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Review Article

Cirrhosis and insulin resistance: current knowledge, pathophysiological mechanisms, complications and potential treatments

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End-stage chronic liver diseases are often associated with insulin resistance (IR) and diabetes mellitus (DM). Indeed, to quantify insulin sensitivity the euglycemic clamp technique was utilized, allowing the following to be stated: in small groups of patients, an IR in almost all cirrhotic patients can be observed, compared with a control group. Additionally, it has been demonstrated that IR in cirrhosis is linked to a decreased peripheral (muscle) glucose uptake rather than an increased liver glucose production. The homoeostasis model of IR (HOMA-IR) technique, devised only later, was then exploited to assess this same phenomenon in a larger sample population. The research established that even in patients with preserved liver function, cirrhosis is associated with significant alterations in glucose homoeostasis levels. The purpose of the present paper is to present the current research around the affiliation of cirrhosis and IR, discuss potential mechanisms explaining the association between cirrhosis and IR (i.e. endocrine perturbation, liver inflammation, altered muscle mass and composition, altered gut microbiota and permeability), complications that can arise as well as treatment options, through a critical review of the literature surrounding this subject. This research will also be investigating the beneficial impact, if there is any, of identifying and curing IR in patients with cirrhosis.

Introduction

Cirrhosis is a liver disease characterized by dissection of the hepatic lobules by fibrous septa. The original lobular architecture of the liver parenchyma is progressively transformed into regenerative nodules through hepatic parenchymal injury, cell loss and cicatricial fibrosis [1].

The three primary etiologies of cirrhosis in Western populations are alcoholic liver disease (ALD), hepatitis C virus (HCV) and non-alcoholic fatty liver disease (NAFLD). Other known causes of cirrhosis include hepatitis B virus (HBV), α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis and autoimmune hepatitis.

Because cirrhosis is in itself asymptomatic and indolent, the severity of chronic liver diseases is determined by the various complications that can emerge following the pathological progression of the disease. Some such complications of cirrhosis are altered liver function, portal hypertension, hepatic encephalopathy and hepatocellular carcinoma (HCC) [2]. Most importantly, the mortality rate associated with cirrhosis is of major concern; for example, in 2008 in Europe, the mortality rate for patients with cirrhosis or HCC exceeded that of breast cancer patients [3].

The chief role of the insulin hormone is to regulate blood glucose levels by inducing glucose uptake into specific insulin-sensitive tissues and by blocking its endogenous production (mainly in the liver), thereby decreasing and restoring glucose homeostasis (Figure 1) [4]. Insulin resistance (IR) is defined by

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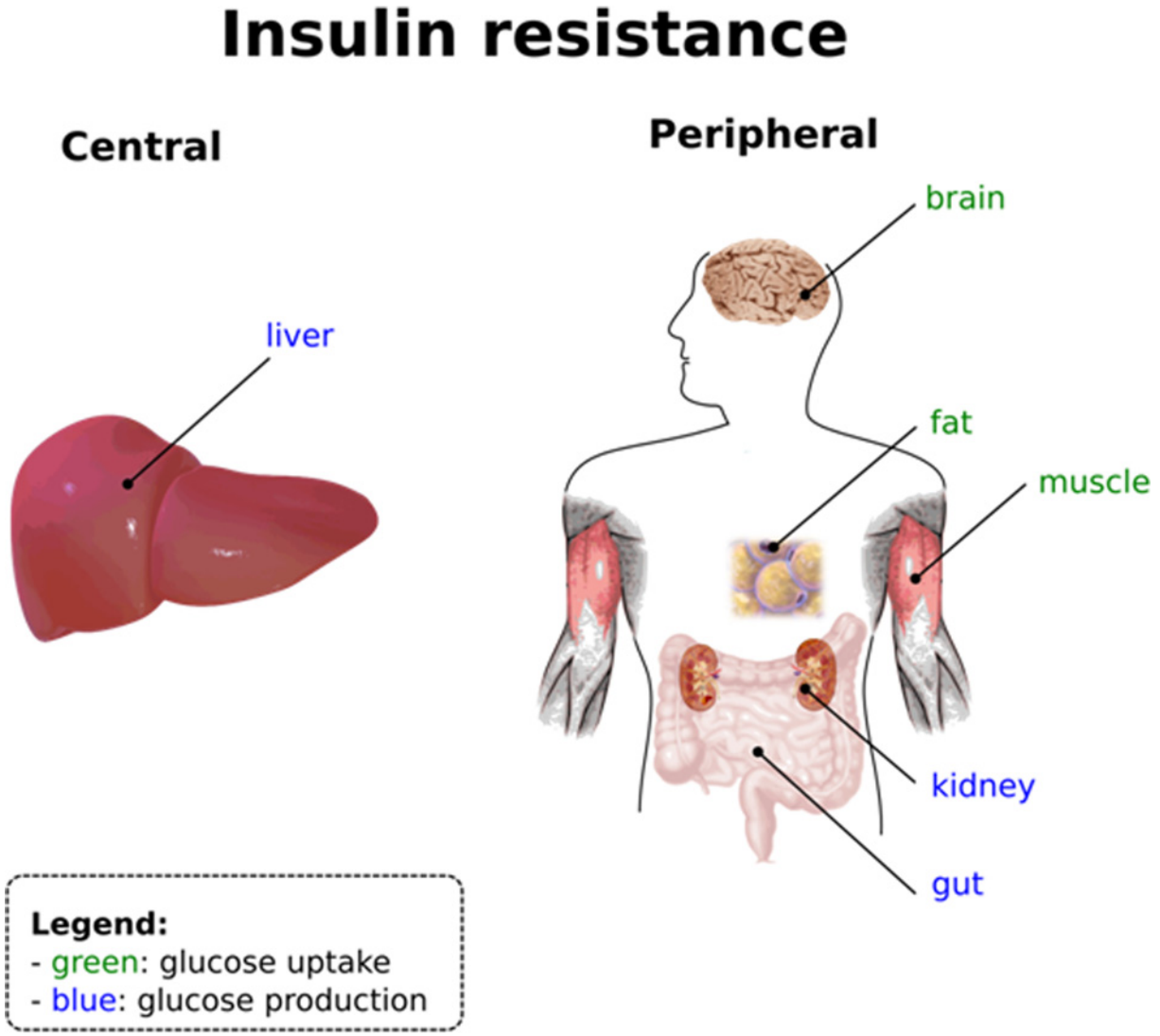

Figure 1. The main sites of insulin action in order to understand IR phenomenon

In insulin-sensitive tissues, insulin exerts its action through binding its receptor. Insulin is then able to block the glucose production within the main sites of endogenous glucose production (EGP): the liver, the kidney and the intestine (in blue). Glucose uptake under the control of insulin takes place in the muscle, the adipose tissue and the brain (in green). Insulin can also suppress food intake via its action on the hypothalamus. All those insulin-sensitive tissues/organs could be affected in a context of IR.

the inability of a given quantity of insulin to prompt normal physiological responses in insulin-sensitive tissues (namely, the liver and peripheral tissues such as skeletal muscle and adipose tissue) (Figure 1) [5]. Other insulin-sensitive tissues are the kidney, pancreas, heart and hypothalamus (Figure 1). Aside from the insulin-sensitive tissues previously listed, a fine glucose regulation without influence from insulin can be encountered in other, non-insulin-sensitive tissues such as the brain, the liver and the red blood cells.

