Hepatic function and the cardiometabolic syndrome

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Abstract: Despite skeletal muscle being considered by many as the source of insulin resistance, physiology tells us that the liver is a central and cardinal regulator of glucose homeostasis. This is sometimes underestimated because, in contrast with muscle, investigations of liver function are technically very difficult. Nevertheless, recent experimental and clinical research has demonstrated clearly that, due in part to its anatomic position, the liver is exquisitely sensitive to insulin and other hormonal and neural factors, either by direct intrahepatic mechanisms or indirectly by organ cross-talk with muscle or adipose tissue. Because the liver receives absorbed nutrients, these have a direct impact on liver function, whether via a caloric excess or via the nature of food components (eg, fructose, many lipids, and trans fatty acids). An emerging observation with a possibly great future is the increase in intestinal permeability observed as a consequence of high fat intake or bacterial modifications in microbiota, whereby substances normally not crossing the gut gain access to the liver, where inflammation, oxidative stress, and lipid accumulation leads to fatty liver, a situation observed very early in the development of diabetes. The visceral adipose tissue located nearby is another main source of inflammatory substances and oxidative stress, and also acts on hepatocytes and Kupffer cells, resulting in stimulation of macrophages. Liberation of these substances, in particular triglycerides and inflammation factors, into the circulation leads to ectopic fat deposition and vascular damage. Therefore, the liver is directly involved in the development of the prediabetic cardiometabolic syndrome. Treatments are mainly metformin, and possibly statins and vitamin D. A very promising avenue is treatment of the leaky gut, which appears increasingly to be an important causal factor in hepatic insulin resistance and steatosis.

Keywords: nonalcoholic liver disease, fatty liver, insulin resistance, cardiometabolic syndrome, pharmacology

Cardiometabolic syndrome: definitions and limits

The prediabetic period, which can last for decades, is characterized by metabolic modifications which eventually lead to frank type 2 diabetes. This situation was initially termed “syndrome X”, but soon evolved to “metabolic syndrome”. With increasing recognition that these metabolic disorders also lead to cardiovascular complications (myocardial infarction, stroke), the terminology was changed further to the notion of “cardiometabolic syndrome”. Indeed, the prevalence of large vessel disease appears to be essentially similar to that of already established type 2 diabetes. Microvascular abnormalities were completely ignored for a long time, but more recent investigations have revealed that modifications such as microalbuminuria, retinal blood flow change, and even signs of nonenzymatic glycation, albeit far less pronounced than in
type 2 diabetes, can be found if screened for before fasting hyperglycemia is present.

Cardiometabolic syndrome is an extremely complicated issue due to the fact that it encompasses a mesh of metabolic pathways (mainly glycemia and lipids) and involves several tissues (liver, fat, muscle, and others). For example, the liver is closely involved not only in regulation of glycemia and lipids but also in inflammation and hemostasis, which are main players (as will be seen) in cardiometabolic syndrome. Moreover, many of these processes operate in a bidirectional manner.

According to the various definitions used to ascertain metabolic syndrome, the prevalence in a “normal” population is around 30%, varying with many parameters, including gender, ethnicity, geographic distribution, standard of living, and smoking. Overweight and obesity are found at some step of the metabolic syndrome in a large majority of subjects, which represents a main bias for interpreting the “mechanistic” evolution of metabolic syndrome and its links with cardiovascular complications.

The “search for the Grail” question therefore is: what comes first? The answer is unknown, and the most likely and reasonable response is that there is no answer. Indeed, several hypotheses have been proposed around the notion of a “common soil”, but none has delivered sufficient proof to establish its validity as the correct explanation. Indeed, even a metabolic syndrome population consists of a heterogeneous grouping of people having different causes for their biologically defined metabolic syndrome. Thus, not all individuals are insulin-resistant, not all insulin-resistant subjects are glucose-intolerant, not all overweight/obese persons are metabolically abnormal, and lean subjects can develop severe metabolic abnormalities. In epidemiologic studies, three or more subpopulations are usually observed. About one third have fatty liver, considered to be a very crucial component in aggravation of metabolic syndrome towards cardiometabolic syndrome (see later), but this also means that two thirds are not falling into this category. Therefore, it is easily understandable that obtaining a unifying conclusion is largely illusory, at least in the present constellation of our knowledge.

