Liver and diabetes. A vicious circle

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Liver and diabetes. A vicious circle

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Abstract

The complex and bi-directional relationship linking the liver and diabetes has recently gained intense new interest. This critical review of the published work aims to highlight the most recent basic and clinical data underlying the development of type 2 diabetes, in those with non-alcoholic fatty liver disease. Moreover, the potentially detrimental effects of type 2 diabetes in liver injury are also discussed in each of the two sections of the present paper. Fatty liver and diabetes share insulin resistance as their chief pathogenic determinant. The roles of the hypothalamus, the intestinal microbiome, white adipose tissue and inflammation are discussed in detail. Molecular insights into hepatocyte insulin resistance as the initiator of systemic insulin resistance are also presented with full coverage of the danger of fatty acids. Lipotoxicity, apoptosis, lipoautophagy, endoplasmic reticular stress response and recent developments in genetics are discussed. Closing the circle, special emphasis is given to biochemical pathways and clinical evidence supporting the role of type 2 diabetes as a risk factor for the development of progressive liver disease, including non-alcoholic steatohepatitis, cirrhosis and primary liver cancer. In conclusion, data support non-alcoholic fatty liver disease as a risk factor for the development of type 2 diabetes which is, in turn, a major contributor to progressive liver disease. This pathway leading from fatty liver to type 2 diabetes and back from the latter to the progressive liver disease is a vicious circle.

Keywords

cholangiocarcinoma; cirrhosis; epidemiology; hepatocellular carcinoma; management; natural history

INTRODUCTION

TYPE 2 DIABETES (T2D) – characterized by hyperglycemia and dyslipidemia caused by islet β-cells being unable to secrete adequate insulin in response to varying degrees of long-standing insulin resistance (IR) in genetically predisposed individuals – poses an enormous burden on modern societies owing to its worldwide explosion, the multi-organ damage and its direct and indirect costs.¹ In recent years, the topic “Hepatogenous diabetes” – a definition coined in 1906 to describe the high incidence of diabetes in cirrhotics² – has gained intense new interest. Clinical observations support that impaired life expectancy of patients with T2D is not only linked to vascular complications and end-stage renal disease but is also associated with cirrhosis and hepatocellular carcinoma (HCC).³ Moreover, insight that non-alcoholic fatty liver disease (NAFLD), the most common liver disorder in many Western countries and an important chronic liver disease in Asia,⁴ may be a forerunner in...
the development of systemic IR and T2D\textsuperscript{5} has gained worldwide attention from basic and clinical investigators alike. Based on these recent clinical observations, we critically reviewed basic and clinical data illustrating the pathways that can lead from NAFLD to the development of T2D via IR, in particular hepatic IR and, conversely, the role that T2D may play in the development of progressive liver disease (i.e. vicious circle). Other hepatological implications of T2D including the risk of bacterial infections in cirrhotic diabetics\textsuperscript{6,7} are beyond the scope of our review.

FROM FATTY LIVER TO DIABETES

Basic evidence that fatty liver plays a role in the development of T2D

Shared pathogenesis of NAFLD and diabetes—AFTER THE INITIAL characterization of NAFLD in 1980,\textsuperscript{8} we have a better understanding of how fatty acid and triglyceride accumulation occurs.\textsuperscript{9} Primary NAFLD is not only the hepatic manifestation of metabolic syndrome (MS), a clinical constellation embracing hypertension, atherogenic dyslipidemia, T2D and obesity,\textsuperscript{10} but also a condition actively promoting the development of MS.\textsuperscript{11} In some patients NAFLD is secondary to specific endocrine derangements\textsuperscript{12} but such contributing factors are beyond the scope of this review.