It is well known that IR and/or diabetes mellitus (DM) constitute typical features of NAFLD-associated cirrhosis. Indeed, impaired glucose tolerance (blood glucose $>$ 100 mg/dl) is one of five composing elements in the diagnosis of a metabolic syndrome [6], a leading risk factor for developing NAFLD. Not only is IR a risk factor for developing NAFLD, it also contributes to the rate of disease progression (development of non-alcoholic steatohepatitis – NASH, fibrosis and cirrhosis) [7]. The scientific literature also asserts that, regardless of the cause of the cirrhosis, most cirrhotic patients suffer from changes in glucose metabolism, not just those with NAFLD-associated cirrhosis. It is following these findings that the term 'hepatogenous diabetes' (HD) was put forth to describe a diabetic state of IR occurring in cirrhotic patients, thought to be secondary to the chronic liver disease. Furthermore, patients presenting

both cirrhosis and IR are known to have a lower survival rate than those with cirrhosis and normal plasma glucose [8–11]. DM is now considered to be a potential complication of chronic liver disease, particularly end-stage chronic liver disease or cirrhosis.

In this literature review, we will first discuss the current research around the affiliation of cirrhosis and IR; second, analyze the comprehensive, hypothesized, pathophysiological mechanisms for IR in relation to cirrhosis in general and depending on cirrhosis etiology; third, describe the possible clinical impact IR has on cirrhosis and finally present the potential ways to manage this association using available treatments.

Current knowledge surrounding the association between cirrhosis and IR

To correctly understand and interpret the trials in this field, it would be of value to first summarize the ways in which IR can be measured. Only then can we seek to elucidate the numerous studies relating to the frequency of IR and DM in cirrhotic patients.

How can we measure IR?

The euglycemic clamp technique is the starting point for many discoveries in the field here discussed. The technique has grown through the 1980s and is currently considered to be the gold standard for determining the effect of insulin on glucose metabolism [12]. With the euglycemic clamp, insulin sensitivity is measured '*in vivo*' by infusing insulin at a continuous rate while plasma glucose concentration is maintained constant by a varied glucose infusion [12]. Insulin sensitivity is directly proportional to the amount of perfused glucose needed to maintain euglycemia. Interestingly enough, with this technique IR can be identified in patients even if they have normal blood glucose levels. Moreover, by using labeled glucose, the clamp technique also allows for the calculation of endogenous glucose production (EGP, mainly from the liver) which is unlabeled, distinguishing it from exogenous/perfused glucose which is labeled. However, this technique is time-consuming, rather invasive, and therefore useful only for small sample populations [4].

Another technique that forecasts IR and that is more appropriate for larger studies is the homeostasis model assessment of IR (HOMA-IR) developed in 1985 [13]. Its formula is presented below and since it is accurate (with good correlation to the clamp technique [14]), faster, cheaper and less invasive than the clamp, it is more often used to assess IR.

$$HOMA - IR = \frac{Fasted\ glucose\ \left[\frac{mmol}{l}\right] \times Fasted\ insulin\ \left[\frac{mU}{l}\right]}{22.5}$$

Compared with the clamp technique which is able to measure IR in both basal conditions and stimulated insulin sensitivity, the HOMA-IR formula only gives an estimate of basal IR [4]. The denominator in the equation is the product of normal fasting plasma glucose (4.5 mmol/l to 80 mg/dl) and normal fasting plasma insulin (5 mU/l to 35 pmol/l), the values mentioned being that of a healthy individual. The model is calibrated in a way that a HOMA-IR value equal to 1 is obtained for an individual with 'normal' insulin sensitivity. Higher HOMA-IR values are compatible with IR. In practice, HOMA-IR cut-offs are placed at different values depending on the appreciation of the risk correlated with the HOMA-IR [15]. For example, a value of 2.5 provided the maximum sensitivity and specificity for the diagnostic test of a metabolic syndrome in young adults [16] and acted as an indicator of cardiometabolic risk, as determined by both the International Diabetes Federation (IDF) and the Adult Treatment Panel III (ATP III) criteria [17].

In addition to the two techniques aforementioned, other techniques used to grade insulin sensitivity are the insulin and oral glucose tolerance tests (OGTTs). The insulin tolerance test analyses the impact that a single fixed insulin injection has on blood glucose levels creating with the euglycemic clamp technique, the most advanced method of directly evaluating insulin sensitivity. The glucose tolerance test, on the other hand, whose objective much resembles that of the insulin tolerance test, does so by indirectly analyzing blood glucose levels following a fixed glucose ingestion or injection irrespective of insulin levels.

Does a link between cirrhosis and IR exist?

The first study examining the association between cirrhosis and IR was published in 1980 by an Australian team. The study [18], performed with 11 cirrhotic and 8 control patients, discovered that basal EGP (reflecting hepatic glucose production) was markedly lower in cirrhotic patients compared with controls and that EGP was suppressed to an equal degree in both groups when tested with the clamp technique. This is compatible with an absence of IR in

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the liver which is in fact hypersensitive to insulin. Remarkably, these findings also substantiated the hypothesis that cirrhotic patients, even those spared of DM, suffer from glucose intolerance which is linked to a peripheral deficit in glucose consumption.

In 1991, Petrides and colleagues [19] further evaluated eight grade A cirrhotic subjects following the Child–Pugh classification (seven biopsy-based diagnoses and one based upon clinical data) and twelve subjects matched for physical features serving as controls. Among the eight cases, the causes of cirrhosis were as follows: four ALD, three postnecrotic and one unknown. By using the euglycemic clamp technique and indirect calorimetry, the authors found that patients with compensated cirrhosis had severe IR compared with controls. This IR can be explained by a significant impairment in glucose uptake due to reduced non-oxidative glucose disposal (glycogen synthesis). This defective glucose uptake can be calculated by a subtraction of the rate of glucose oxidation (deduced from continuous calorimetric measurements) from the rate of total body glucose uptake. In accordance with the previous article [18], the authors also found that suppression of EGP by insulin in cirrhotic patients was not significantly different than controls.

In 1993, Selberg et al. [20] also studied IR in seven patients with cirrhosis using the euglycemic clamp technique. Whole-body glucose disposal rate (GDR) was approximated as the mean glucose infusion rate during steady state. Glucose oxidation rates were also assessed by indirect calorimetry, and non-oxidative glucose disposal was again calculated by subtracting the glucose oxidation rate from the GDR. Glucose uptake by the thigh muscles was measured with an ^{18}F-fluorodeoxyglucose PET scan. The patients studied had biopsy-proven cirrhosis (three postnecrotic, one ALD, two biliary cirrhosis and one cryptogenic cirrhosis). These seven different cases were compared with five healthy volunteers correlated for anthropomorphometric criteria relating to muscle mass (triceps skin fold thickness, mid-arm circumference and 24-h urinary creatinine excretion). A 69% decrease in glucose uptake by the skeletal muscle ($P<0.003$), as well as a significant reduction in GDR and non-oxidative glucose disposal in cirrhotic patients were observed. EGP was not measured during the present study due to the high insulin levels used in suppressing EGP to negligible values in both controls and cases.

In 2002, Greco et al. [21] used the clamp technique to identify diminished insulin sensitivity in nine cirrhotic patients (all due to HCV), compared with controls. Furthermore, the study showed that cirrhotic patients presented a massive hypersecretory insulin response in isolated conditions and in response to glucose. They also discovered that insulin clearance and insulin extraction from the liver were not lowered in cirrhotic patients. On the contrary, a 10% higher insulin clearance was observed in these patients.

In 2006, Gupta et al. [22] performed OGTTs and insulin suppression tests in 20 cirrhotic and 20 control patients. They assessed IR in cirrhotic patients and found that the state of IR was not related to the severity of the cirrhosis as graded by the Child–Pugh taxonomy. In contrast with the previous publication, the authors found that glucose and insulin clearance were significantly lowered in cirrhotic patients compared with controls. In the study discussed here, all patients had HBV-induced cirrhosis, which could be a source of confounding bias when comparing the results of the present study with the previous one.

