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Original article

Patients with chronic liver diseases are at risk for diabetes even before development of cirrhosis

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ABSTRACT

Background and aims: The prevalence of insulin resistance (IR) and type 2 diabetes mellitus (T2DM) is higher in patients with cirrhosis, compared to control patients without liver disease. The exact mechanism for this is unknown but could include liver inflammation. In this study we investigate whether cirrhosis is the *primum movens* of IR or if impaired insulin sensitivity is already present in non-cirrhotic patients with chronic liver diseases.

Methods: Patients were recruited and divided into three groups: control (CTL), chronic liver disease without cirrhosis (CLD) and cirrhosis (CIR). In patients not taking pharmacological treatment for T2DM, IR was quantified using the homeostasis model assessment of insulin resistance (HOMA-IR). The proportion of patients with T2DM as well as HOMA-IR levels among different disease etiologies were recorded and compared.

Results: 532 patients were included in our study. Median glycemia and insulinemia and therefore HOMA-IR values were significantly different between the three cohorts (p-value <0.001): IR levels in CLD subjects lie between those seen in CTL and CIR subjects. The proportion of diabetic patients in the two case categories also differs (p-value $= 0.027$): one quarter of CLD subjects and one third of CIR patients suffer from T2DM. Finally, HOMA-IR levels vary according to disease etiology (p-value <0.001): metabolic steatosis and chronic viral hepatitis C are at greater risk than alcohol and other disease causes.

Conclusion: CLD is already a predisposing factor to T2DM, regardless of the presence of CIR. CIR is a factor which elicits additional increase in insulin levels. Metabolic steatosis and hepatitis C are associated with more severe IR.

Acronyms

IR	Insulin resistance
T2DM	Type 2 diabetes mellitus
CIR	Cirrhosis
CLD	Chronic liver disease
CTL	Control
HOMA-IR	Homeostasis model assessment of insulin resistance
MASLD	Metabolic dysfunction-associated steatotic liver disease
HCV	Hepatitis C virus
ALD	Alcohol-related liver disease
HBV	Hepatitis B virus
TE	Transient elastography
GGT	γ-glutamyl transferase
A1-AT	α−1 antitrypsin
BMI	Body mass index
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
INR	International normalised ratio
HbA1c	Glycated hemoglobin

Introduction

Over the past few decades, an important surge in the prevalence of type 2 diabetes mellitus (T2DM) has been recorded among western populations. In addition to this, diabetes has been ranked the ninth leading cause of death due to its cardiovascular complications, which explains why it is of major concern in the public health sector [1]. Diabetes is a heterogeneous group of metabolic disorders characterised by a state of chronic hyperglycemia (fasting plasma glucose ≥ 126

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mg/dL) [2,3].

Insulin resistance (IR) is the precursor of T2DM and is defined as the inability of a given quantity of insulin to prompt a normal physiological response in insulin-sensitive tissues [3]. Originally, when glucose enters the bloodstream in a post-prandial context, insulin promotes glucose uptake in the skeletal muscle and adipose tissue and suppresses *de novo* glucose production in the liver [4]. When these mechanisms are dysfunctional and insulin signalling is altered (e.g. in the context of obesity and T2DM) [5], the terms peripheral and hepatic IR are used [6].

To measure IR, the euglycemic clamp technique is considered today to be the gold standard for determining the effect of insulin on glucose metabolism [7]. However, this technique is time-consuming and therefore reserved for small sample populations [6]. A second technique which is more appropriate for larger studies and that estimates IR is the homeostasis model assessment of insulin resistance (HOMA-IR) developed in 1985 [8]. It is a robust tool that indirectly measures global IR and correlates well with the clamp technique [9].

The frequency of chronic liver diseases (CLD) has steadily increased overtime [10]. While the prevalence of the majority of CLD (alcohol--related liver disease, hepatitis B viral liver disease) has remained generally stable, metabolic dysfunction-associated steatotic liver disease (MASLD) has risen in Europe and in the USA and accounts for the overall increase in CLD [10–13]. CLD develop through a process spanning over a period of minimum 6 months during which the liver parenchyma is progressively destroyed through inflammation, apoptosis, necrosis and ultimately cicatricial fibrosis [14]. In the terminal stages of CLD, also known as cirrhosis (CIR), dissection of the hepatic lobules by fibrous septa transforms the original lobular architecture of the liver parenchyma into regenerative nodules.