IR and the fatty liver: from “two-hit” to the “multiple parallel hits” hypothesis—Day and colleagues, among the first researchers to link NAFLD to IR, initially proposed the so-called “two hit hypothesis” in which the first hit was the accumulation of triglycerides, steatosis, a consequence of systemic IR.\textsuperscript{13} The second hit was thought to be a consequence of long-term storage of triglycerides that resulted in hepatic oxidative stress. Such stress would result in an imbalance between glutathione and oxidized equivalents (GSH/GSSH), impaired mitochondrial energy production and dysfunctional β-oxidation of fatty acids. Free radicals along with lipid peroxidation products resulted in hepatocyte injury by direct disruption of cell organelles and membranes, the consequences of which lead to necrotic cell death or apoptosis as well as recruitment of inflammatory mediators. In this paradigm, perpetual chronic injury would be established leading to eventual fibrosis, cirrhosis and/or HCC. Subsequent studies revealed that hyperinsulinemia (the first hit) does indeed precede the development of fatty liver in humans\textsuperscript{14} and the second-hit has been much more refined. More recently, other models have been proposed such as the “four step” theory which emphasizes the role of lipid release and hepatic venular obstruction in the progression to cirrhosis.\textsuperscript{15} This model is particularly effective in explaining the morphogenesis of disease and might be useful in understanding conditions other than NAFLD. Tilg and Moschen have proposed the “multiple parallel hits hypothesis”.\textsuperscript{16} This model emphasizes that a number of very diverse parallel processes might contribute to the development of liver inflammation – notably including the contribution from extrahepatic tissues such as the gut and/or the adipose tissue – and that hepatic inflammation may precede steatosis, cirrhosis and HCC in at least a proportion of cases. The advantages of the multiple parallel hits hypothesis are that it is verifiable and has bearings on novel treatment strategies. In this review, the first part focuses on an approach to hepatocyte fatty acid handling including biosynthesis and secretion as these biochemical activities relate to hepatic IR. The second part will “close the circle” by discussing the deleterious consequences of T2D on the liver.

The liver plays a key role in regulating both glucose and lipid metabolism, derangements of which occur in NAFLD and T2D. In T2D, fasting hyperglycemia results from unopposed endogenous glucose production due to IR and postprandial hyperglycemia from the inability to store glucose as glycogen after a meal. Both fasting and postprandial hyperglycemia are, at least in part, linked to the amount of hepatic steatosis. Conversely, lifestyle interventions
aimed at reducing bodyweight of as low as 8% are associated with reduced steatosis and improved IR in those with obesity and T2D.\textsuperscript{17,18}

The “general rule” seems to be that fatty liver is closely associated with IR\textsuperscript{19} and there seem to be few exceptions to this. Such exceptions, featuring a dissociation of IR from fatty liver, are mainly restricted to examples of NAFLD occurring in experimental pathology\textsuperscript{20} or in the setting of specific genetic conditions affecting lipid metabolism.\textsuperscript{21–25}

**Does the hypothalamus play a role in the development of IR?**—In recent years, data have been accumulating concerning the potential role of the hypothalamus in the development of IR.

One possibility is that primary peripheral IR might induce IR in the brain via the blood–brain barrier ceramide trafficking leading to brain IR mediated by neuronal degenerative phenomena.\textsuperscript{26}

Additionally, the finding that uptake and storage of fatty acids are increased in the hypothalamus of those individuals with MS, a disturbance which is reversed by bodyweight loss,\textsuperscript{27} is also supportive evidence that primary hypothalamic involvement may play a role in aggravating IR. This would establish a complex pathogenesis involving cross-talk between the hypothalamus and visceral organs (gut, liver, pancreas and white adipose tissue [WAT]).\textsuperscript{28} Hence, hypothalamic storage of particular types of fat such as free fatty acids or ceramide, might also damage hypothalamic neurons secondary to lipotoxicity.\textsuperscript{29}

Complementing experimental studies, evidence for a role of the hypothalamus in the development of human non-alcoholic steatohepatitis (NASH) has recently been reviewed.\textsuperscript{12}

**Importance of the intestinal microbiome in IR**—Recent demonstrations indicate that while germ-free mice consume more calories than their wild-type lean littermates, the latter gain significantly more weight.\textsuperscript{30,31} Furthermore, feeding rodents a high-fat diet will alter the intestinal bacterial flora and can impair the host defense by affecting the innate immune function negatively.\textsuperscript{31} Several studies in Toll-like receptor knockout (TLR-KO) mice demonstrate that high-fat feeding increases the bacterial load in the intestines of the mice and change the respective bacteria flora. Upon transferring gut flora derived from the TLR-KO mice to germ-free mice, all of the findings associated with MS including weight gain, IR, hyperglycemia, NAFLD and hypertriglyceridemia were also transferred.\textsuperscript{32} The change in the bacterial flora or gut microbiome, and impaired host defenses to combat such changes, results in increased paracellular intestinal permeability which may be the etiologic factor in inflammation, production of lipopolysaccharide and tumor necrosis factor (TNF-\( \alpha \)) and impaired function in adipose tissue, skeletal muscle and the liver (Fig. 1).\textsuperscript{32–34} Increased free fatty acid (FFA) released from WAT is also a well-established contributing factor in hepatocyte triglyceride and fatty acid storage which contributes to the development and exacerbation of hepatic IR.