In 2010, Goral et al. [23] measured HOMA-IR levels for 79 cirrhotic patients and 50 controls. HOMA-IR levels were elevated in all cirrhotic patients (mean 3,14 $\pm$ 3,26) and these levels differed according to the cause of the cirrhosis. However, no correlation was found between cirrhosis etiology and IR severity. Using a cut-off value of 2.7, 40.5% of patients were deemed to have IR. More particularly, the authors also detected increased levels of inflammatory mediators in cirrhotic patients (namely tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6) that the control group did not exhibit.

Taguchi et al. traced in 2014 [24] peripheral glucose uptake by using a clamp technique combining insulin and intravenous glucose perfusion as well as oral glucose administration adapted to body weight. The researchers were able to recruit 61 cirrhotic patients and 34 controls without liver disease, matched for age. Compared with controls, all subjects with cirrhosis had IR in peripheral tissues (skeletal muscle and adipose tissue) as demonstrated by the clamp technique. Measurements of fasting plasma glucose could not be used to reach the same conclusion since fasting plasma glucose levels proved to be normal in more than 80% of patients with cirrhosis.

In 2014, Goswani et al. [25] studied 100 patients with cirrhosis originating from varying causes of which 70 were euglycemic and 30 diabetic. HOMA-IR was measured in all patients and the results were stratified depending on cirrhosis etiology. The authors discovered that some etiologies were associated with particular degrees of IR. For example, IR was more prominent in NAFLD and HCV cirrhosis compared with ALD and HBV cirrhosis. These findings suggest the existence of specific mechanisms at the core of IR development. However, the number of patients in some etiology subgroups was too low to definitively conclude which etiology is associated with a more severe IR.

One year later, a study featuring 106 patients with cirrhosis linked to HBV and using an OGTT to qualify glucose metabolism was published. The researchers Guo et al. [26], corroborated the results of the previous studies presented;

Table 1 Studies evaluating IR in cirrhosis

First author (year of publication)	Number of patients (number of controls)	Method to assess IR	IR	Principal findings
Proietto (1980)	11 (8)	Clamp	100%	No liver IR Defect in peripheral glucose utilization
Petrides (1991)	8 (12)	Clamp Indirect calorimetry	100%	Defect in glucose peripheral uptake and gycogen synthesis explains IR
Selberg (1993)	7 (5)	Clamp ^{18}F-FDG PET scan	100%	Primary site of IR is skeletal muscle
Greco (2002)	9 (7)	Clamp	/	Child B patients, IR correlates with insulin secretion No lower insulin clearance by the liver
Gupta (2006)	20 (20)	OGTTs Insulin suppression test	100%	No association between IR and cirrhosis severity Lower glucose and insulin clearance
Goral (2010)	79 (50)	HOMA-IR > 2,7	40,5%	High level of inflammatory mediators in cirrhosis
Taguchi (2014)	61 (34)	Clamp	100%	Peripheral IR
Goswami (2014)	70 (30)	HOMA-IR > 1,64	69%	Discrepancy of IR levels depending on cirrhosis etiology
Guo (2015)	106 (37)	HOMA-IR + OGTT	/	Positive correlation between IR and cirrhosis severity
Marselli (2016)	300	OGTT	47%	35% of patient presented overt glucose metabolism alteration (DM, IGT or IFG)

Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

there was no difference in fasting plasma glucose levels between the cirrhotic group and the control group. Nevertheless insulin levels were significantly higher in the cirrhotic group with a mean HOMA-IR of 3.98 $\pm$ 1.89 compared with 2.06 $\pm$ 0.98 for control patients.

Finally, Marselli et al. [27] studied characteristics of glycemic equilibrium in 300 pre-transplant patients in 2016, monitoring fasting blood glucose levels, glycated hemoglobin and OGTT. The cause of liver disease was mainly viral hepatitis (HBV and HCV). The results showed that 35% of pre-transplant patients suffered from DM and 12% from pre-diabetes (defined by impaired fasting glycemia or impaired glucose tolerance). Curiously, no correlation between the severity of glucose metabolism impairment and the proportion of patients with advanced cirrhosis was established. This translates to the absence of statistically significant data discerning the distribution of cirrhosis severity in diabetic and non-diabetic patients, as classified by the Child–Pugh score.

All the data aforementioned are chronologically arranged in Table 1. Collectively, the results support the premise that cirrhosis and IR are linked. This link concerns peripheral tissues (reduced uptake of glucose by peripheral tissues, i.e. the skeletal muscle) and not the liver. There are however conflicting results with regard to the potential role of an alteration in insulin clearance and its association with the severity of cirrhosis.

How does cirrhosis induce IR?

The data presented above show that cirrhosis is associated with a change in insulin sensitivity and/or glucose and insulin metabolism. Furthermore, it would seem that particular causes of cirrhosis are more prone to exhibit IR and more severe IR. The next portion of the present paper will therefore focus on the potential mechanisms playing a role in the development of IR in cirrhosis. Any additional mechanisms linked to specific cirrhosis etiologies that may have an impact on insulin sensitivity will also be explored.

Common mechanisms, independent from cirrhosis etiology

IR appears to be the hallmark of cirrhosis, whatever the cause of the chronic liver disease. Here, summarized are potential common mechanisms explaining this phenomenon, such as a possible decrease in insulin clearance (by portal hypertension or decreased hepatocyte mass), endocrine perturbation, liver inflammation, sarcopenia, gut alterations, advanced glycation end products and ceramides. All the aforementioned mechanisms are tabulated in Figure 2.

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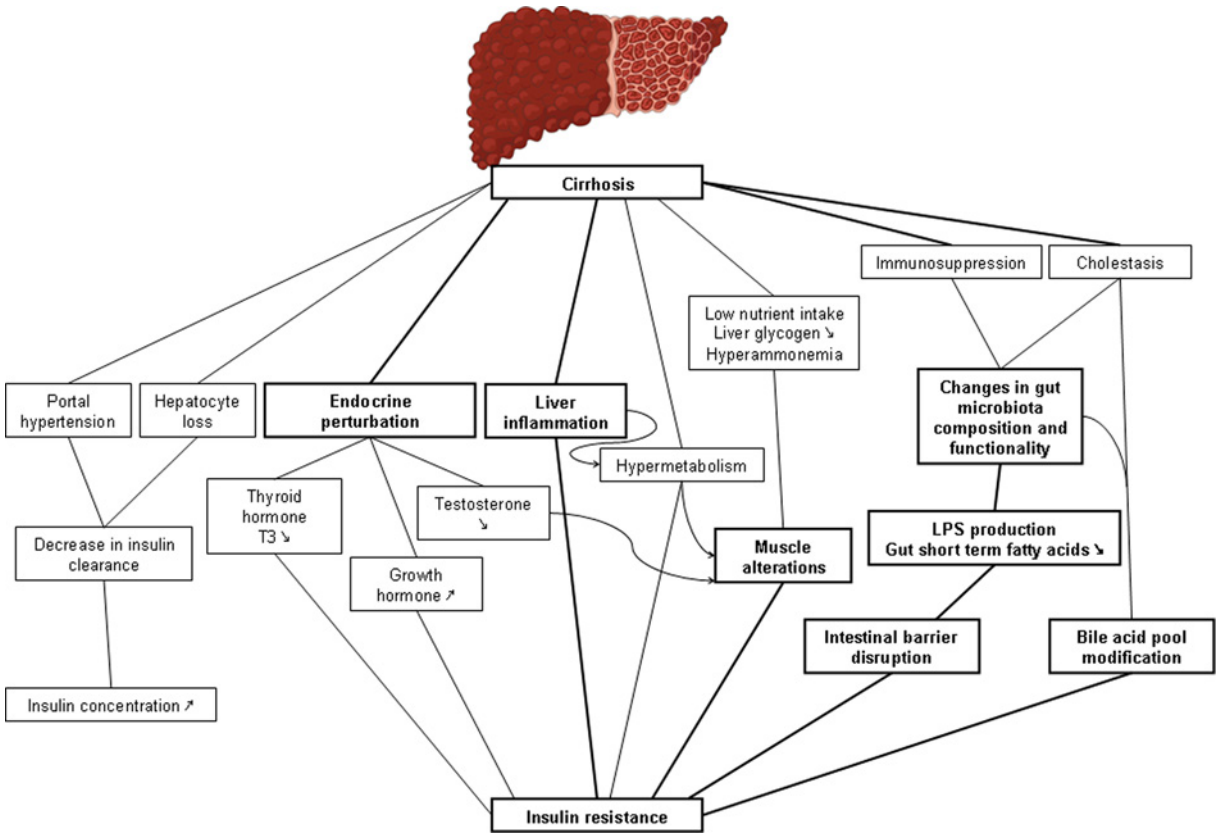