A link between CIR and IR has been proven based on various clamp studies and HOMA-IR calculations done on cirrhotic patients compared to healthy controls [15,16]. It has been shown that CIR alters glucose metabolism by decreasing glucose uptake in the skeletal muscle or adipose tissue [15,17,18].

However, the link between CLD in general and IR is less clearly established: the majority of research in the field of CLD focuses on MASLD rather than CLD as a whole. In patients with MASLD, fasting plasma glucose levels are increased compared to controls [19]. The close relationship between MASLD and T2DM is indeed well documented [20–22] with the steatotic liver already participating in the genesis of IR in the early stages of the disease [23–25]. Currently, there are no prospective studies investigating IR in patients with ALD [26]. Literature available on hepatitis B viral liver disease (HBV) is also meagre [15]. Only one recent trial studied IR in patients with autoimmune liver diseases, but did not discriminate based on presence of CIR [27]. Interestingly, the same researchers also analysed other data from the United Kingdom Biobank and showed that the risk of diabetes in patients with autoimmune liver disease is clearly associated with the presence of CIR [28]. Concerning hepatitis C virus (HCV) liver disease, the available data show a positive correlation between IR and onset of disease and disease severity [29,30].

Since some mechanisms which explain the development of IR in the context of CIR may already be present in patients with CLD (eg. liver inflammation) [15], the question remains whether CIR is required for the development of IR or whether the presence of CLD before the development of CIR is a necessary and sufficient condition. We will address this as well as examine whether specific CLD etiologies influence insulin sensitivity more than others and to what extent.

Methods

Sample population

Between 2015 and 2020, patients were prospectively recruited during their visit in the gastro-enterology and hepatology units for a routine check-up of their CLD (cases) or for a different reason (CTL). Our research protocol complies with the ethical principles of the 1975 Declaration of Helsinki and was subsequently approved by the ethics committee of our institution (numbers: 2015/10NOV/605, 2014/15OCT/514, 2014/14AOU/438, 2015/30OCT/571, 2015/06OCT/536, 2020/07JUI/446).

Our sample population consisted of three different groups: CTL, CLD and CIR. Inclusion in each of these categories was contingent on specific criteria. The inclusion criteria for the CTL cohort were the absence of liver infection or disease and any affection altering glucose homeostasis. Additionally, no significant steatosis was allowed in patients where transient elastography (TE) was available (controlled attenuation parameter $<$252 dB/m).

The case cohort consisted of patients with either CLD or CIR for which no treatment was taken. Specifically, four disease profiles made up these categories: MASLD, ALD, chronic HCV and 'other' (chronic HBV and α−1 antitrypsin deficiency). Diagnosis of ALD was based on elevated transaminase and/or γ-glutamyl transferase (GGT) levels as well as an alcohol consumption $>$30 g/day in men and 20 g/day in women [31]. Elevated liver enzymes in overweight or obese patients whose alcohol consumption was below the cut-off values for ALD and where no other cause was found made up the MASLD group [11]. Inclusion in the chronic HCV and HBV cohorts depended on the presence of HCV/HBV antibodies as well as positive serum HCV-RNA for chronic HCV [32] and positive HBV-DNA and HBV surface antigen for chronic HBV. Patients with α−1 antitrypsin deficiency (A1-AT) had decreased α−1 antitrypsin enzyme levels and were homozygous following phenotype testing.

At the time of inclusion, all patients received a full clinical evaluation in addition to a blood test. Biologic parameters of interest included a lipid panel, hepatic enzymes (aspartate aminotransferase or AST, alanine aminotransferase or ALT, alkaline phosphatase, GGT), total and conjugated bilirubin, fasted glycemia and insulinemia (in patients without any medication for T2DM) and glycated hemoglobin (in patients receiving medication for T2DM). Platelet count was also recorded. Patients having previously undergone a TE exam also had a measure of liver steatosis (controlled attenuation parameter) and stiffness (elasticity) linked to fibrosis. Where available, data provided by liver biopsies was also logged.