The role of main tissues/organs regulating glycemic and lipidic metabolism is another subject of endless debate. Largely due to technical aspects (clamp technique), skeletal muscle has been increasingly and excessively considered as the initial location of insulin resistance, the latter being considered as one (if not the only) principal common denominator responsible for metabolic syndrome and subsequent type 2 diabetes. This view is partly biased by the fact that it is difficult to investigate deep-lying organs, typically the liver. Techniques for evaluating hepatic insulin resistance, such as stable isotopic methods, are available, but in daily medical practice the diagnosis mostly relies on blood parameters. However, one should bear in mind that the liver is the main organ controlling sugar and lipid metabolism, which is illustrated in its crucial anatomic positioning: it receives products from the digestive system as well as from the periphery of the body, transforms and detoxifies various substances, and delivers glucose, lipids, and inflammatory and hemostatic factors, amongst others, to the rest of the body. It is also closely under the control of the brain as well as an intrinsic nervous network in the liver. To complicate the situation further, recent findings indicate that the tissues involved in metabolic regulation, and consequently in cardiometabolic syndrome, exhibit constant cross-talk. For example, experimentally induced changes in skeletal muscle glucose transport capacity can lead to fat accumulation in the liver, and the severity of hepatic steatosis is linked to skeletal muscle adiposity; conversely, the liver sends substances capable of inducing peripheral insulin resistance in skeletal muscle into the bloodstream. For example, it was recently reported that the triglyceride content of skeletal muscle is associated with hepatic but not peripheral resistance. The same holds true for adipose tissue, which is considered by many to be the crucial player in the initiation of insulin resistance and evolution towards metabolic syndrome. Because of these interplays, arguments for “initial causality” can be found for any of at least five organs, ie, pancreas, liver, adipose, skeletal muscle, and brain. More recent research has revealed that functional (possibly inherited) abnormalities of microvascular mechanisms can initiate insulin resistance in skeletal muscle or adipose tissue, and that this may function in a bidirectional fashion, eg, in the case of sleep apnea and insulin resistance.

The present review therefore deals mainly with what is known and believed to be the case for the “bulk” of the cardiometabolic syndrome population, and focuses on the particular role of the liver and its links with cardiovascular and metabolic syndrome-related diseases. The accompanying bibliography is, by definition, a subjective but well updated selection where readers can easily find further references for more detailed information.

**Crucial role of the liver in cardiometabolic syndrome**

The liver clears, metabolizes, detoxifies, and redistributes the absorbed content of food. Its role in established type 2 diabetes is well demonstrated, but increasing evidence
implicates this organ in the very early stages of prediabetes. One major finding of the last decade has been the recognition of a prevalence rate of 30% for hepatic steatosis in the general population, with an even higher prevalence in obese and elderly populations. About 15%–30% will progress towards a more severe form, known as nonalcoholic steatohepatitis, where severe inflammation and fibrosis develop, leading eventually to liver cancer. These various forms of the disease are grouped under the term “nonalcoholic fatty liver disease”. Given that the present review deals mainly with early prediabetes, our focus is limited to hepatic steatosis, ie, fatty liver.

Factors inducing hepatic insulin resistance and steatosis
Many but not all metabolic pathways of glucose and lipid metabolism in the liver are under the control of insulin which regulates hepatic glucose output and lipid synthesis. Therefore, any impairment in hepatic insulin sensitivity is rapidly reflected in glucose homeostasis and triglyceride levels. Today, fatty liver is considered as the “hepatic expression of metabolic syndrome”. Hepatic insulin resistance is severe in fatty liver, regardless of the glycemic tolerance status of patients.

Nutritional factors
High carbohydrate diets and/or excessive dietary fat leading to exaggerated free fatty acid delivery result in hepatic insulin resistance, diminished fatty acid oxidation, and de novo lipogenesis with triglyceride accumulation in hepatocytes, a situation which can be clinically observed either by changes in plasma levels of hepatic enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), and high-sensitivity C-reactive protein, or by echosonography of the liver. The anatomic position of the liver places this organ in close contact with abdominal fat, a tissue known to be highly lipolytic and to liberate many cytokines, including inflammation factors. An increase in visceral fat, usually as a result of high caloric intake, is therefore a preferential source of substrates impacting on the liver.