**Inflammation and WAT**—In the 1990s, the seminal discovery of leptin,\textsuperscript{35–37} derived from the ancient Greek word \textit{λεπτός} (leptòs) meaning “thin”, by Friedman, initiated a decade-long study of visceral WAT, where this 16-kDa protein is synthesized. Soon, adiponectin,\textsuperscript{38} resistin,\textsuperscript{39} TNF-\( \alpha \) and interleukin (IL)-6\textsuperscript{40} were all recognized as being synthesized by WAT.\textsuperscript{41} The endocrine community recognized that obesity was not just a consequence of diet and impaired insulin sensitivity, but was also a chronic inflammatory disease.\textsuperscript{42} As a target organ of chronic inflammatory processes, WAT is bombarded with the recruitment of macrophages; and when taken together, WAT releases not only adipocytokines, noted above, but paradoxically releases FFA into the circulation. Because most WAT is in the abdominal cavity – and not in subcutaneous tissue – the delivery of FFA

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as well as adipokines are destined directly to the liver via the portal vein. These seminal developments in endocrinology and metabolism occurred in parallel with the recognition that inflammation was critical to the development and progression of other major human disease, for example, cardiovascular diseases. Specifically, vascular biologists recognized that inflammation of blood vessel walls, or endothelia, resulted in endothelial dysfunction. Similarly, in hepatology we came to recognize that storage of triglycerides (steatosis) and later FFA storage were key components driving IR in the liver. At the core of all these clinical maladies were hyperglycemia, hyperinsulinemia and the failure of adipose tissue to store FFA; while, paradoxically, releasing FFA into the circulation results in hepatocyte gluconeogenesis and de novo lipogenesis.

**Skeletal and cardiac muscle**

Insulin resistance in skeletal and cardiac muscle also impairs their ability to transport glucose for fuel in part by the inhibition of the Glut4 transporter. Because circulating triglycerides and FFA are also high in accord with WAT release and impaired insulin action, muscle deposits of fat are also seen on pathological specimens (myocellular steatosis). The impairment of normal uptake of glucose by adipocytes and muscle cells and the paradoxical storage of FFA in muscles and release from adipocytes perpetuates peripheral IR. These metabolic perturbations are intimately involved with the concept of hepatocyte IR (Fig. 2).

**Hepatocyte IR: molecular insights into the initiator of systemic IR**—The exact mechanisms of hepatocyte IR tend to be more and more precisely elucidated. In addition to the role of WAT, adipokines, the microbiome and inflammation most likely contribute to hepatocyte IR. Lifestyle – specifically diet and exercise – is involved. Although physical exercise, by reversing muscle IR, decreases hepatic de novo lipogenesis and hepatic triglyceride synthesis after a carbohydrate-rich meal in experimental conditions, diet ameliorated central adiposity and liver enzymes and exercise training did not confer significant incremental benefits in a recent study mimicking clinical conditions more closely. Consumption of the highly lipogenic sugar fructose is associated with IR, MS, NAFLD and NASH. Smoking favors hepatic lipogenesis and fibrotic progression in NAFLD as well as the development of T2D.

Conversely, moderate alcohol and coffee consumption may prevent the development of both NAFLD and T2D. These findings, however, do not translate into specific lifestyle suggestions so far. Consumption of dairy products may be associated, via increased Trans-palmitoleate (trans-16:1n-7) serum levels, with improved glicolipidic metabolic profile and diabetes prevention; nonetheless, the role of dairy products in association with NAFLD, if any, is unsettled. Hepatic protein kinase C (PKC) isoforms promote hepatocyte IR by inhibiting insulin signaling in human liver biopsy samples. In a study published by Shulman’s group, antisense oligonucleotide (ASO) against PKCe markedly improved clinical parameters of MS associated with a significant reduction in hepatocyte IR, including intrahepatic triglycerides and fasting plasma insulin concentrations. Their work provides a molecular explanation for the derangements associated with hepatocyte IR by demonstrating that PKCe ASO restores insulin receptor substrate-2 (IRS-2) phosphorylation and protein-serine-threonine kinase activity. A more recent study by the same group developed this line of research further by demonstrating that hepatic diglycerol content in cytoplasmic lipid droplets, which was strongly associated with activation of hepatic PKCe activity, was the best predictor of IR, being responsible for 64% of the variability in insulin sensitivity. Gupta et al. recently published the effect of exendin-4, a glucagon-like peptide 1 (GLP-1) analog as promoting insulin-sensitizing effects by way of PKCC. Finally, FFA, which are causally linked to the development of steatosis, have been recognized as inducers of IR via activation of protein kinases. Although
requiring further study, this line of research underscores the importance of fatty liver as a
precursor lesion to the development of systemic IR accounting for the finding that NAFLD
individuals are twice as likely to develop T2D as those without NAFLD. Clearly, the
mechanisms leading from hepatic steatosis to long-lasting IR and, in predisposed
individuals, to T2D are critical.