Most importantly, diagnosis of T2DM was recorded and based on whether pharmacological treatment was taken for the condition, as in other studies [33,34]. Diagnosis of CIR was based on the presence of fibrotic nodules consistent with a F4 fibrosis stage upon histological analysis of a liver biopsy or by the clear association of biological parameters and imaging results consistent with CIR (dysmorphic liver, low platelet count and high liver elasticity based on cut-offs depending on disease etiology).

Statistical analysis

Statistical analyses were carried out using the IBM® SPSS® software platform. Normal distribution of data was verified using the Kolmogorov-Smirnov and Shapiro-Wilks tests. Student t or Mann-Whitney U tests were used to calculate p-values for normally or non-normally distributed variables respectively. To compare more than two sets of data at once a one-way Anova or a Kruskall-Wallis test was used. Data are presented as mean ± standard deviation or as median and range where appropriate. A p-value $<$0.05 was considered statistically significant.

Results

Of the 532 patients included in our study, 35 were controls, 369 had a CLD and 128 were cirrhotic. Patients were then divided based on the presence or absence of T2DM (Fig. 1).

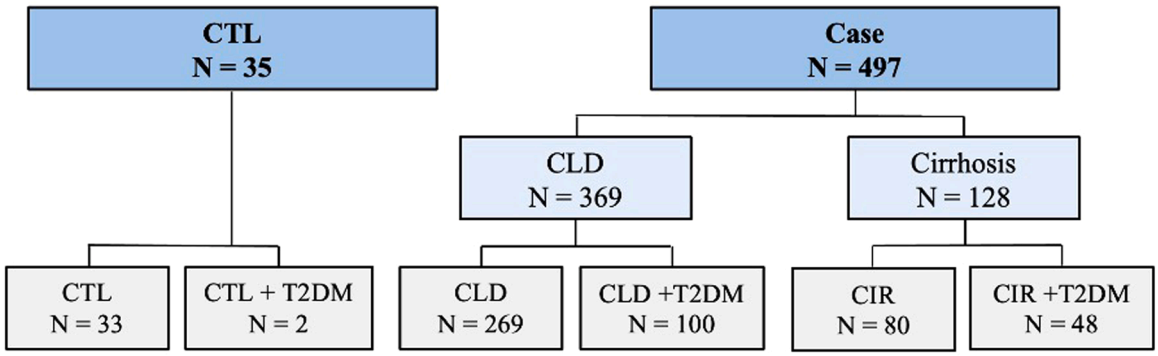

Fig. 1. Sample population and patient categorisation. CTL: Control, CLD: Chronic liver disease, CIR: Cirrhosis, T2DM: Type 2 diabetes mellitus, *N* = number of patients.

Non-diabetic patients with chronic liver disease already have insulin resistance but it is less severe than in non-diabetic patients with cirrhosis

Clinical, biological and radiological characteristics for these three patient categories are shown in Table 1 which represents CTL, non-diabetic CLD and non-diabetic CIR subjects.

Patients are on average middle-aged in the CTL cohort and are progressively older in the CLD and CIR cohorts (Table 1). While the sex ratio is balanced in the CTL and CLD groups, there are 2.5 times more men than women in the CIR group. There is no statistically significant difference in median BMI between the categories with all three BMI lying in the overweight category of 25–30 kg/m^2.

Blood test results show normal liver enzymes in the CTL cohort. In patients with CLD, AST are within the normal range whereas ALT are increased. This trend is reversed for patients with CIR. Alkaline phosphatase levels are normal in both CLD and CIR groups but GGT are 2.5 times greater in cirrhotic patients compared to the normal values seen in patients with CLD (Table 1).

For the 33 CTL without T2DM patients who underwent TE testing, no significant steatosis or fibrosis was recorded. TE results from patients with CLD or CIR show that both populations exhibit similar degrees of steatosis (moderate to severe). However, as expected, fibrosis varies greatly between our two patient categories: mild fibrosis seen in CLD patients contrasts with the extensive fibrosis recorded in CIR subjects (Table 1).