Figure 2. Mechanisms linking cirrhosis and high insulin levels or IR

Abbreviation: LPS, lipopolysaccharide.

Decrease in insulin clearance?

This mechanism of decreased insulin clearance is usually considered to be the main factor accounting for IR in cirrhosis [28]. However, some clarification is needed here. The liver is responsible for the binding and subsequent degradation of insulin mainly through the activity of its hepatocytes and, in a minor proportion, its non-parenchymal cells (Kupffer cells and endothelial cells) [29]. It is therefore reasonable to speculate that cirrhosis, due to the partial replacement of liver parenchymal (functionally active) cells by fibrous tissue, could be responsible for reduced insulin clearance by the liver. This is true even in the absence of significant portal hypertension and shunting. In addition, shunting of the liver in itself could lead to a reduction in insulin clearance through decreased blood flow to the liver.

In our view, there are currently no trials assessing IR or insulin clearance with varying liver volumes or functional liver hepatocytes in humans with cirrhosis. Nevertheless, we know from animal testing that partial hepatectomy induces a transient fivefold increase in insulin and subsequent decrease in glucose levels [30].

In cirrhotic patients with so-called HD, a correlation between the severity of DM and hepatic venous pressure gradient has been observed [31]. As fibrosis progresses in a cirrhotic liver, this gradient is raised leading to liver shunting. Liver shunting entails reduced blood flow to the hepatocytes resulting in less insulin being cleared by the liver [32]. Multiple studies [33–35] have shown that in cirrhotic patients, when portocaval shunts (which bypass the blood flow outside the liver) are suppressed, insulin clearance by the liver is ameliorated. In contrast, when transjugular intrahepatic porto-systemic shunts (TIPSS) are placed, blood glucose as well as hepatic and peripheral insulin sensitivity levels remain unchanged in contrast with insulin levels which are elevated [36,37].

Balloon-occluded retrograde transvenous obliteration, through suppression of portocaval shunts, seems to effectively circumvent this with minimal risks of complication [38]. However, the impact of such a treatment on insulin sensitivity has not yet been researched.

Collectively, these results may explain the hyperinsulinemia observed in portal hypertension [31]. Whether this hyperinsulinemia participates in the development of peripheral IR (due to down-regulation of peripheral insulin receptors [18]) remains to be seen. One could also speculate that, in a context of portal hypertension, insulin's effect

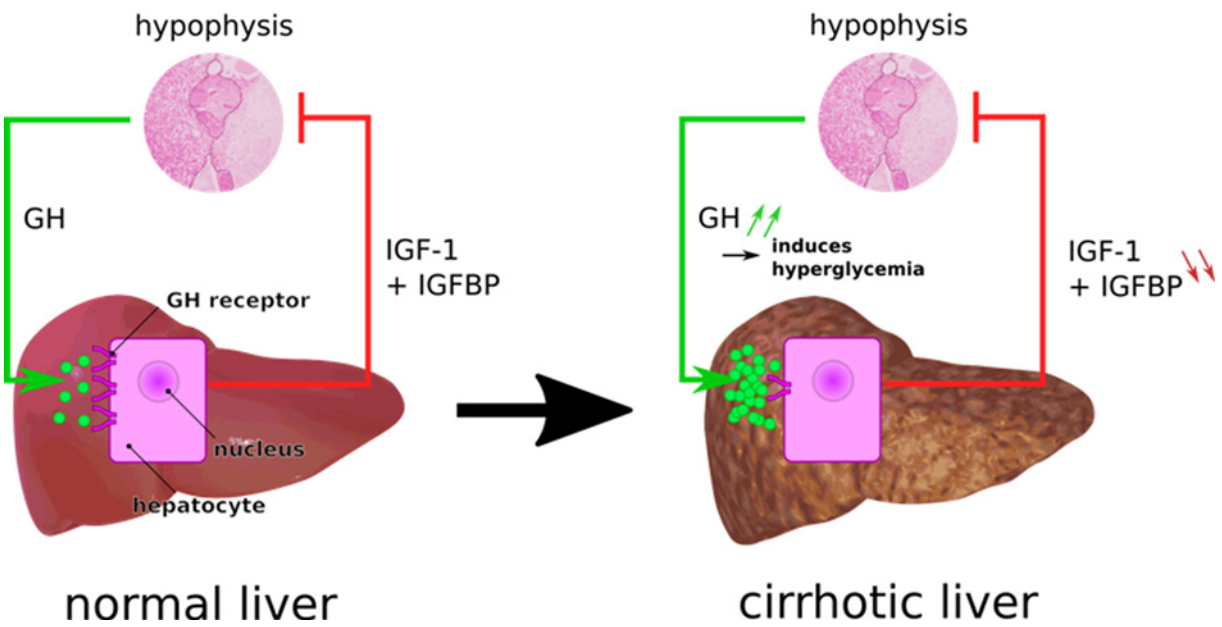

Figure 3. Perturbation of the hypothalamic–pituitary–liver axis in the context of cirrhosis

on the liver is thus minimal due to liver shunting and insulin is unable to correctly target the hepatocytes to block EGP contributing to IR, as is suggested when portocaval shunts are suppressed [33–35]. However, hepatic IR has not been identified as a cause for systemic IR in the numerous clamp studies carried out in which EGP was stable or even increased [18].

In conclusion, decreased insulin clearance can be observed in cirrhosis and explains the presence of higher plasma insulin levels, as seen in studies using the HOMA-IR technique. However, reduced insulin clearance does not explain why peripheral IR and lower glucose uptake in peripheral tissues are observed.

Endocrine perturbation

The liver plays a major role in the synthesis and metabolism of cytokines. Therefore, any changes in the liver's structure and function may cause dysregulation of its intrinsic endocrine system [39]. In the case of a cirrhotic liver where tissular architecture is modified and hepatocytic mass is reduced, production of insulin-like growth factor 1 (IGF-1) and IGF-1 binding protein (IGFBP) is lowered. Taking into account this lowered IGF-1 production as well as the fact that IGF-1 is responsible for the negative feedback on growth hormone (GH) production on the pituitary gland, the negative feedback is not as strong in cirrhosis. A weaker negative feedback response results in an increase in GH plasma concentration (Figure 3). In addition to this, sick hepatocytes also tend to express less GH receptors (Figure 3). The resulting increase in GH concentration and decrease in IGF-1 production may be responsible for metabolic disturbances such as more circulating fatty acids and higher blood glucose levels [39]. GH inhibits glucose oxidation and insulin-mediated activation of glycogen synthase in skeletal muscles, which decreases glucose uptake by the muscles and therefore leads to an increased glucose concentration in the blood [40].