Lipotoxicity remains key to the pathogenesis of T2D. Stated otherwise, the presence of
long-standing IR per se is not sufficient to lead to full-blown T2D in the absence of β-cell
failure.

Therefore, morphological evidence of fatty changes in the pancreas could be a better marker
of pancreatic lipotoxicity. Recent studies suggest that steatosis of the pancreas is visible
through endoscopic ultrasound. Interestingly, risk factors for “fatty pancreas” tend to
overlap with those for fatty liver suggesting a shared pathogenesis in lipotoxicity, the
ectopic, extra-adipose tissue storage of lipids eventually conducive to tissue damage and
organ dysfunction.

Assessment of mediators of IR is of critical importance: Fetuin-A and IL-6 could be such
mediators. Fetuin-A, a protein secreted by the liver and associated with the development of
IR in animals and with fatty liver in humans, has been proposed as one such mediator.
Stefan et al. in a large prospective case cohort – EPIC-Potsdam study –observed fetuin-A
to be an independent predictor of T2D. IL-6 – a major pro-inflammatory cytokine, the
expression of which is increased in experimental NAFLD, resulting in systemic IR – could
be another mediator. Wieckowska et al. reported that the expression of IL-6 in the
hepatocytes, which is selectively induced by saturated FFA, is positively correlated with
hepatic inflammatory fibrotic changes and systemic. These data account for the well-
known matching of IR with hepatic fibrosis observed, for instance, in chronic hepatitis C
virus infection and explain why blockade of IL-6 signaling improves liver injury in a
rodent model of NASH.

Sources of hepatocyte fatty acids in NAFLD— Three chief sources of FFA are
available to the hepatocyte in the IR state. The first reservoir of hepatocyte FFA is from
digestion and transfers across the intestinal epithelium to hepatocytes. The second source of
FFA is from digestion and transfers across the intestinal epithelium to hepatocytes, as
mentioned previously. Finally, hepatocytes increase the production of FFA, a process
termed de novo lipogenesis, or DNL.

Danger of fatty acids and the concept of lipotoxicity: not all fatty acids are
created equal

Studies of DGAT2 reveal that hepatocyte triglycerides may be innocuous. The concept
that triglycerides may serve as a protective reservoir in the pathogenesis of NAFLD was the
result of two important studies. The first performed by Diehl and colleagues in which the
ASO for the enzyme diacylglycerol acetyltransferase 2 (DGAT2) was given to db/db mice
fed a methionine-choline deficient diet for up to 8 weeks. Their findings were striking in that
mice administrated ASO for DGAT2 had significantly higher levels of lipid peroxidation
products, hepatic fibrosis and FFA, but diminished hepatocyte steatosis. To underscore the
importance of DGAT in preventing both hepatocyte and systemic IR, Monetti and
colleagues created mice that overexpressed DGAT2, and found that the mice had significant
steatosis and diacylglycerol but failed to develop IR indicating that hepatic steatosis arising
from impaired triglyceride assembly does not result in IR.

In vitro fat loading studies: The vast majority of proteins that a cell secretes or displays on
its surface first enter the endoplasmic reticulum (ER), where they fold and assemble. Only
properly assembled proteins advance from the ER to the cell surface. To ascertain fidelity in protein folding, cells regulate the protein folding capacity in the ER according to need. The ER responds to the burden of unfolded proteins in its lumen (ER stress) by activating intracellular signal transduction pathways, collectively termed the unfolded protein response. Researchers have used transformed hepatocyte cell lines and have loaded cells with specific fatty acids. Saturated fatty acids, such as palmitate, or stearate, but not oleate, resulted in increased hepatocyte apoptosis and this cell death was mediated by ER stress.

