclercq, I.A., 2010. Kupffer cell activation is a causal factor for hepatic insulin resistance. Am. J. Physiol. Gastrointest. Liver Physiol 298, G107–G116.
Lee, H.Y., Birkenfeld, A.L., Jornayvaz, F.R., Jurczak, M.J., Kanda, S., Popov, V., et al., 2011. Apolipoprotein CIII overexpressing mice are predisposed to diet-induced hepatic steatosis and hepatic insulin resistance. Hepatology 54, 1650–1660.
Lee, Y.K., Mazmanian, S.K., 2010. Has the microbiota played a critical role in the evolution of the adaptive immune system? Science 330, 1768–1773.
Ley, R.E., Backhed, F., Turnbaugh, P., Lozupone, C.A., Knight, R.D., Gordon, J.I., 2005. Obesity alters gut microbial ecology. Proc. Natl. Acad. Sci. U.S.A. 102, 11070–11075.
Ley, R.E., Turnbaugh, P.J., Klein, S., Gordon, J.I., 2006. Microbial ecology: human gut microbes associated with obesity. Nature 444, 1022–1023.
Li, H., Fang, Q., Gao, F., Fan, J., Zhou, J., Wang, X., et al., 2010. Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. J. Hepatol 53, 934–940.
Loomba, R., Lutchman, G., Kleiner, D.E., Ricks, M., Feld, J.J., Borg, B.B., et al., 2009. Clinical trial: pilot study of metformin for the treatment of non-alcoholic steatohepatitis. Aliment. Pharmacol. Ther 29, 172–182.
Lumeng, C.N., DelProposto, J.B., Westcott, D.J., Saltiel, A.R., 2008. Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. Diabetes 57, 3239–3246.
Marchesini, G., Bugianesi, E., Forlani, G., Cerrelli, F., Lenzi, M., Manini, R., et al., 2003. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 37, 917–923.
Mattace Raso, G., Simeoli, R., Russo, R., Iacono, A., Santoro, A., Paciello, O., et al., 2013. Effects of sodium butyrate and its synthetic amide derivative on liver inflammation and glucose tolerance in an animal model of steatosis induced by high fat diet. PLoS ONE 8, e68626.
McKenney, R.L., Short, D.K., 2011. Tipping the balance: the pathophysiology of obesity and type 2 diabetes mellitus. Surg. Clin. North Am 91, 1139–1148 vii.
Michael, M.D., Kulkarni, R.N., Postic, C., Previs, S.F., Shulman, G.I., Magnuson, M.A., et al., 2000. Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction. Mol. Cell 6, 87–97.
Mittendorfer, B., Magkos, F., Fabbrini, E., Mohammed, B.S., Klein, S., 2009. Relationship between body fat mass and free fatty acid kinetics in men and women. Obesity (Silver Spring) 17, 1872–1877.
Miura, K., Seki, E., Ohnishi, H., Brenner, D.A., 2010. Role of toll-like receptors and their downstream molecules in the development of nonalcoholic Fatty liver disease. Gastroenterol. Res. Pract 2010, 362847.
Musaiger, A.O., 1996. Nutritional status of infants and young children in the Arabian Gulf countries. J. Trop. Pediatr 42, 121–124.
Musso, G., Gambino, R., Bo, S., Uberti, B., Biroli, G., Pagano, G., et al., 2008. Should nonalcoholic fatty liver disease be included in the definition of metabolic syndrome? A cross-sectional comparison with Adult Treatment Panel III criteria in nonobese nondiabetic subjects. Diabetes Care 31, 562–568.
Musso, G., Gambino, R., Cassader, M., Pagano, G., 2011. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann. Med 43, 617–649.
Ogden, C.L., Carroll, M.D., Kit, B.K., Flegal, K.M., 2012. Prevalence of obesity in the United States, 2009–2010. NCHS Data Brief 1–8.
Onat, A., 2011. Metabolic syndrome: nature, therapeutic solutions and options. Expert Opin. Pharmacother 12, 1887–1900.