Other endocrine pathways are also affected by a state of cirrhosis. With regard to the thyroid, its volume is increased compared with non-cirrhotic patients. Since the liver is involved in the transformation of thyroxine (T4) to triiodothyronine (T3) [41,42], and T3 is responsible for peripheral glucose uptake [43], a thyroid dysfunction could lead to impaired glucose metabolism [44]. We could therefore presume that reduced peripheral and increased liver sensitivities are due to these endocrine changes [45].

Adrenal insufficiency and hypogonadism are endocrine perturbations that patients with cirrhosis may also exhibit. A decrease in testosterone levels (anabolic hormone) could be associated with lowered muscle mass and therefore participate in the development of sarcopenia, frequently observed in patients with cirrhosis [46]. Whether sarcopenia could play a role in IR will be discussed below. These perturbations of the endocrine system could also, *per se*, impact the survival rate in cirrhosis [39].

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Inflammation

The inflammatory process, defined by parenchymal cell necrosis and progressive fibrosis, that takes place within a cirrhotic liver also partly explains how cirrhosis evolves. In animals, liver-specific activation of inflammatory mediators induces both hepatic and systemic IR [47]. An increase in local as well as blood concentrations of pro-inflammatory cytokines (TNF-α and IL-6) [23] and HOMA-IR levels are observed in cirrhotic subjects compared with controls [48]. Additionally, a positive correlation between TNF-α, IL-6, other inflammatory cytokine levels and the severity of cirrhosis is observed, independently from etiological factors [49]. The reason for this is that cytokines are classically linked with the development of IR (prominently present in cirrhosis) as they are able to alter the insulin receptor signaling cascade [50].

In addition to the 'classical' pro-inflammatory cytokines previously mentioned, other chemokines produced by the liver called 'hepatokines' (as opposed to adipokines in the adipose tissue) were found to be key players in IR pathogenesis, mainly in the context of obesity and NAFLD [51]. Two hepatokines, selenoprotein-P and fetuin-A, are capable of inducing IR in peripheral tissues such as the muscle for selenoprotein-P [52] and adipose tissue for fetuin-A [53]. The fetuin-A hepatokine predicts the risk of developing DM in women [54] since it reaches high levels within diabetic subjects [55]. However, the level of those hepatokines in other chronic liver diseases remains to be specifically addressed.

Sarcopenia and myosteatosis

Malnutrition is highly prevalent in patients with cirrhosis and negatively impacts survival among these patients [56]. Decreased muscle quantity or muscle wasting, also known as sarcopenia, usually features in patients with cirrhosis due to a decrease in nutrient intake, inadequate synthesis and absorption of nutrients and a hypermetabolic state [57]. Moreover, in a fully functioning liver, glycogen is responsible for *de novo* gluconeogenesis in physiological conditions. In contrast, patients with cirrhosis have lower liver glycogen, meaning that to keep up with the substrate demands for gluconeogenesis, muscle proteins need to be catabolized into amino acids. This muscle catabolism in patients with cirrhotic livers inevitably leads to sarcopenia (Figure 2).

Low muscle mass in cirrhotic subjects can also be explained by an increased level of ammonia. Indeed, the nodular architecture of a cirrhotic liver hinders greatly the elimination of ammonia, the muscle therefore steps in and ensures the uptake of ammonia. Ammonia could be responsible for myostatin activation, thus inhibiting protein synthesis and contributing to sarcopenia [58]. More recently, decrease in muscle quality, due to fat infiltration in the muscle, was detected in patients with cirrhosis by computed tomography measurement of muscle radiodensity in Hounsfield units [59]. This seems to be highly prevalent (50%) among cirrhotic subjects and is indicative of myosteatosis.

Whether this diminished quantity and/or quality of muscle in patients with cirrhosis is a cause or a consequence of the IR observed remains to be seen. However, it seems reasonable to think that changes in muscle mass and composition in cirrhosis could be at fault for decreased glucose consumption in the muscle. Indeed, in long-term high fat-fed animals, muscle fat infiltration is associated with pronounced defects in insulin signaling pathway (down-regulation of insulin receptor and insulin receptor phosphorylation) and *in vivo* peripheral IR [60].

Gut alterations

A clear distinction can be made between the microbiota stool composition of healthy subjects and cirrhotic subjects, although many confounding factors (such as reduced exercise, modified hormonal and nutritional status) exist between these two patient categories [61]. Indeed, the status of the liver can impact gut integrity. In physiological conditions, bile acids protect the gut and exert their antimicrobial properties. It has been shown that mice with bile duct ligation exhibit rapid gut bacterial overgrowth, increased intestinal permeability and bacterial translocation [62]. Similarly, reduced excretion of primary bile acids in the bile ducts and then the intestine occurs in cirrhotic patients [61,63]. It is this decrease in primary bile acids coupled with the immunosuppression that characterizes cirrhosis that accounts for changes in microbiota composition in cirrhotic subjects (Figure 2).

Gut microbes play an important role in gut bioactive metabolite synthesis [64]. A decrease in autochthonous commensal microbes (i.e. Lachnospiracea, Ruminococcaceae) leads to a decline in the production of metabolites such as short chain fatty acids. Additionally, an increase in potentially pathogenic taxa (i.e. Enterobacteriaceae) is responsible for the production of endotoxins, such as lipopolysaccharide. This results in a reduction in short chain fatty acids (mainly butyrate and propionate) and an increase in gut endotoxin levels leading to a disruption in the intestinal barrier and subsequent systemic inflammation [61,65] (Figure 2). The causative role of the translocation of gut-derived endotoxins via impaired intestinal tight junctions, which results in the activation of the toll-like receptor dependent inflammatory pathway, is a well-known mechanism of IR pathogenesis [66].

Finally, gut microbiota also play an important role in host-produced primary bile acids and their transformation into secondary bile acids [67]. In addition to their effect on dietary lipid absorption, due to their micelle-forming properties, bile acids are also natural ligands of the intestinal farnesoid X receptor (FXR) and the Takeda G protein coupled receptor (TGR5). The two aforementioned receptors have insulin-sensitizing effects on carbohydrate metabolism and also have anti-inflammatory properties. The primary bile acid chenodeoxycholic acid (CDCA) and the secondary bile acid lithocholic acid (LCA) are strong activators of FXR and TGR5, respectively [67]. A change in total bile acids (primary and secondary), as seen in the context of cirrhosis [63], could therefore modulate the activity of these receptors and thus impact liver inflammation and glucose metabolism (Figure 2).

Advanced glycation end products and ceramides

Advanced glycation end products are the result of a reaction between a sugar (often glucose) and a polypeptide without the involvement of an enzyme. Advanced glycation end products are often found in diabetic patients due to chronic hyperglycemia and are responsible for numerous complications, namely retinopathy, microangiopathy and nephropathy, likely by an increase in cellular oxidative stress. The liver, like the kidney, is involved in the clearance of these products [68]. A decrease in the clearance of advanced glycation end products, as seen in chronic liver diseases and cirrhosis, logically encourages their accumulation, further contributing to the development of IR [68]. Advanced glycation end products could therefore be solely responsible for a state of IR [69].