The CTL group is characterised by normoglycemia and normoinsulinemia resulting in a median HOMA-IR value well below the IR cut-off of 2.5. CLD subjects are also normoglycemic and normoinsulinemic although both values sit at the top end of the normal range resulting in a high HOMA-IR index (median of 3.3). Although glycemia values are similar in CLD and CIR patients, CIR patients are hyperinsulinemic with a median HOMA-IR significantly higher than in the CLD group (Table 1 and Fig. 2).

Table 1
Clinical, biological and radiological characteristics of the control, CLD and CIR without T2DM cohorts expressed as median – range. Statistically significant values following Kruskall-Wallis test and chi-square test, for age variable, are shown in bold. CLD: chronic liver disease, CIR: cirrhosis, T2DM: type 2 diabetes mellitus, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyl transferase, HOMA-IR: homeostasis model assessment of insulin resistance.

	CTL *N* = 33	CLD *N* = 269	CIR *N* = 80	P-value
Clinical data				
Age (years)	45.0 – 55.0	48.0 – 59.0	62.0 – 54.0	**<0.001**
Sex (M/F)	14/19	152/117	58/22	**0.005**
BMI (kg/m^2)	27.2 – 13.0	28.0 – 62.1	27.3 – 20.1	0.220
Biological data				
AST (UI/mL)	24.0 – 78.0	35.0 – 1879.0	42.5 – 291.0	**<0.001**
ALT (UI/mL)	27.0 – 141.0	45.0 – 915.0	31.0 – 425.0	**<0.001**
GGT (UI/mL)	20.0 – 255.0	64.0 – 3716.8	129.0 – 1493.0	**<0.001**
Alkaline phosphatase (UI/mL)	61.5 – 151.0	78.5 – 347.0	94.0 – 231.0	**<0.001**
Total bilirubin (mg/dL)	0.4 – 2.4	0.5 – 7.0	1.0 – 8.5	**<0.001**
Glycemia (mg/dL)	91.0 – 44.0	97.0 – 134.1	99.0 – 165.6	**0.007**
Insulinemia (pmol/L)	51.0 – 111.0	84.2 – 734.0	132.8 – 1950.0	**<0.001**
HOMA-IR	1.9 – 5.5	3.3 – 32.7	5.7 – 32.7	**<0.001**
Platelets (x10^3/mm^3)	248.0 – 176.0	250.0 – 435.0	121.0 – 377.0	**<0.001**
Radiological data				
Steatosis (dB/m)	218.0 – 113.0	307.0 – 280.0	290.0 – 277.0	**<0.001**
Elasticity (kPa)	4.9 – 3.7	6.0 – 72.2	24.2 – 71.4	**<0.001**

Higher proportion of diabetic patients in the cirrhotic group compared to the chronic liver disease group

The same comparison was done for patients with T2DM (Supplementary Table 1). The differences in age and sex ratio observed between the CLD and CIR with T2DM cohorts are similar to those in patients without T2DM: patients with CIR are on average older than those with CLD and while the sex ratio is relatively balanced in CLD patients, the CIR group is mostly made up of men (73 % compared to 43 %). Median BMI in patients with T2DM is higher than in those without T2DM and for both of these categories, BMI is lower for the CIR cohort compared to the CLD cohort. Differences in ALT, GGT, alkaline phosphatase and total bilirubin between the CLD and CIR cohorts in the T2DM category mirror those seen in the normoglycemic category (Supplementary Table 1).

Results from TE show that steatosis is significantly higher in T2DM subjects with CLD compared to those with CIR (Supplementary Table 1). However, elasticity is higher in patients with CIR compared to those with CLD and this difference is statistically significant (median 28.9 and 8.9 kPa respectively).

The proportion of non-diabetic and diabetic patients in the CLD and CIR cohorts differs: approximately three quarters of subjects have no treatment for hyperglycaemia in the CLD cohort compared to two thirds in the CIR cohort and this difference is statistically significant (p-value = 0.027) (Figs. 1 and 3).

