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Readily Available Index of Insulin Sensitivity Is Associated with Metabolic Dysfunction-Associated Steatotic Liver Disease and Liver Fibrosis in Patients with Type 2 Diabetes

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Abstract: Background/Objectives: Insulin resistance is a key factor in the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD), but accurately measuring it in patients with type 2 diabetes (T2D) remains challenging. This study examines the relationship between a recently proposed insulin resistance index and the presence of liver steatosis and fibrosis in individuals with T2D. **Methods**: This cross-sectional study utilized data from the 2017–2020 National Health and Nutrition Examination Survey. Patients with T2D who did not have chronic viral hepatitis or significant alcohol intake were included. The insulin sensitivity (IS) index was calculated using a formula incorporating body mass index, urine albumin-to-creatinine ratio, triglycerides, and gamma-glutamyl transferase. Liver stiffness and steatosis were assessed through transient elastography. MASLD was defined as a controlled attenuation parameter (CAP) of $\geq$274 decibels/meter (dB/m), while significant liver fibrosis was defined as a liver stiffness measurement (LSM) of $\geq$8 kPa. Multivariable logistic regression models, adjusted for potential confounders, were used to evaluate the association between IS and these liver outcomes. **Results**: A total of 1084 patients with T2D were analyzed. The prevalence of MASLD and significant liver fibrosis was 74.1% (95% CI 68.7–78.9) and 25.4% (95% CI 21.2–30.2), respectively. After adjusting for age, sex, waist circumference, and race/ethnicity, lower IS scores (indicating higher insulin resistance) were independently associated with increased odds of both MASLD (quartile 1 vs. quartile 4: OR 2.66, 95% CI 1.23–5.71) and significant liver fibrosis (quartile 1 vs. quartile 4: OR 3.30, 95% CI 1.45–7.51). These findings remained consistent across subgroups stratified by age, sex, and obesity status. **Conclusions**: This novel IS model, derived from commonly available clinical and biochemical markers, is independently associated with liver steatosis and fibrosis. Its application may help identify patients with more advanced MASLD, facilitating early intervention and risk stratification.

Keywords: insulin resistance; MASLD; fibrosis; fibroscan

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) represents by far the most common chronic liver disorder worldwide, with a prevalence of approximately 33% among adults [1] and 10% among children and adolescents [2]. Its prevalence increased in recent decades, in parallel with the increase in obesity and diabetes rates [3]. While the absolute risk of dying from liver-related events for the overall MASLD population is relatively low compared to the competing risks of cardiovascular disease and cancer, its extremely high prevalence made it one of the most common causes of end-stage liver disease, liver mortality and liver transplantation [4].

It is well known that, apart from genetically determined forms of the condition [5], MASLD is strictly related to insulin resistance [6] and some authors consider it the hepatic manifestation of the metabolic syndrome [7,8]. This is also supported by the finding of a much higher prevalence among patients with severe obesity and type 2 diabetes (T2D) [9,10]. Recent studies have also shown that insulin resistance does not only play a role in MASLD development but also in its progression towards more advanced histologic lesions such as steatohepatitis (MASH) and advanced liver fibrosis [11]. Fibrosis in particular represents the feature that best predicts future development of cirrhosis and clinically significant liver-related events such as decompensation and mortality [12,13]. While the association between insulin resistance and MASLD/fibrosis has been studied in several pathophysiologic studies, its assessment in clinical practice is rarely performed, as gold-standard measures of both insulin sensitivity (the euglycemic hyperinsulinemic clamp) and liver fibrosis (liver biopsy) require time-consuming and invasive techniques [14–16]. Among noninvasive alternatives for assessing fibrosis, vibration-controlled transient elastography (VCTE) has gained popularity due to its ease of use, a high degree of validation in different populations and underlying liver disorders and good performance [17]. Furthermore, we recently proposed a new index of insulin sensitivity (IS) specifically developed for patients with T2D based on readily available clinical and laboratory features that is also associated with mortality outcomes [18].

Based on these pieces of evidence, the aim of the present study is to evaluate the association between IS and MASLD/liver fibrosis in a large and unselected population of patients with T2D using noninvasive measures. To achieve this goal, we used data from the 2017–2020 cycle of the National Health and Nutrition Examination Survey (NHANES).