Non-nutritional factors
The nervous system closely controls hepatic metabolism. Therefore, stress is another factor likely to affect the liver via neurotransmitters and glucocorticoids. Stimulation of the hypothalamic-pituitary-adrenal axis by chronic or even mild stress is a favored explanation for the cause of cardiometabolic syndrome. The stress response is largely mediated by cortisol, a substance to which liver cells are exquisitely sensitive and respond to by rapid development of insulin resistance. An association between cortisol concentrations measured...
Markers of hepatic insulin resistance/steatosis

Circulating levels of lipids, in particular triglycerides, are a convenient manner to suspect hepatic insulin resistance, but show no specificity. Early good markers are plasma levels of hepatic enzymes, such as ALT, AST, and GGT. High levels of ALT are linked with the severity of hepatic insulin resistance, and this relationship appears to be independent of other factors. Interestingly, the association between ALT and insulin resistance seems stronger than with dyslipidemia, suggesting that ALT might be a good and very early indicator of liver damage, while AST appears to be more linked to central obesity. However, ALT is poorly linked to cardiovascular disease, in contrast with GGT. Although it is a marker of metabolic syndrome, GGT is claimed to be associated more with abdominal obesity, and possibly linked to the presence of oxidative stress. However, it should be mentioned that liver failure may be observed in the absence of these enzymatic changes. Some studies suggest that bilirubin, which is inversely related to insulin resistance and oxidative stress, may be another interesting marker of fatty liver.

Mechanisms of hepatic insulin resistance/steatosis

As stated above, insulin resistance in the liver can be induced by many different factors acting directly in the liver or originating from other tissues, such as fat and skeletal muscle. Free radicals and proinflammatory cytokines, such as interleukin-6, are the most widely known ones. Oxidative stress, often linked to inflammation, is considered to be a main factor in the pathogenesis of fatty liver. However, the specificity of oxidative stress markers is questionable, given that this process is common to all forms of insulin resistance. Inflammation plays a major role in fatty liver; it can originate from visceral fat and reach the liver, but can also be generated within the liver as a consequence of triglyceride accumulation and endoplasmic reticulum stress.

The liver contains the largest reservoir of macrophages in the body. Kupffer cells, once activated by xenobiotics, generate inflammation, and these cells can be proinflammatory or anti-inflammatory, which explains some apparently contradictory data showing protection or otherwise by experimental Kupffer cell depletion against high fructose feeding. Thus, the filtering Kupffer cells can lead to liver inflammation by their reaction to an excess of incoming substrates. Complement C3 is involved in all forms of metabolic disorder and interferes with the coagulation system, so is now proposed as another risk factor for cardiometabolic syndrome.

Although a matter of debate, iron overload is increasingly considered to be an integral part of the pathology of nonalcoholic fatty liver disease. Elevated ferritin levels are associated with the development of metabolic syndrome over 5 years, and appear to be a good predictor of vascular damage. A combination of high ferritin and low transferrin saturation is characteristic of prediabetes. Hepcidin increases with the number of features of metabolic syndrome, promoting release of cytokines and oxidative stress and leading to apoptosis in macrophages. Interestingly, a high fat/high fructose diet has recently been shown to induce iron overload via a hepcidin-independent pathway, which occurs before develop of hepatic steatosis and insulin resistance.

Links between hepatic disorders and cardiovascular events

The inflammatory state of the liver in prediabetic states is expected to impact on the cardiovascular system. There is indeed a well known interplay between insulin resistance, inflammation, obesity, and heart disease. According to data from the Cremona study, fatty liver is linked to mortality, cancer, and cardiovascular disease, the relationship being explained by insulin resistance. Insulin-resistant individuals of normal weight have a 2.5-fold increase in risk for heart failure. Conversely, it must be noted that up to 80% of patients with heart failure have liver dysfunction, possibly explained by a disturbed hepatic microcirculation, diminished endotoxin clearance, and increasing cytokine levels.

In this context, nonalcoholic fatty liver is now considered to be a cardiovascular risk factor. Despite similar myocardial blood flow, it appears that myocardial blood reserve is diminished in subjects with fatty liver, whereby the coronary microcirculation becomes impaired. There exists a well known (bidirectional?) link between insulin.
resistance and carotid intima thickness, which is even seen in children with metabolic syndrome. Subjects with fatty liver show increased carotid intima/media thickness if there is also metabolic syndrome, but others have found this to be independent of metabolic syndrome. It was reported that, despite many common features, nonalcoholic fatty liver is more closely linked than alcoholic fatty liver to cardiovascular disease. Cardiac structure is altered in fatty liver, as reflected in left ventricular thickness, while cardiac metabolism appears intact. Flow-mediated dilation was shown to be reduced by 30% in patients with fatty liver. Venular blood flow velocity has been reported to be increased in the eye, reflecting microvascular damage to the retina.