Ozcan, U., Cao, Q., Yilmaz, E., Lee, A.H., Iwakoshi, N.N., Ozdelen, E., et al., 2004. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science 306, 457–461.
Ozcan, U., Yilmaz, E., Ozcan, L., Furuhashi, M., Vaillancourt, E., Smith, R.O., et al., 2006. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. Science 313, 1137–1140.
Ozes, O.N., Akca, H., Mayo, L.D., Gustin, J.A., Maehama, T., Dixon, J.E., et al., 2001. A phosphatidylinositol 3-kinase/Akt/mTOR pathway mediates and PTEN antagonizes tumor necrosis factor inhibition of insulin signaling through insulin receptor substrate-1. Proc. Natl. Acad. Sci. U.S.A. 98, 4640–4645.
Palermo, A., Maggi, D., Maurizi, A.R., Pozzilli, P., Buzzetti, R., 2014. Prevention of type 2 diabetes mellitus: is it feasible? Diabetes Metab. Res. Rev 30 (Suppl. 1), 4–12.
Pardina, E., Baena-Fustegueras, J.A., Catalan, R., Galard, R., Lecube, A., Fort, J.M., et al., 2009. Increased expression and activity of hepatic lipase in the liver of morbidly obese adult patients in relation to lipid content. Obes. Surg 19, 894–904.
Park, H.S., Sim, S.J., Park, J.Y., 2004. Effect of weight reduction on metabolic syndrome in Korean obese patients. J. Korean Med. Sci 19, 202–208.
Pawlak, M., Bauge, E., Bourguet, W., De Bosscher, K., Lalloyer, F., Tailleux, A., et al., 2014. The transrepressive activity of peroxisome proliferator-activated receptor alpha is necessary and sufficient to prevent liver fibrosis in mice. Hepatology 60, 1593–1606.
Perry, R.J., Samuel, V.T., Petersen, K.F., Shulman, G.I., 2014. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. Nature 510, 84–91.
Petersen, K.F., Oral, E.A., Dufour, S., Befroy, D., Ariyan, C., Yu, C., et al., 2002. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J. Clin. Invest 109, 1345–1350.
Petersen, K.F., Befroy, D., Dufour, S., Dziura, J., Ariyan, C., Rothman, D.L., et al., 2003. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science 300, 1140–1142.
Petersen, K.F., Dufour, S., Feng, J., Befroy, D., Dziura, J., Dalla Man, C., et al., 2006. Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. Proc. Natl. Acad. Sci. U.S.A. 103, 18273–18277.
Petersen, K.F., Dufour, S., Savage, D.B., Bilz, S., Solomon, G., Yonemitsu, S., et al., 2007. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. Proc. Natl. Acad. Sci. U.S.A. 104, 12587–12594.
Petersen, K.F., Dufour, S., Hariri, A., Nelson-Williams, C., Foo, J.N., Zhang, X.M., et al., 2010. Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N. Engl. J. Med 362, 1082–1089.
Petta, S., Amato, M., Cabibi, D., Camma, C., Di Marco, V., Giordano, C., et al., 2010. Visceral adiposity index is associated with histological findings and high viral load in patients with chronic hepatitis C due to genotype 1. Hepatology 52, 1543–1552.
Popkin, B.M., 1994. The nutrition transition in low-income countries: an emerging crisis. Nutr. Rev 52, 285–298.
Promrat, K., Lutchman, G., Uwaifo, G.I., Freedman, R.J., Soza, A., Heller, T., et al., 2004. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology 39, 188–196.
Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., et al., 2012. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 490, 55–60.
Reaven, G., 2002. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. Circulation 106, 286–288.
Reynolds, K., Wildman, R.P., 2009. Update on the metabolic syndrome: hypertension. Curr. Hypertens. Rep 11, 150–155.
Romeo, S., Kozlitina, J., Xing, C., Pertsemlidis, A., Cox, D., Pennacchio, L.A., et al., 2008. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty

liver disease. Nat. Genet 40, 1461–1465.