2. Materials and Methods

The current analysis utilizes publicly available data obtained from the National Center for Health Statistics. This analysis is based on the 2017–2020 NHANES cycles, a comprehensive U.S. survey conducted by the National Center for Health Statistics. NHANES is an ongoing cross-sectional study designed to include non-institutionalized individuals of all ages from the general population. Detailed data collection methods are available elsewhere [19,20]. The original survey was approved by the CDC Research Ethics Review Board, with written informed consent obtained from all adult participants. Since this study uses a fully de-identified dataset, we did not seek further approval from our institution. The coronavirus disease 2019 pandemic required suspension of the NHANES 2019–2020 field operations in March 2020. Therefore, the partial 2019–2020 data were combined with the full dataset from the previous cycle (2017–2018) to create nationally representative 2017–March 2020 pre-pandemic data files. All analyses reported in this study were performed according to specific guidance from the National Center for Health Statistics (NCHS) [21].

2.1. Clinical and Laboratory Data

Participants self-reported their age, sex, race/ethnicity (classified as non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian, or other), education level, smoking history, and medical background. Additionally, body measurements were taken during the Mobile Examination Center (MEC) visit.

Trained physicians measured blood pressure using a mercury sphygmomanometer with an appropriately sized cuff. After a 5 min seated rest, three consecutive readings were obtained via the auscultatory method, and their average was used for systolic and diastolic values. Hypertension was defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg or the use of antihypertensive medication [22]. The remaining participants were classified into three groups based on European Society of Cardiology guidelines [23].

Methods for measuring total cholesterol, HDL cholesterol, ALT, AST, GGT, platelet count, and albumin are detailed elsewhere [24]. Hepatitis C infection was identified through viral RNA detection and/or a confirmed antibody test, while hepatitis B was confirmed by a positive surface antigen test [24]. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation [25], with chronic kidney disease (CKD) defined as eGFR < 60 mL/min/1.73 m^2. Alcohol consumption, based on self-reported intake over the past year, was considered significant if exceeding 30 g/day for men and 20 g/day for women [26]. Participants were classified as having diabetes if they responded affirmatively to the question, "Other than during pregnancy, have you ever been informed by a doctor or health professional that you have diabetes or sugar diabetes?" Additionally, individuals were considered to have diabetes if they met at least two of the following criteria: HbA1c level of $\geq$6.5%, random plasma glucose level of $\geq$200 mg/dL, or fasting plasma glucose level of $\geq$126 mg/dL [27]. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel criteria [28] if at least three of the following criteria were met: (1) fasting plasma glucose $\geq$ 100 mg/dL or drug treatment for elevated blood glucose; (2) HDL cholesterol < 40 mg/dL in men and <50 mg/dL in women or drug treatment for low HDL cholesterol; (3) triglycerides $\geq$ 150 mg/dL or drug treatment for elevated triglycerides; (4) waist circumference $\geq$ 102 cm in men and $\geq$ 88 cm in women; (5) blood pressure values $\geq$ 130/85 mmHg or drug treatment for hypertension.

2.2. Identification of Liver Steatosis and Fibrosis

In the 2017–2020 cycles, vibration-controlled transient elastography (VCTE) was performed by NHANES technicians after a 2-day training program with an expert technician, using the FibroScan® model 502 V2 Touch (Echosens, Paris, France) equipped with medium (M) and extra-large (XL) probes. The M probe was used initially unless the machine indicated use of the XL probe. Inter-rater reliability between health technicians and expert FibroScan® technicians (tested on 32 subjects) was 0.86 for stiffness (mean difference 0.44 $\pm$ 1.3 KPa) and 0.94 for CAP (mean difference 4.5 $\pm$ 19.8 db/m). Exams were considered reliable only if at least 10 liver stiffness measurements (LSM) were obtained after a fasting time of at least 3 h, with an interquartile (IQRe) range/median < 30%. Median controlled attenuation parameter (CAP) values $\geq$ 274 dB/m were considered indicative of steatosis in accordance with a recent study by Eddowes et al. [29]. A median LSM $\geq$ 8.0 KPa was considered indicative of significant ($\geq$F2) fibrosis [30].

2.3. Assessment of Insulin Sensitivity

Insulin sensitivity was assessed in the present study using an index that we recently developed [18]. Briefly, it was aimed at estimating insulin resistance in patients with T2D, a population of patients in which traditional indexes such as HOMA-IR and QUICKI perform in a suboptimal fashion. It was derived in a population of 140 Italian patients with T2D as

a proxy for the total body glucose disposal rate (GDR, mg kg^{-1} min^{-1}) measured by the euglycemic hyperinsulinemic clamp technique. It correlated well with the measured GDR in both the derivation and validation cohorts (r = 0.77 and 0.74, respectively), and it was independently associated with all-cause and cardiovascular mortality in a US cohort. The formula used to calculate it is the following: $\log_e$GDR = 5.3505 − 0.3697 × log(GGT, IU/L) − 0.2591 × log(triglycerides, mg/dL) − 0.1169 × log(UACR, mg/g) − (0.0279 × BMI, kg/m^2). We also applied the eGDR formula proposed by Williams et al. [31].