Insulin resistance status differs with disease etiology

IR was then compared in patients based on the 4 different disease etiologies: MASLD, ALD, HCV liver disease and 'Other' (Table 2). The four groups also differ in aspects other than IR. Patients with HCV derived CLD or CIR are slightly older than those with MASLD, ALD or other liver disease etiologies. BMI is similar in the ALD, HCV and 'other'

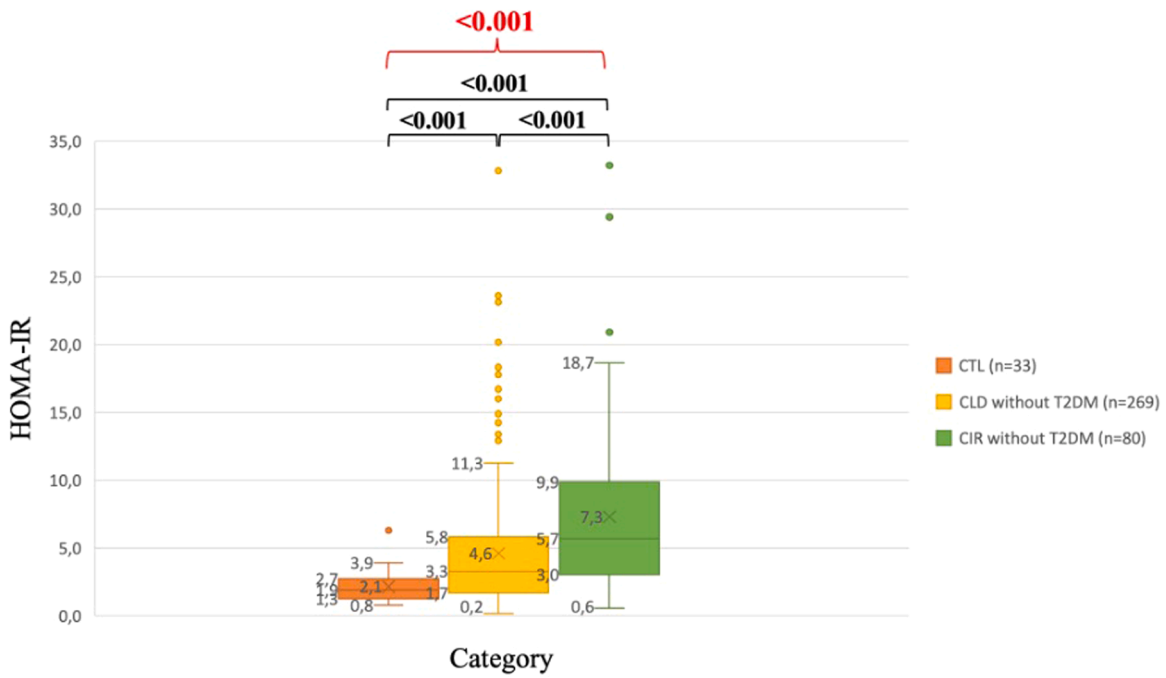

Fig. 2. Comparison of HOMA-IR values in three cohorts: control, CLD without T2DM and CIR without T2DM. Statistically significant values following Mann-Whitney U (black) and Kruskall-Wallis (red) tests are shown in bold. CTL: Control, CLD: Chronic liver disease, CIR: Cirrhosis, T2DM: Type 2 diabetes mellitus, HOMA-IR: homeostasis model assessment of insulin-resistance, x = mean, line = median.

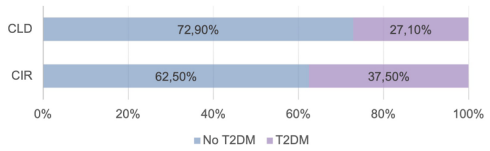

Fig. 3. Proportion of normoglycemic and diabetic patients within CLD and CIR cohorts. CLD: Chronic liver disease, CIR: Cirrhosis, T2DM: Type 2 diabetes mellitus. P-value following chi-square test = 0.027.

groups whereas it is higher in patients with MASLD. IR measurements in non-diabetic patients with CLD or CIR differ based on disease etiology: MASLD and HCV liver disease are associated with higher HOMA-IR values compared to the lower values seen in ALD and other liver disease etiologies. A multi-group comparison shows that the four groups are different in regards to IR status (p-value <0.001) (Fig. 4).