Sabapathy, K., Hochedlinger, K., Nam, S.Y., Bauer, A., Karin, M., Wagner, E.F., 2004. Distinct roles for JNK1 and JNK2 in regulating JNK activity and c-Jun-dependent cell proliferation. Mol. Cell 15, 713–725.
Samuel, V.T., Liu, Z.X., Qu, X., Elder, B.D., Bilz, S., Befroy, D., et al., 2004. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. J. Biol. Chem 279, 32345–32353.
Samuel, V.T., Liu, Z.X., Wang, A., Beddow, S.A., Geisler, J.G., Kahn, M., et al., 2007. Inhibition of protein kinase Cepsilon prevents hepatic insulin resistance in nonalcoholic fatty liver disease. J. Clin. Invest 117, 739–745.
Sanyal, A.J., Chalasani, N., Kowdley, K.V., McCullough, A., Diehl, A.M., Bass, N.M., et al., 2010. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N. Engl. J. Med 362, 1675–1685.
Savage, D.B., Murgatroyd, P.R., Chatterjee, V.K., O'Rahilly, S., 2005. Energy expenditure and adaptive responses to an acute hypercaloric fat load in humans with lipodystrophy. J. Clin. Endocrinol. Metab 90, 1446–1452.
Schattenberg, J.M., Singh, R., Wang, Y., Lefkowitch, J.H., Rigoli, R.M., Scherer, P.E., et al., 2006. JNK1 but not JNK2 promotes the development of steatohepatitis in mice. Hepatology 43, 163–172.
Schwiertz, A., Taras, D., Schafer, K., Beijer, S., Bos, N.A., Donus, C., et al., 2010. Microbiota and SCFA in lean and overweight healthy subjects. Obesity (Silver Spring) 18, 190–195.
Shi, H., Kokoeva, M.V., Inouye, K., Tzameli, I., Yin, H., Flier, J.S., 2006. TLR4 links innate immunity and fatty acid-induced insulin resistance. J. Clin. Invest 116, 3015–3025.
Shimomura, I., Hammer, R.E., Ikemoto, S., Brown, M.S., Goldstein, J.L., 1999. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature 401, 73–76.
Shiri-Sverdlov, R., Wouters, K., van Gorp, P.J., Gijbels, M.J., Noel, B., Buffat, L., et al., 2006. Early diet-induced non-alcoholic steatohepatitis in APOE2 knock-in mice and its prevention by fibrates. J. Hepatol 44, 732–741.
Simons, L.A., Simons, J., Friedlander, Y., McCallum, J., 2011. Is prediction of cardiovascular disease and all-cause mortality genuinely driven by the metabolic syndrome, and independently from its component variables? The Dubbo study. Heart Lung Circ 20, 214–219.
Singh, R., Wang, Y., Xiang, Y., Tanaka, K.E., Gaarde, W.A., Czaja, M.J., 2009. Differential effects of JNK1 and JNK2 inhibition on murine steatohepatitis and insulin resistance. Hepatology 49, 87–96.
Sinn, D.H., Gwak, G.Y., Park, H.N., Kim, J.E., Min, Y.W., Kim, K.M., et al., 2012. Ultrasonographically detected non-alcoholic fatty liver disease is an independent predictor for identifying patients with insulin resistance in non-obese, non-diabetic middle-aged Asian adults. Am. J. Gastroenterol 107, 561–567.
Smits, L.P., Bouter, K.E., de Vos, W.M., Borody, T.J., Nieuwdorp, M., 2013. Therapeutic potential of fecal microbiota transplantation. Gastroenterology 145, 946–953.
So, J.S., Hur, K.Y., Tarrio, M., Ruda, V., Frank-Kamenetsky, M., Fitzgerald, K., et al., 2012. Silencing of lipid metabolism genes through IRE1alpha-mediated mRNA decay lowers plasma lipids in mice. Cell Metab 16, 487–499.