These recent studies implicate the role of ER stress and the ability to discriminate between what is a normal unfolded protein response which the ER can handle without resort to cell death when the stress mechanism is overwhelmed.

**Hepatocyte apoptosis and the potential for dysfunctional ER stress response**

—Czaja and colleagues clearly implicated Janus Kinase 1 (JNK1) as a principal player in driving the pathogenesis of NASH and hepatocyte apoptosis. Death by apoptosis is currently felt to be the major player resulting in progression of NASH. While this discussion cannot review the details of ER stress, the reader is referred to other sources. Three key trans-membrane proteins in the ER – PERK, ATF-4 and XBP-1 – manage misfolded proteins. If, however, XBP-1 and ATF-6 cannot induce the key ER chaperone GRP78 or BIP, then c-β homologous protein, or CHOP, will be expressed which leads to downstream effectors of apoptosis. It should be mentioned, however, that the role of CHOP in human NASH as a driver of hepatocyte apoptosis is in dispute.

**Lipoautophagy**

Finally, despite a clear pathway of understanding in the development of hepatic IR, the discovery by Czaja and colleagues that the elimination of fat stores by lysosomal degradation pathway, or autophagy, may have profound implications for not just NAFLD but hepatic IR because the storage of FFA may be dangerous and also perpetuate hepatocyte IR. Furthermore, the process of rapid clean up of fats either by macroautophagy or chaperone-mediated autophagy promotes hepatocyte resistance to oxidative stress. Although limited here, for further review readers are encouraged to see the most recent review on autophagy and the liver because data implicate the failure of hepatocyte autophagic function can lead to the development of a fatty liver.

**Recent developments in genetics**—The issue of susceptibility of race or ethnicity to NAFLD progression was recently highlighted by the discovery of a point mutation in the gene encoding for adiponutrin, or PNPLA3, in which Hispanics were far more likely to have more hepatic fat and inflammation if they had an allelic variant. Conversely, non-Hispanics and African-Americans were more likely to have a protective allelic variant, and were less likely to have either excess hepatocyte fat or inflammation. It should be noted that the association between PNPLA3 polymorphisms and NAFLD is independent of IR.

**Clinical evidence that fatty liver plays a role in the development of T2D**—

Studies have shown an association between fatty liver and altered glucose tolerance/diabetes alone or in the setting of MS. Such an association is found in cross-sectional and confirmed by prospective studies. Although limited by their study design, cross-sectional studies offer some interesting hints. For instance, they indicate that the pathogenesis of NAFLD could be sex-specific; that NAFLD patients display metabolic abnormalities indistinguishable from those observed in diabetic and obese patients; and that it is difficult
to dissociate the development of T2D alone from the development of the MS on the grounds that NAFLD is a risk factor for both.\textsuperscript{94,95} Finally, NAFLD is associated with IR rather than with impaired β-cell viability,\textsuperscript{95,96} implying that the development of T2D will not occur other than in the presence of a genetic predisposition.

Prospective studies provide the most robust evidence, given that they are based on both surrogate indices, hepatobiliary enzymes\textsuperscript{97–104} and on the natural history of NAFLD.\textsuperscript{105–108} It should be acknowledged that liver enzymes are insensitive and non-specific for the diagnosis of NAFLD. Moreover, imaging studies have been performed in Asian populations alone.

A recent meta-analytical study quantified that NAFLD has a twofold risk of T2D.\textsuperscript{5} Knowledge of subsets of NAFLD patients particularly prone to developing T2D is critical in envisaging strategies of prevention. In this regard, a study reported that it is NASH rather than pure fatty liver that is associated with T2D\textsuperscript{105} and another study suggested that those with pre-diabetes, elevated glutamyl transeptidase, triglycerides and insufficient physical activity are the patients more in need of specific interventions to prevent T2D.\textsuperscript{106}

In conclusion, data strongly support NAFLD to be a risk factor for the future development of impaired glucose tolerance/diabetes alone, or in the setting of MS. They also provide useful clinical clues to identifying subjects who, being particularly prone to developing the disease, may benefit most from strategies of prevention and early treatment.

**Role of insulin sensitizers in the treatment of NASH**—If, as we have postulated, there is a strong pathogenic role linking NAFLD and IR/T2D, insulin sensitizers should be used with beneficial effects in non-diabetic NASH patients.