Furthermore, the MASLD and HCV cohorts are associated with a higher proportion of diabetic patients (40.8 % and 52.5 % of patients respectively) which contrasts with the 12.8 % and 20.8 % in the ALD and other liver disease groups.

Discussion

Results from prospective trials and existing literature are clear: IR is present in patients with CIR and even more so if the disease is severe and this IR is associated with increased morbidity and mortality [15,35]. Additionally, it has been shown that this IR is related to decreased glucose uptake in peripheral tissues such as the skeletal muscle (but not the liver) leading to a hypersecretory insulin response [17,36]. These findings lead us to question the origin of such IR and investigate whether CIR is the primum movens of IR or if impaired insulin sensitivity is already present in non-cirrhotic CLD using the HOMA-IR calculation and the proportion of patients with T2DM.

Our results demonstrate that IR is already present in patients with non-cirrhotic CLD (median HOMA-IR 3.3) and that HOMA-IR levels lie between those seen in CTL and CIR patients (median 1.9 and 5.7). These findings are corroborated by an article published in *Diabetes Care* in 2012 although the data is limited to patients with MASLD [37]. In our sample population, one quarter of CLD patients and one third of CIR patients suffer from T2DM, the majority of which is made up of MASLD which tallies 40.8 % of diabetic patients. These figures are much higher than the 10.2 % of T2DM recorded in the general population [38].

Furthermore, our study shows that in patients without T2DM, median glycemia and insulinemia are higher in the CLD group. This leads us to conclude that CLD could be a predisposing factor to T2DM through the development of IR [6,39], and that CIR is a factor which in itself elicits an additional increase in fasted insulin levels. At present it is not yet clear whether these elevated levels of insulin in the CIR group are due to more significant IR or to reduced insulin clearance [15].

Our study also reveals that certain disease etiologies are associated with more severe IR: MASLD and HCV liver disease have higher levels of IR compared to other disease etiologies. In particular, the presence of ALD is not associated with marked IR. This is reflected in the prevalence of T2DM among our different CLD etiologies: etiologies most associated with IR are those where the number of T2DM patients is higher. These findings echo those from a study which found that IR was more prominent in MASLD and HCV-associated CIR compared to ALD and HBV-associated CIR [40]. With regards to IR in CLD with varying etiologies, our article is the first in its kind so no comparison with previous findings can be made. Concerning IR in steatotic liver diseases (SLD), there is a clear distinction between MASLD and ALD: although both diseases are characterised by liver steatosis, the mechanism of steatosis, as well as the metabolic environment, are different [41,42]. In MASLD, it is characterised by inflammatory visceral adipose tissue which contributes not only to an increase in free fatty acids in the circulation but also to IR through the production of adipocytokines [43,44]. Fatty infiltration of the skeletal muscle in the case of MASLD may also contribute to this IR [45–48].

Our real-life data also illustrate differences in age among the three cohorts such that CTL patients are the youngest of the three, CIR patients are the oldest and those with CLD are in the middle. It seems logical that patients with CIR would be older than patients with non-cirrhotic CLD simply because of the extra time needed to develop to an advanced stage

Table 2
Clinical, biological and radiological characteristics in non-diabetic and diabetic patients with a chronic liver disease or cirrhosis based on disease etiology expressed as median – range. Statistically significant values following Kruskall-Wallis test and chi-square test, for age variable and proportion of diabetic patients, are shown in bold. MASLD: metabolic dysfunction-associated steatotic liver disease, ALD: alcoholic liver disease, HCV: hepatitis C viral liver disease, T2DM: type 2 diabetes mellitus, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyl transferase, HOMA-IR: homeostasis model assessment of insulin resistance.