Ceramides are sphingolipids generated from fatty acids and sphingosine. They contribute to the structure of the lipid bilayer but also have cell signaling properties. Indeed, they inhibit insulin signaling, induce oxidative stress and inflammation. Ceramides are also able to alter GLUT4 translocation in the muscle and hence decrease glucose uptake [70]. An increase in ceramides has been observed not only in a context of increased liver free fatty acid delivery (such as in NAFLD), but also after ethanol exposure (and thus ALD). Considering their potential role in liver fibrosis, targeting of ceramides has been acknowledged as a viable therapeutic option in the treatment of fibrosis. However, while ceramides are usually presented as up-regulated in cirrhosis [71], the exact level of hepatic ceramide in cirrhosis is not known. In patients with ALD cirrhosis, mRNA levels of proceramide genes, and therefore ceramide synthesis, were shown to be increased compared with control livers. Ceramide immunoreactivity [72] was also described as heightened. In contrast, a different study observed a significant decrease in circulating ceramide levels in patients with cirrhosis, compared with controls, and this decrease was correlated with disease severity and hepatic decompensation [73]. These findings lead us to conclude that the impact of a putative increase in hepatic ceramide levels on peripheral IR in the context of cirrhosis remains to be established.

Others

Cirrhosis is often associated with increased resting energy expenditure where basal energy consumption is increased. It has been hypothesized that elevated resting energy expenditure, like IR, is the result of low-grade chronic inflammation caused by the liberation of inflammatory cytokines by the cirrhotic liver. Increased resting energy expenditure is therefore in itself associated with IR, regardless of cirrhosis [74].

Cirrhosis is also associated with a systemic state of low-grade hypoxia, the severity of which is linked to the severity of the disease [75]. A class of transcriptional regulators sensitive to hypoxia called hypoxia-inducible factors are found in nearly all tissues. They are crucial in the fine regulation of glucose metabolism. This mechanism is complex: for example, in tumors, hypoxia-inducible factors are expressed in a greater number and promote high glucose avidity [76]. However, in a context of hypoxemia, hypoxia-inducible factors also trigger an inflammatory response which has a role in pancreatic β-cell reserve [77].

Using ultrasound imaging, Japanese scientists have shown that there is a reduction in blood flow to the pancreas of cirrhotic subjects. A correlation between this pancreatic congestion and insulin secretion has been established, proving that decreased blood flow contributes to the development of HD [78].

Specific mechanisms in play in different cirrhosis etiologies

As previously discussed, cirrhosis is often linked to IR. This could also be due to the fact that, in certain circumstances, the mechanism that is responsible for cirrhosis also causes IR. In this case, IR can be identified before cirrhosis develops and it becomes interesting to investigate whether cirrhosis exacerbates the degree of IR. This is what will be explored in the following section of this article, with particular attention brought to the principal well-known mechanisms explaining the emergence of both IR and chronic liver diseases.

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NAFLD

Liver steatosis, defined as the accumulation of fat in the liver, is associated with IR even in lean subjects and before the potential development of fibrosis or cirrhosis [79]. The process responsible for IR in these conditions is peripheral inflammation, mainly in the adipose tissue [80], changes in microbiota composition and altered gut permeability [64] as well as liver inflammation [50]. Recruited adipose tissue macrophages produce inflammatory cytokines called 'adipokines' that play a role in the down-regulation of the insulin signaling cascade [80]. In the liver, similar activation of resident macrophages (Kupffer cells) also occurs [81–83]. As mentioned earlier, chemokines called hepatokines produced by the liver in the context of liver inflammation due to NAFLD are also recognized as key players in IR pathogenesis such as selenoprotein-P and fetuin-A [51]. Further deterioration of insulin sensitivity is observed with disease progression (i.e. fibrosis and cirrhosis development), suggesting that cirrhosis itself has an additional damaging effect on glucose metabolism [84–86]. As mentioned above, hepatic ceramides play a role in NAFLD, NASH and fibrosis, and IR pathogenesis [87]. However, to date and to our knowledge, the potential impact of ceramides on IR progression in the context of NAFLD-related cirrhosis has not been investigated.

Weight reduction achieved through lifestyle changes leads to improvements in liver histology in NASH [88,89] and in insulin sensitivity [90]. No study specifically addressed the question of IR in NASH cirrhosis. Similarly, weight loss obtained with bariatric surgery is also associated with total regression of NASH and significant amelioration of fasting blood glucose and IR after 1 year. Having said that, no patient with NASH cirrhosis was included in this study [91].

These observations can be extrapolated and applied to other drugs tested in NASH recently. Some drugs are associated with histological regression of NASH or fibrosis but none of the studies include patients with cirrhosis and furthermore, results of IR are variable. In particular, five large randomized controlled Phase II trials are available [92]. Their findings were that obeticholic acid improved liver histology and was associated with worsened IR evaluated by HOMA-IR [93]. Elafibranor, a dual peroxisome proliferator-activated receptor (PPAR) α/δ agonist, also lead to reduced inflammation in severe NASH but reduced the HOMA-IR index compared with a placebo only in diabetic patients[135]. In contrast, previous results of clamp studies using the two compounds mentioned (obeticholic acid and elafibranor), showed improvements in *in vivo* insulin sensitivity [94,95]. Cenicriviroc, a dual C–C chemokine receptor type 2 and 5 (CCR2-5) inhibitor, was also tested in NASH with fibrosis and no cirrhosis and induced regression of fibrosis but did not have any impact on insulin sensitivity [96]. Selonsertib, a molecule inhibiting the apoptosis signal-regulating kinase 1 (ASK1) resulted in an improvement in both fibrosis and inflammation [97] but was associated with an increase in HOMA-IR values. Treatment by resmetirom, a selective thyroid hormone receptor-β agonist, was able to significantly reduce hepatic fat content but did not improve glucose homeostasis [98].

Hepatitis C

The pairing of glucose and lipid metabolism perturbations in relation to HCV infections is well described. Chronic HCV is associated with a twofold increase in DM [99]. Similar to NAFLD, HCV induces IR before the development of cirrhosis. This IR is present in the liver but also in the peripheral tissues, as is examined by euglycemic clamp studies [100].

Few mechanisms have been offered to explain the onset of IR in HCV-infected patients [101]. Direct interaction between the virus and the insulin signaling pathway, production of pro-inflammatory cytokines, and an increase in β-cell sensitivity are a few of the mechanisms suggested. A study [21] involving nine cirrhotic patients, all of whom had HCV induced cirrhosis and a grade B Child–Pugh score, and seven control subjects matched for age, sex and body mass index was performed in 2002 [21]. The results were that a hyperinsulinemic state in the nine cirrhotic patients was the consequence of increased β-cell sensitivity to glucose. The authors devised a mathematical model simulating insulin secretion based on the concentration of C-peptide. It represented insulin secretion as a sum of three main components: a dynamic Sd(t), a static Ss(t) (which includes circadian modulation) and a residual component Sr(t). After determination of these components in patients and controls, the β-cell dose–response function was shifted upward in patients with cirrhosis. Not only was the absolute insulin secretion elevated, but also the secretion in relation to glucose. The present study also suggests that hepatic insulin clearance does not play a significant role in the occurrence of IR in cirrhotic patients. These results seem to contrast those published in a 2005 study [102] in which scientists studied all causes of cirrhosis. Coupling the OGTT and ^{3}H-Glucose clamp technique, they found that IR in cirrhotic patients was due to impaired glucose uptake rather than changes in β-cell function or glucose production. This leads us to posit the existence of disease-specific mechanisms in HCV cirrhosis.