Solinas, G., Karin, M., 2010. JNK1 and IKKbeta: molecular links between obesity and metabolic dysfunction. FASEB J. 24, 2596–2611.
Spranger, J., Kroke, A., Mohlig, M., Hoffmann, K., Bergmann, M.M., Ristow, M., et al., 2003. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes 52, 812–817.
Taniguchi, C.M., Emanuelli, B., Kahn, C.R., 2006. Critical nodes in signalling pathways: insights into insulin action. Nat. Rev. Mol. Cell Biol 7, 85–96.
Tarantino, G., Finelli, C., Colao, A., Capone, D., Tarantino, M., Grimaldi, E., et al., 2012. Are hepatic steatosis and carotid intima media thickness associated in obese patients with normal or slightly elevated gamma-glutamyl-transferase? J. Transl. Med 10, 50.
Targher, G., Bertolini, L., Rodella, S., Lippi, G., Franchini, M., Zoppini, G., et al., 2008. NASH predicts plasma inflammatory biomarkers independently of visceral fat in men. Obesity (Silver Spring) 16, 1394–1399.
Tilg, H., Moschen, A.R., 2010. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology 52, 1836–1846.
Tran, T.T., Yamamoto, Y., Gesta, S., Kahn, C.R., 2008. Beneficial effects of subcutaneous fat transplantation on metabolism. Cell Metab 7, 410–420.
Tuncman, G., Hirosumi, J., Solinas, G., Chang, L., Karin, M., Hotamisligil, G.S., 2006. Functional in vivo interactions between JNK1 and JNK2 isoforms in obesity and insulin resistance. Proc. Natl. Acad. Sci. U.S.A. 103, 10741–10746.
Vanni, E., Bugianesi, E., Kotronen, A., De Minicis, S., Yki-Jarvinen, H., Svegliati-Baroni, G., 2010. From the metabolic syndrome to NAFLD or vice versa? Dig. Liver Dis 42, 320–330.
Veniant, M.M., Komorowski, R., Chen, P., Stanislaus, S., Winters, K., Hager, T., et al., 2012. Long-acting FGF21 has enhanced efficacy in diet-induced obese mice and in obese rhesus monkeys. Endocrinology 153, 4192–4203.
Vrieze, A., Van Nood, E., Holleman, F., Salojarvi, J., Kootte, R.S., Bartelsman, J.F., et al., 2012. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 143, 913–916 e917.
Webber, L., Divajeva, D., Marsh, T., McPherson, K., Brown, M., Galea, G., et al., 2014. The future burden of obesity-related diseases in the 53 WHO European-Region countries and the impact of effective interventions: a modelling study. BMJ Open 4, e004787.
Weiss, R., Taksali, S.E., Dufour, S., Yeckel, C.W., Papademetris, X., Cline, G., et al., 2005. The "obese insulin-sensitive" adolescent: importance of adiponectin and lipid partitioning. J. Clin. Endocrinol. Metab 90, 3731–3737.
Wu, A.L., Kolumam, G., Stawicki, S., Chen, Y., Li, J., Zavala-Solorio, J., et al., 2011. Amelioration of type 2 diabetes by antibody-mediated activation of fibroblast growth factor receptor 1. Sci. Transl. Med 3, 113ra126.
Wu, G.D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.Y., Keilbaugh, S.A., et al., 2011. Linking long-term dietary patterns with gut microbial enterotypes. Science 334, 105–108.
Xu, C., Bailly-Maitre, B., Reed, J.C., 2005. Endoplasmic reticulum stress: cell life and death decisions. J. Clin. Invest 115, 2656–2664.
Xu, J., Lloyd, D.J., Hale, C., Stanislaus, S., Chen, M., Sivits, G., et al., 2009. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. Diabetes 58, 250–259.
Zhang, X., Yeung, D.C., Karpisek, M., Stejskal, D., Zhou, Z.G., Liu, F., et al., 2008. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 57, 1246–1253.