In this connection, two recent meta-analytic reviews provide somewhat conflicting results. Musso \textit{et al.} found that thiazolidinediones improved steatosis and inflammation.\textsuperscript{109} However whether glitazones are effective agents against fibrosis remains quite controversial\textsuperscript{110,111} suggesting that IR is an early agent in the development of NASH\textsuperscript{112,113} and that it may trigger other pathogenic mechanisms, such as oxidative stress and de novo lipogenesis, that likely contribute to ongoing inflammatory fibrotic changes independent of IR.

**FROM T2D TO PROGRESSIVE LIVER DISEASE**

**Vicious circle completed: basic pathogenic mechanism of ongoing liver damage in patients with T2D**

HAVING DISCUSSED POTENTIAL mechanisms whereby NAFLD could be linked to the development of T2D in predisposed individuals through long-standing hepatic IR, now we are going to examine how T2D might mechanistically induce progressive liver damage. This topic may be schematically divided into two sections: fibrogenesis and carcinogenesis.

**Fibrogenesis**—Interestingly, fibrosis in the liver might progress parallel to atherogenesis. Associated with obesity and TNF-α, increased expression of plasminogen activator inhibitor 1 (PAI-1) in human hepatocytes may lead to the development of atherosclerosis and hepatic fibrosis in individuals with IR via impaired fibrinolysis.\textsuperscript{114}

White adipose tissue adipokines appear to play a critical role in hepatic fibrosis, particularly in NASH.
Inflammatory cytokines are differentially expressed in the adipose tissue of fibrosing NASH, as well in NASH associated with T2D pointing to pathogenic cross-talk of adipose inflammatory cytokines, T2D and liver fibrosis leading to cirrhosis and end-stage liver disease.\textsuperscript{115} In addition, the greater IR an individual has, the more apoptosis is induced.\textsuperscript{116} Apoptosis of hepatocytes, a key histological feature of NASH, is induced by FFA and correlates with inflammatory fibrotic changes.\textsuperscript{81} NASH-induced apoptosis is currently the principle mediator of ongoing liver injury and setup for liver fibrosis. A comprehensive review of our understanding of the molecular pathways connecting lipotoxic IR and hepatic fibrogenesis is specifically discussed elsewhere.\textsuperscript{117}

**Hepatic carcinogenesis**—Hepatocellular carcinoma, the most common primary liver cancer, ranks fourth among the most prevalent malignancies worldwide and third leading cause of cancer-related deaths.\textsuperscript{118} Most cases of HCC occur as a late complication of infection with either hepatitis B or C virus. However, the etiology of disease remains unclear in up to half of HCC cases suggesting that T2D and obesity, via the development of NASH (with or without cirrhosis), might play a role.\textsuperscript{119,120}

Several mechanisms could favor the development of HCC in the setting of NAFLD, including abnormal glucose metabolism, hepatocyte iron deposition, age and advanced fibrosis. The subclinical inflammatory state associated with IR, steatosis, oxidative stress and unbalanced adipocytokine ratio (i.e. increased IL-6, leptin TNF-\(\alpha\) and decreased adiponectin) could all play a major role in cell growth kinetics and promotion of DNA damage all of which provide a favorable environment for the development of HCC.\textsuperscript{119–121}

The phosphoinositide 3-kinase (PI3K)/phosphatase and tensin homolog (PTEN)/Akt axis is a key regulator of crucial cellular functions such as insulin and other growth factor signaling, glycolipidic homeostasis, cell survival and apoptosis.\textsuperscript{122} In this pathway, PTEN acts as a phosphoinositide phosphatase, which terminates PI3K-propagated signaling by dephosphorylating PtdIns(3,4)P(2) and PtdIns(3,4,5)P(3).\textsuperscript{122} Not only is PTEN a tumor suppressor but, interestingly, it is dysregulated in obesity, IR and T2D, therefore representing an ideal metabolic pathway accounting for the development of HCC in the setting of metabolic disorders such as IR, T2D and NAFLD.\textsuperscript{122,123}

Interestingly, recent studies suggest that the type of antidiabetic drug treatment used may modulate the risk of developing HCC, insulin increasing and insulin sensitizers decreasing it.\textsuperscript{124–126}