The causal link between these HCV patients and IR was further demonstrated by the reversibility of IR and DM following a sustained virological response obtained with antiviral treatment. This was observed mainly in genotype 1 patients [103], but not in genotype 2 and 3 patients. In patients with genotype 4 HCV infection, a recent study

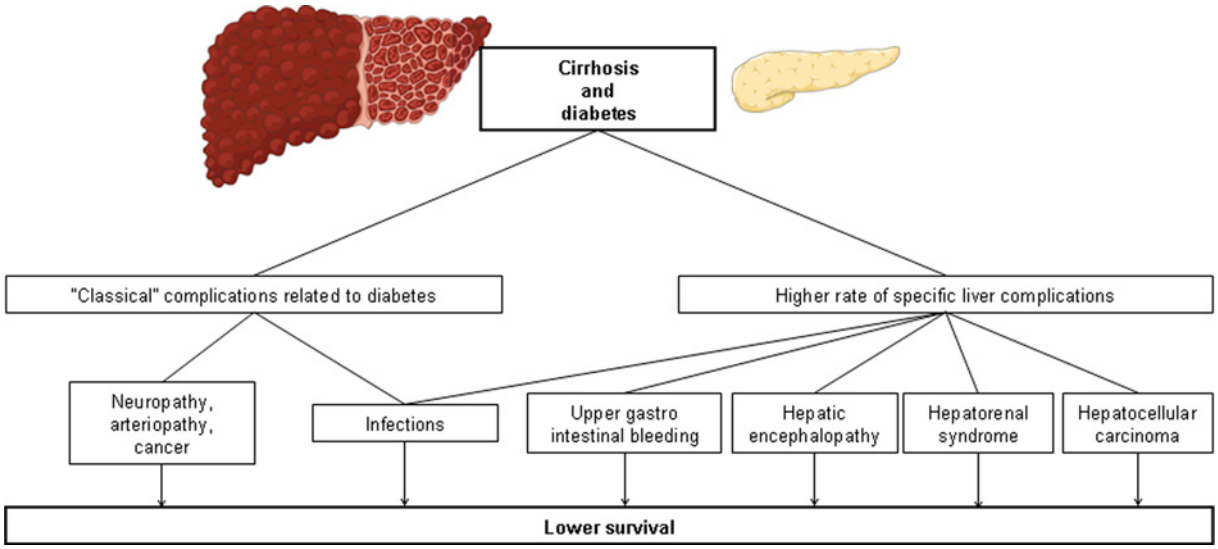

Figure 4. Potential complications in the context of cirrhosis and DM coexistence

revealed that novel direct antiviral agents were also able to decrease IR. However, this improvement was smaller in patients with advanced cirrhosis or long-lasting DM [104].

ALD

Although moderate alcohol consumption is recognized as having a beneficial effect on cardiovascular health [105], a meta-analysis shows that a consumption of 12–24 g of ethanol per day is associated with development of cirrhosis [106]. While cirrhosis is often associated with IR, it is thought that alcohol contributes to the likelihood that IR occurs. Indeed, in mice, an administration of ethanol induces IR in the liver and in peripheral tissues, without encouraging cirrhosis [107–109]. Interestingly, hepatic ceramides were reported to be increased in alcoholic cirrhosis and could therefore play a role in IR associated with this liver condition [72] as previously mentioned. Additional influence of chronic ethanol toxicity resides in the pancreas where a deficit in insulin secretion can be observed [110].

Complications due to the association between cirrhosis and IR

As DM evolves, blood glucose concentrations rise above a basal level. In such a context, glucose becomes deleterious; it can lead to peripheral neuropathy [111], arteriopathy [112] and harbor an increased risk of cancer [113,136]. Apart from the previous complications observed in both non-cirrhotic and cirrhotic patients, other more specific complications of IR in cirrhosis exist (Figure 4).

IR, *per se*, is associated with a lower survival rate. Two prospective studies [9,115] analyzed the survival rates of patients with cirrhosis who had glucose metabolism alterations. The first study, by Nishida et al. [9], concluded that in cirrhotic patients with impaired glucose homeostasis, the mortality rates were higher than that of patients with normal glucose tolerance. The second study, by Quintana et al. [115] researched the potential impact of DM on the mortality of patients with compensated cirrhosis; they found that the cumulative survival was lower in patients with DM. The main cause of death originated from liver and kidney complications such as upper gastrointestinal bleeding, hepatic encephalopathy and hepatorenal syndrome. The higher occurrence of hepatic encephalopathy in DM was also confirmed in another prospective trial [116].

DM is also believed to significantly increase the risk of bacterial infections among cirrhotic subjects, as reported in a study in 2014 [117]. Urinary tract infections, followed by pneumonia and spontaneous bacterial peritonitis were the most frequent infections seen.

DM is also responsible for an increase in HCC occurrence in cirrhosis, as evaluated in a meta-analysis comparing 28 studies [118]. Not only was HCC incidence in diabetic patients compared with non-diabetic patients significantly higher, but so was HCC-related mortality. A suggested mechanism is that hyperinsulinemia promotes farnesylation of the Ras protein that contributes to the mitogenic responsiveness of cells to various growth factors. This farnesylation could therefore subsequently promote progression of cancer and atherosclerosis [119].

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It has also been determined that, for newly diagnosed HCC patients with a history of HCV infection, IR levels predict the existence of esophageal varices, regardless of the presence of DM [120].

For patients with HCV benefitting from a liver transplant, the post-transplant IR measured by HOMA-IR is strongly associated with a higher risk of rapidly progressing fibrosis [121].

Potential treatments

While it seems logical to treat DM in the context of cirrhosis and target a stable glycemia, no trial has been done to show the benefit of this strategy on liver complications such as end-stage liver disease. A positive effect on the reduction in HCC has however been seen with some drugs.

Treatment of the underlying disease?

It seems logical to imagine that treating the cause of cirrhosis will also (at least in part) treat DM if IR is caused by cirrhosis. Still, as discussed above, other than for HCV, there are no clear data on this subject. Indeed, to date, the possible improvement of insulin sensitivity in patients with non-HCV cirrhosis (such as auto-immune hepatitis, chronic HBV, . . .) after specific treatment based on cirrhosis etiology has not yet been determined. In one recent case report, IR was shown to be associated with primary biliary cholangitis (at a non-cirrhotic stage) and DM disappeared after starting treatment by ursodeoxycholic acid suggesting that liver inflammation plays a role in glucose homeostasis dysregulation [122]. However, even for frequent diseases such as ALD or NAFLD, we do not have any data concerning the potential improvement of IR related to cirrhosis in case of regression of the underlying inflammatory condition. As discussed above, if future treatments prove effective in NASH cirrhosis, it would be interesting to analyze the specific effect they have on IR.

General management: lifestyle changes

Weight loss obtained through nutritional and behavioral counselling is the first line of treatment widely recommended for patients with DM or IR [123]. Ideally, these recommendations should be applied to patients with cirrhosis plus DM or obesity. However, they remain theoretical since in practice, they have not been evaluated in patients with cirrhosis. It is important to mention the need for a comprehensive nutritional assessment before making any such recommendations as many cirrhotic patients suffer from sarcopenia or malnutrition [124]. In the context of NASH-associated cirrhosis and cirrhosis from other causes associated with obesity, the goal of dietary counselling and lifestyle changes should be the loss of fat, in particular in its abdominal and perivisceral location [80], and the correction of sarcopenia [125]. It is paramount that exercise be tailored to each patient and their condition. A moderately hypocaloric diet (–500 to 800 kcal/day compared with daily caloric intake) with high protein intake (>1.5 g proteins/kg/day) yields a 5–10% weight loss in obese cirrhotic patients [125] and can therefore be advised in order to reduce cirrhosis-associated complications. To elaborate more precise guidelines on this topic, additional trials are required.