Metabolic syndrome and inflammatory mediators, such as interleukin-6, C-reactive protein, and fibrinogen, increase the risk of heart failure by up to 20% if combined. GGT has been linked to carotid thickness. Indeed, GGT is closely linked to the existence of plaques. Patients with a fatty liver index >60 show an increased risk of atherosclerosis, which is tentatively explained by incorporation of GGT into plaques, where it might trigger iron-dependent oxidation of low-density lipoprotein. A high fructose intake is also linked with an elevated incidence of cardiovascular disease. There is likely a prominent role for high triglycerides, in that while inert triglycerides are harmless, triglycerides containing saturated fatty acids are harmful. Excessive secretion of very low-density lipoprotein by the fatty liver increases circulating triglyceride levels, resulting in ectopic fat deposition, notably at perivascular and pericardial locations.

**Treatment**

In view of the complex etiology and multiple interconnecting mechanisms involved in hepatic insulin resistance and nonalcoholic fatty liver disease, many therapeutic approaches can be envisaged, the main ones being summarized here. Indeed, targets can either focus on factors inducing hepatic steatosis or intrahepatic mechanisms involved in glucose or lipid metabolism. Most subjects with cardiometabolic syndrome, but not all, show insulin resistance, which therefore represents a preferential target in the available arsenal of therapeutic measures. The key measure is of course a healthy lifestyle, ie, adequate diet and exercise, with weight loss shown to improve hepatic steatosis, at least in subjects who achieve a weight loss greater than 7%. Recent research suggests that new notions of nutrition, such as chronobiology, should be integrated into dietary measures. Nevertheless, the extent to which lifestyle measures prevent an evolution which often seems ineluctable is still uncertain and the findings of preventive clinical trials are contradictory. Lifestyle measures are advised in any case, however, whether alone or combined with pharmacologic interventions. Beneficial effects are observed, as expected, but are hampered by practical application, often motivation limitations. It should also be mentioned that some scientists view insulin resistance, and particularly hepatic insulin resistance, as a protective mechanism against substrate overload, a notion which is worthy of deeper analysis.

**Insulin sensitizers**

Given the importance attributed to insulin resistance in the cardiometabolic syndrome, this defect has been the major target for therapy and, consequently, various types of drugs considered to alleviate insulin resistance have been tested. Indeed, re-establishing insulin signaling in hepatocytes is expected to correct defects in both glycemic and lipid metabolic pathways, although it must be borne in mind that not all of these are controlled by insulin.

**Metformin**

The biguanide metformin is the leading antidiabetic treatment worldwide, but has many other effects in addition to reducing fasting hyperglycemia; one of its main actions is to improve insulin sensitivity, and many reports have shown that the liver is the preferential target for this compound. Several mechanistic targets have been identified for metformin in the liver, including stimulation of the postreceptor protein, IRS-2. In high-fat feeding models, metformin reduced hepatic glucose production by inhibiting gluconeogenesis and glucose-6-phosphatase, as well as restoring insulin-sensitive liver blood flow. As mentioned earlier, fructose is another main nutrient prone to promoting hepatic steatosis when consumed in high amounts, and several studies have demonstrated the capacity of metformin to improve fat accumulation in the liver. Attenuation of lipid peroxidation, reduction in gene expression of the Toll-like receptor-4 cascade, and lipid metabolism regulated by plasminogen activator inhibitor type-1, as well as inhibition of intestinal permeability, reduction in intra-abdominal fat mass, and activation of AMP-activated protein kinase against interleukin-6-induced insulin resistance, are some mechanisms involved in the action of this drug.

Metformin has shown mixed results in humans, with an effect superior to that of diet seen in a randomized trial. Interestingly, a recent study investigated the vascular consequences of treatment with metformin in...
patients with nonalcoholic fatty liver disease, and reported improvement in arterial stiffness in addition to changes in blood metabolic parameters and liver enzymes. However, the latter effect might also be independent of the hepatic action, given that metformin is a pleiotropic drug with many favorable effects on large and especially small vessels.

**Thiazolidinediones**

A more recent class of compounds developed as insulin sensitizers are the thiazolidinediones (TZDs). Pioglitazone, the newest TZD, improves histologic parameters in the liver, although patients gain weight. Pioglitazone also shows beneficial effects in steatohepatitis.

Limited comparisons of metformin versus TZDs have yielded mixed results, with the TZDs ultimately appearing better when considering liver fat and function. Combining both types of drugs (eg, rosiglitazone + metformin) showed only a transient improvement in hepatic insulin sensitivity but a sustained reduction in ALT.

Here again one should take into consideration the question of surrogate versus final outcome parameters. A recent survey of insulin sensitizers in subjects with nonalcoholic fatty liver disease points to the lack of evidence for beneficial effects of these treatments. On the other hand, caution is advised with TZDs due to their potential to aggravate cardiovascular parameters.