	MASLD $N = 211$	**ALD** $N = 203$	**HCV** $N = 59$	**Other** $N = 24$	P-value
Clinical data					
Age (years)	54.0 – 69.0	55.0 – 52.0	60.0 – 50.0	52.0 – 57.0	**<0.001**
Sex (M/F)	96/115	147/56	28/31	17/7	**<0.001**
BMI (kg/m^2)	32.4 – 41.3	25.5 – 20.2	28.7 – 24.0	27.4 – 15.2	**<0.001**
Biological data					
AST (UI/mL)	35.0 – 247.0	44.0 – 321.0	37.0 – 265.0	35.0 – 432.0	**0.001**
ALT (UI/mL)	48.0 – 249.0	36.0 – 224.0	35.0 – 425.0	33.0 – 913.0	**0.002**
GGT (UI/mL)	64.0 – 734.0	112.0 – 1609.0	54.5 – 1170.0	34.0 – 617.0	**<0.001**
Alkaline phosphatase (UI/mL)	73.0 – 212.0	90.0 – 462.0	82.0 – 156.0	81.0 – 194.0	**<0.001**
Total bilirubin (mg/dL)	0.5 – 3.6	0.6 – 8.6	0.5 – 2.0	0.7 – 5.3	**0.002**
HOMA-IR in patients without T2DM	5.3 – 33.0	2.5 – 29.3	4.9 – 11.2	3.3 – 17.0	**<0.001**
Proportion of T2DM (N, (%))	86 (40.8)	26 (12.8)	31 (52.5)	5 (20.8)	**<0.001**
Platelets (x10^3/mm^3)	240.0 – 400.0	155.0 – 377	182.0 – 360.0	188.0 – 261.0	**<0.001**
Radiological data					
Steatosis (dB/m)	330.0 – 182.0	290.0 – 280.0	235.0 – 265.0	241.0 – 229.0	**<0.001**
Elasticity (kPa)	8.0 – 62.0	7.3 – 72.2	8.2 – 33.8	6.2 – 21.8	0.578

of liver disease. T2DM, and therefore IR, has also been shown to increase with age: prevalence of T2DM in adults aged ≥ 65 years old is 22–33 % which exceeds that recorded in the total population [49]. This means that although our findings show a gradual increase in IR in the CTL, CLD and CIR cohorts, the potential impact of age as a factor contributing to increased IR in patients with CIR cannot be discarded and must be investigated.

The trend in transaminases is inverted between CLD and cirrhotic patients: AST are higher in patients with CIR while ALT are higher in patients with CLD. In patients with CLD, ALT are increased in response to liver damage. In patients with CIR this is also the case but a different process, whereby AST increases, is predominant. Interestingly, AST can come from the liver but also from the muscle [50]. As explained previously, high AST levels in patients with CIR may partly be due to the accumulation of ammonia which enhances myostatin expression and muscle proteolysis [15,51]. AST are also increased in patients with CIR since there is less liver glycogen available for gluconeogenesis meaning that the body resorts to catabolising muscle proteins to keep up with substrate demands eventually leading to loss in muscle quantity [15,51,52]. In patients with CIR, elevated AST levels could therefore be a marker for disease severity.

The primary strength of our study is that it is the first of its kind. Articles comparing IR between CTL and CIR cohorts exist and have allowed our knowledge of these pathologies to progress. However, to date and to our knowledge there is no research which analyses IR in patients with CLD and compares them to a CTL and a CIR group. Additionally, our inclusion criteria were strict and all patients who fit these criteria were included without exception. This allowed us to decrease any potential selection bias while also yielding optimal sample populations and *in fine* more reliable results. Furthermore, no specific funding was received for the present study and no specific outcome was preferred meaning that impartiality was maintained throughout our research.

One downfall of our study resides in the smaller number of patients with HCV, HBV and A1-AT deficiency. To respect our inclusion criteria, we could only include patients who weren't treated for their CLD since such a treatment would almost surely influence IR levels and therefore interfere with our results. The way in which antiviral therapy in non-