Pharmacological intervention

Potential treatments of DM are summarized in Table 2 with their benefits and side effects. The metformin first-line therapy is a good option to treat IR. Some studies suggest a positive effect of metformin in cancer prevention too. Rather notoriously, it has been claimed that metformin could prevent HCC development in HCV infected patients with cirrhosis [126]. It was also stated that metformin could reduce the incidence of advanced colorectal adenoma in diabetic patients [127]. However, the use of metformin in cirrhotic patients with liver failure or renal insufficiency is challenging since prescription of this drug in this situation could lead to lactic acidosis and be potentially life threatening [128]. Large trials in patients with (decompensated) cirrhosis show however that this drug is safe even in subjects with Child C severity chronic liver disease [129]. The risk of lactic acidosis is especially present in patients with alcohol abuse and renal injury [130].

Acarbose, an α-glucosidase inhibitor, induces disaccharide degradation in the intestine, thereby reducing postprandial hyperglycemia and fasted blood glucose. Its efficacy has been demonstrated in NAFLD cirrhosis. Furthermore, this treatment is also able to reduce hepatic encephalopathy [131,132].

Thiazolidinediones are PPARγ agonists also used as treatment for hyperglycemia in type 2 diabetic patients. In a recent large trial on diabetic subjects, a reduction in HCC was observed in diabetic cirrhotic patients using thiazolidinediones although it was not statistically significant [133]. Drugs that are metabolized in the liver and stimulate insulin secretion (sulfonylureas, meglitinides) can induce severe hypoglycemia and should be avoided in Child–Pugh B and C chronic liver diseases.

Table 2 Potential strategies for type 2 diabetes in the context of cirrhosis

Treatment	Counseling in the context of cirrhosis and type 2 diabetes	Advantages	Disadvantages
Weight loss and lifestyle changes (caloric restriction and exercise)	Indicated in cases of overweight, adiposity or NAFLD	Impact on prognosis Theoretical reduction in sarcopenia and adiposity Improvement of histological features of NAFLD	Difficulty of implementation Possible worsening of malnutrition
Insulin	Useful	Rapid effect Simple adjustments in hospitalized patients Preferred drug in Child C cirrhosis	Risk of hypoglycemia Difficulty of follow-up and dose adaptation Close follow-up needed Subcutaneous injection (or intravenous administration)
Metformin (biguanides)	Useful	Simple No (liver) metabolism Reduction in cancers	Contra-indicated in renal insufficiency and in advanced liver failure (with alcohol abuse)
Acarbose (glucosidase inhibitor)	Maybe useful if encephalopathy	Reduction in fasted and postprandial hyperglycemia Benefit on hepatic encephalopathy	Diarrhea/flatulence Low efficacy on glucose level
Sulphonylureas (insulin secretagogues)	Not recommended	/	Increased risk of hypoglycemia with liver insufficiency No modification of IR
Meglitinides	Caution required	Short half life	Liver metabolization Gastrointestinal symptoms May induce hypoglycemia Contra-indicated in advanced liver insufficiency
Thiazolidinediones	Caution required	Beneficial effects on NASH	Inadequate metabolization by the liver in cirrhosis
GLP-1 agonists	Useful	Low liver metabolization Beneficial effects on NASH	Nausea Subcutaneous injection
DPP-4 inhibitors	Useful	Low liver metabolization Reduction in plasma glucose level without hypoglycemia	Nausea
SGLT-2 inhibitors	Useful	Well tolerated	No long-term safety profile in patients with cirrhosis Careful administration in patients with risks of hypovolemia Contra-indicated in renal insufficiency
Specific NASH drugs with an effect on IR (such as elafibranor, lanifibranor)	Not yet recommended	Possible reduction in liver inflammation, steatosis, fibrosis in the context of NASH	Currently investigated in patients with fibrosis but without cirrhosis
Bariatric surgery	Maybe useful if morbid obesity	Sustained weight loss	Contra-indicated in Child–Pugh B or C patients and patients with portal hypertension
Liver transplantation	Not recommended only for diabetes Indication: liver insufficiency with high MELD score or liver cancer	Improvement of insulin sensitivity Treatment of liver disease	Organ transplantation drawbacks

Abbreviations: DPP-4, dipeptyl peptidase-4; GLP-1, glucagon-like peptide-1; MELD, model for end-stage liver disease; SGLT-2, sodium-glucose co-transporter 2.

Incretin-based therapies (glucagon-like peptide-1 (GLP-1) receptor agonists and inhibitors of dipeptyl peptidase-4 (DPP-4)) are safe for cirrhotic patients as only a very small portion is metabolized by the liver. However, in decompensated patients they should be cautiously administered. Selective renal sodium glucose co-transporter 2 (SGLT2) inhibitors induce glucosuria and osmotic diuresis and thus require more care when used in patients with liver cirrhosis and circulatory dysfunction. The liver toxicity is low.

When DM cannot be managed with oral treatment, there is a need for recombinant insulin. When starting a therapy by recombinant insulin, close monitoring is necessary to prevent hypoglycemia, particularly in patients with reduced liver function (due to the altered liver insulin metabolism in this condition). To date, there is no standard insulin regimen advised for cirrhotic patients.

Bariatric surgery

Along with weight loss, bariatric surgery sees an improvement of histological features in NAFLD and reduced complications associated with obesity. It can therefore be considered as a treatment option for patients exhibiting

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eligibility criteria (severe/morbid obesity and DM for example). The presence of compensated cirrhosis is not a contra-indication for bariatric surgery. Portal hypertension or decompensated liver disease is however associated with a higher rate of complications [92].

Liver transplantation

An improvement of IR is observed after liver transplantation. However, full restoration is not achieved [74]. Interesting PET studies using fluorodeoxyglucose (FDG) tracer are going in the same direction: they show that skeletal muscle glucose uptake is significantly reduced in patients with cirrhosis compared to control subjects and improves after orthotopic liver transplantation. Nevertheless, it remains significantly lower than in control subjects [134]. IR can still be present after liver transplantation and prompt the development of DM. This is of utmost importance as post-transplant IR is strongly associated with a higher risk of rapidly progressing fibrosis [121].

Conclusion and place for future research

While cirrhosis has an important prevalence, pathophysiological mechanisms leading to IR in this context are still poorly understood. The following attractive factors could play a part in this setting: muscle alterations, changes in gut microbiota, liver inflammation and endocrine perturbation. The prevalence and incidence of complications linked to IR in cirrhosis have yet to be properly determined, statistically analyzed and reported. A much better understanding of the mechanisms underlying IR in cirrhosis will allow for the identification of high risk patients and potentially targeted therapies. For example, the clinical benefit of screening for IR (on potential complications and mortality) through HOMA-IR calculation also needs to be approved. Whether specific IR treatments will aid in reducing complications of cirrhosis such as infections, esophageal variceal bleeding, HCC and liver failure remains also to be specifically addressed.

The role that metformin occupies within the treatment of cirrhotic patients with IR is still debated as it seems that it could decrease HCC occurrence. Similar advantages of novel drugs aimed at treating DM or background liver disease could also be of use.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

ALD, alcoholic liver disease; DM, diabetes mellitus; EGP, endogenous glucose production; FXR, farnesoid X receptor; GDR, whole-body glucose disposal rate; GH, growth hormone; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HD, hepatogenous diabetes; HOMA-IR, homeostasis model assessment of insulin resistance; IGF-1, insulin-like growth factor-1; IL, interleukin; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OGTT, oral glucose tolerance test; PET, positron emission tomography; PPAR, peroxisome proliferator-activated receptor; T3, triiodothyronine; TGR5, Takeda G protein coupled receptor; TNF-α, tumor necrosis factor-α.

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