**Statins**

Reducing cholesterol and triglycerides is a logical approach when diet fails. Based on their beneficial effect on cholesterol and their potential to protect against cardiovascular disease, statins are increasingly used in nonalcoholic fatty liver disease. In addition to their effects on blood lipids, these drugs are able to reduce tumor necrosis factor alpha, an inflammatory cytokine. However, although ameliorating surrogate markers, statins are not considered to have a convincing effect in nonalcoholic fatty liver disease.

Moreover, some caution is advised, given that statins are prone to augmenting the risk of diabetes.

**Antioxidants and anti-inflammatory drugs**

Although oxidative stress is considered a hallmark of prediabetes and diabetes, there is little evidence that antioxidants (usually vitamin E) have clearcut beneficial effects in clinical terms. Few relevant data are available in nonalcoholic fatty liver disease. A survey by the Cochrane database reported that enzyme changes were observed, but no conclusion could be drawn. A very recent review on this question also reached the same conclusion.

In addition to and in combination with oxidative stress, inflammation is another main cause of the metabolic syndrome. The classical concept states that inflammation originates from adipose tissue due to lipid overload in fat cells. However, it should be borne in mind that the liver is also an important source of inflammation factors, such as C-reactive protein, and a major reservoir of macrophages. In mice, a high-fat diet first leads to hepatic insulin resistance and then secondarily to inflammation. Any anti-inflammatory drug may be potentially useful, but no liver-specific treatment has been yet established.

**Prebiotics/probiotics**

One of the most interesting findings in recent times has been the role of intestinal permeability in hepatic steatosis, allowing many toxic factors to reach the liver and cause steatosis. Probiotics can improve this defect, and thus appear to be promising agents in the treatment of nonalcoholic fatty liver disease. In an experimental high-fat model, combined administration of *Lactobacillus curvatus* and *Lactobacillus plantarum* suppressed the metabolic abnormalities induced by this diet.

Improving the operative capacity of microbiota by providing prebiotics is another more indirect approach. How these microbiotic changes can impact host tissue metabolism and gene expression has been reviewed recently. Unfortunately, few data are actually available in this field and further clinical proof is awaited, which will hopefully confirm this promising potential.

**Vitamins**

Lack of vitamin D has been independently linked to steatosis in subjects with fatty liver and normal enzyme profiles. A recent meta-analysis concluded that most subjects with nonalcoholic fatty liver are deficient in vitamin D. Some studies suggest that administration of high-dose vitamin D might lower the risk of liver steatosis in healthy persons.

At present, it is not possible to draw conclusions about the efficacy of treatment in nonalcoholic fatty liver disease (excluding nonalcoholic steatohepatitis), although various approaches sound promising. Indeed, it should be stressed that most studies are of average quality, and importantly, mid-term or long-term clinical studies are essentially missing in this field. Moreover, mainly surrogate parameters, such as blood lipids or plasma hepatic enzymes, have been measured, but final clinical outcomes, such as prevention...
or reversal of cardiometabolic syndrome, are lacking, in particular for vascular disorders.

**Conclusion**

The anatomic position of the liver confers to this organ a central role in the regulation of nutrient absorption, handling, and redistribution. Consequently, it also has a key role in glucose homeostasis, being able to trap or liberate either stored or newly synthesized glucose, functions which are under the control of many mechanisms and more particularly insulin, to which it is exquisitely sensitive. The quantity and quality of absorbed food closely determines hepatic insulin sensitivity. Visceral fat also directly influences these processes. The liver also exchanges information with peripheral organs, notably skeletal muscle, in an ongoing manner. Excess calories from sugars or lipids, and also from qualitative alimentary components, eg, trans fatty acids and high fructose, directly induce hepatic inflammation and/or oxidative stress and hepatic steatosis. It is now clear that a large proportion of prediabetic individuals have excessive fat accumulation in the liver, a situation which can be detected easily by measuring plasma hepatic enzymes or ultrasound imaging of the liver. Liberation by the liver of inflammatory factors, products of oxidative stress, and triglycerides impacts the vascular system, notably the heart. Therapeutic prevention can be achieved by insulin sensitizers (mainly metformin) and possibly the statins and vitamin D. However, the long-term efficacy of these treatments remains to be demonstrated. The recent recognition of increased intestinal permeability (leaky gut), which enables access of unfavorable gut factors to the liver, is another very promising therapeutic strategy, either by eating pro/prebiotics or by administering treatments specifically dedicated to blocking intestinal permeability.

**Disclosure**

The author reports no conflict of interest in this work.

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