**Clinical evidence of T2D impact on the development and progression of liver disease**

Adams’ group has contributed to identifying the chief distinguishing features of the ominous interaction of T2D with NAFLD: Diabetic patients (with elevated body mass index and low fibrosis stage) are at risk for higher rates of fibrosis progression.\textsuperscript{127} Mortality among community-diagnosed NAFLD patients is associated with impaired fasting glucose (further to older age and cirrhosis)\textsuperscript{128} and T2D.\textsuperscript{129} These data and those from other groups support the notion that the presence of T2D and MS is associated with NAFLD, fibrosing liver disease, including cirrhosis and increased risk of developing HCC.\textsuperscript{130–138} As a result, increased risk of liver-related mortality, from both cirrhosis and HCC has been reported consistently in T2D patients.\textsuperscript{3,138,139}

Based on data presented, here it is concluded that NAFLD associated with T2D represents a “red flag” per se of a more severe clinical course and this carries major clinical implications. First, these individuals will tend to have NASH rather than pure fatty liver and therefore should preferentially receive a biopsy as opposed to non-invasive diagnosis. Further, the risk for cirrhosis is also increased and therefore aggressive therapeutic intervention is warranted.
in these patients. Importantly, they may be prone to developing HCC against a background of non-cirrhotic livers.\textsuperscript{135,136} Finally, studies tend to suggest that not only HCC but also cholangiocarcinoma might occur in those with either NAFLD or MS.\textsuperscript{140–142} While such findings may result in more liberal use of screening policies to implement an early diagnosis of primary liver cancer when the disease is radically curable, it should be kept in mind that the incidence of HCC is quite low in non-cirrhotic NAFLD, which represents a very high proportion of the general population. Therefore, markers identifying those individuals at a high risk of HCC are necessary.

**CONCLUSIONS**

WE HAVE REPORTED on the pathways leading from fatty liver to T2D and return from T2D to progressive liver damage, hence the definition of a “vicious circle” (Fig. 3). Fatty liver is a major determinant in the development of T2D in predisposed individuals. However, once T2D is fully developed, not only will it further contribute to steatogenesis, but also contribute to progressive liver damage including NASH, fibrosis, cirrhosis and possibly to HCC in a subset of patients.

On these grounds, diagnostic and early therapeutic interventions are warranted in treating NASH patients at risk for developing T2D, as well as to prevent, or make an early diagnosis of, progressive liver disease in those with T2D.

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Figure 1.
Is metabolic syndrome in humans an infectious disease? In genetically engineered mice lacking Toll-like receptor 5 (TLR5), an intestinal mucosa component which protects from infections, metabolic syndrome results from hyperphagia.\textsuperscript{31,32} Interestingly, metabolic derangements are correlated with altered composition of the intestinal microbial system to such an extent that transfer of the intestinal microbiota from TLR5-deficient mice also transmits to the recipient wild-type germ-free mice many features of metabolic syndrome.\textsuperscript{33} Data are in agreement with the novel theory that the intestinal microbiota is an essential mediator linking high-fat diet with metabolic adaptation.\textsuperscript{34} Is this true for humans? Reprinted with permission.\textsuperscript{33}
Figure 2.
Biochemistry of normal insulin sensitivity and insulin resistance. (a) Physiological state. Normal glucose levels are maintained by insulin action which effectively stimulates glucose uptake in adipose tissue and skeletal muscles and inhibits hepatic glucose output. Moreover, insulin contributes to normal plasma lipid levels by stimulating lipid storage in the adipose tissue through inhibition of the activity of hormone-sensitive lipoprotein lipase. (b) Insulin-resistant state. Hyperglycemia and compensatory hyperinsulinemia result from decreased glucose uptake by peripheral tissues and decreased inhibition of hepatic glucose output. Moreover, atherogenic hyperlipidemia results from impaired inhibition of lipoprotein lipase, leading to lipotoxicity, namely tissue malfunction and damage from excess lipid depots in non-adipose tissues such as liver, muscles and kidney. In addition, adipocytokines are unbalanced so contribute to perpetuating insulin resistance. Reprinted with permission.
Figure 3.
Molecular mechanisms involved in the vicious circle linking fatty liver to diabetes and diabetes to progressive liver injury. Left, the first part of the journey, leading from initial insulin resistance to fatty liver and eventually to the development of T2D in those predisposed individuals in whom pancreatic lipotoxicity occurs. Right, the mechanism which – triggered by long-lasting/decompensated T2D – may be conducive to progressive liver disease including primary liver cancer in predisposed individuals. HCC, hepatocellular carcinoma; IL, interleukin; NASH, non-alcoholic steatohepatitis; PTEN, phosphatase and tensin homolog; T2D, type 2 diabetes.