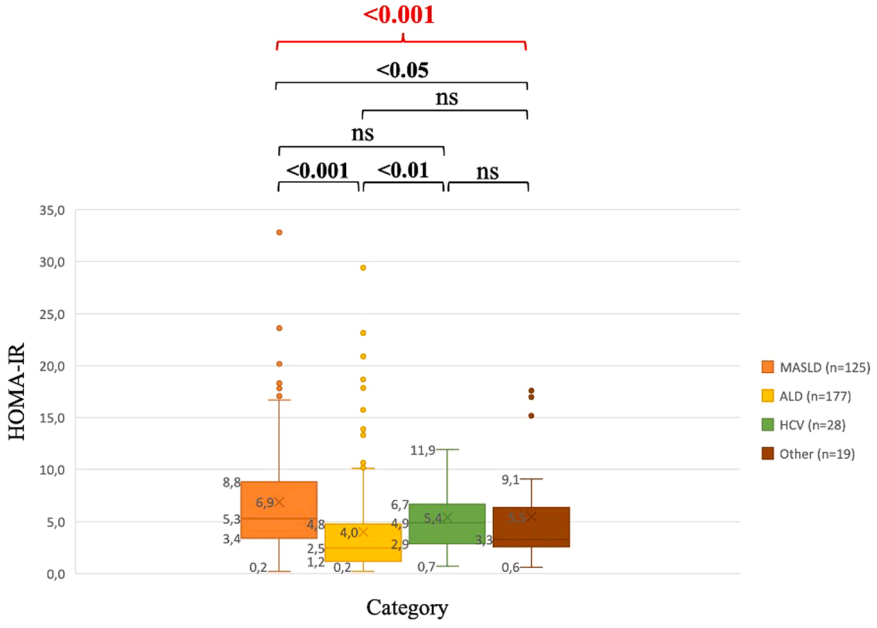

Fig. 4. Comparison of HOMA-IR values in non-diabetic patients with CLD or CIR following disease etiology. Statistically significant values following Mann-Whitney U (black) and Kruskall-Wallis (red) tests are shown in bold. HOMA-IR: Homeostasis model assessment of insulin resistance, MASLD: Metabolic (dysfunction) associated steatotic liver disease, ALD: Alcohol-related liver disease, HCV: Hepatitis C virus, x = mean, line = median.

diabetic chronic HCV patients affects IR was described in an article by G. Gastaldi et al.: clamp analysis showed significant improvement in peripheral IR following administration of direct-acting antivirals [53]. Similarly, use of ursodeoxycholic acid in patients with primary biliary cholangitis and T2DM could allow for normalisation of liver tests, glycemia and glycated hemoglobin (HbA1c) compatible with disappearance of T2DM [54]. It is also important to note that in our study, like in any study where meticulous data collection and analysis is required, slight methodical or logistical errors may arise potentially resulting in data bias. Finally, an analysis of body composition using bio-impedancemetry [34] and more particularly computed tomography [50] and/or magnetic resonance imaging [55,56] would be an attractive tool in assessing hepatic steatosis and any myosteatosis [48,57], subcutaneous or visceral adiposity [44] associated with insulin resistance.

The high proportion of T2DM patients seen in our sample population can be explained by the definition of what constitutes a diabetic subject used in our study. Diagnosis of T2DM was based on the presence or not of diabetic pharmacological treatment (as is the case for most studies [33,34]) and not on fasted plasma glucose levels following interruption of such medication. Thus, our "diabetes" subgroup may include patients with pre-diabetes if they took medication (e.g. metformin) for their condition. Faced with the above it would be of interest to carry out an analysis with matched groups for parameters such as age and BMI in our CLD and CIR groups to evaluate their impact on IR levels, thus allowing a revised definition of diabetes.

Although the present study succeeds in answering some of the initial questions, others arise as a consequence. We do not know whether early screening for IR using the HOMA-IR tool would be of benefit to patients with CLD and whether earlier administration of hypoglycaemic treatments would reduce potential complications. Therefore, further research is needed to assess the effect, if any, that these findings would have on clinical practice guidelines.

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CRediT authorship contribution statement

Georgia Bale: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Frédéric Clarembeau:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Peter Stärkel:** Writing – review & editing, Project administration, Investigation, Conceptualization. **Géraldine Dahlqvist:** Writing – review & editing, Investigation. **Yves Horsmans:** Writing – review & editing, Investigation. **Nicolas Lanthier:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data supporting this study are available upon reasonable request.

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Supplementary materials

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