In the present study, patients were categorized in quartiles of IS for statistical analyses. We also calculated another score of insulin sensitivity known as the Quantitative Insulin Sensitivity Check Index (QUICKI) as proposed by Katz et al. [32], who showed that by taking both the logarithm and the reciprocal of the insulin-glucose product, one can improve the correlation with the gold-standard insulin clamp.

2.4. Statistical Analyses

All analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA), incorporating the complex NHANES design. Weighting was applied as recommended by the NCHS to ensure estimates are representative of the U.S. adult population. Data are presented as weighted proportions (standard error [SE]) for categorical variables and weighted means (SE) for continuous variables. Differences in participant characteristics based on the presence of MAFLD and IS quartiles were assessed using linear regression for continuous variables and the design-adjusted Rao–Scott chi-square test for categorical variables. Multivariable logistic regression analysis was performed to evaluate the association between IS and both MASLD and liver fibrosis. Confounders included in the model were age, sex, waist circumference and race–ethnicity. The IS score was split into quartiles, with patients in Q4 (the most insulin-sensitive) serving as the reference group. Multicollinearity was tested by calculating the variance inflation factor (VIF). We found no significant collinearity (VIF $\geq$ 2) between the variables included in our model. A two-tailed value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Analysis Sample

Among a total of 9232 participants older than 20 years, 8544 attended a mobile examination center visit. We initially excluded 6966 individuals without T2D. Among the remaining 1578 patients with T2D, 264 did not have a complete VCTE examination, while 148 were excluded because of significant alcohol consumption or viral hepatitis. Furthermore, after the exclusion of 82 patients without data to calculate the IS index, the final sample consisted of 1084 patients with complete data.

3.2. Features of the Study Population

Clinical and laboratory features of the overall population as well as according to the presence or absence of MASLD are shown in Table 1. 746 participants had CAP $\geq$ 274 dB/m (weighted prevalence 74.1%, 95% CI 68.7–78.9). Participants with MASLD were significantly younger, more frequently Hispanic, had a higher BMI, higher SBP, worse glycemic control, higher liver enzyme and triglyceride levels and a lower HDL level. No significant differences were present in sex, prevalence of CKD and CVD and cigarette smoke. Finally, patients with MASLD had lower IS (i.e., they were more insulin resistant) and a higher prevalence of significant liver fibrosis.

Table 1. Features of the study participants segregated by the presence or absence of MASLD.

	Total	**CAP < 274 dB/m**	**CAP ≥ 274 dB/m**	***p*-Val**
N	1084	338	746	
Age (years)	60.7 (0.9)	63.3 (1.4)	59.5 (1.0)	0.002
Females (%)	45.6 (2.4)	48.8 (5.6)	44.5 (2.9)	0.525
Race–ethnicity				0.001
NHW	57.7 (3.7)	54.5 (3.1)	58.8 (4.3)	
Hispanic	16.9 (2)	14.3 (2.2)	17.8 (2.3)	
NHB	13 (2.1)	20.2 (2.9)	10.5 (1.9)	
Other	12.4 (1.4)	11 (1.7)	12.9 (1.8)	
BMI (Kg/m^2)	33.5 (0.3)	29.2 (0.5)	34.8 (0.5)	<0.001
SBP (mmHg)	128.0 (0.9)	133.8 (1.7)	126.3 (1.1)	<0.001
DBP (mmHg)	74.6 (0.6)	74.8 (1.2)	74.9 (0.7)	0.860
Diabetes duration (years)	9.4 (0.4)	10.6 (0.8)	8.8 (0.6)	0.099
HbA1c (%)	7.3 (0.1)	7.1 (0.1)	7.4 (0.1)	<0.001
AST (IU/L)	21.9 (0.6)	19.1 (0.8)	22.5 (0.5)	0.003
ALT (IU/L)	24.7 (0.8)	18.1 (1.0)	26.8 (1.0)	<0.001
GGT (IU/L)	36.1 (1.0)	28.8 (2.3)	38.5 (1.1)	0.002
Total cholesterol (mg/dL)	177.7 (2.4)	175.4 (3.8)	178.5 (2.8)	0.426
Triglycerides (mg/dL)	192.1 (7.5)	146.9 (4.9)	208.3 (9.9)	<0.001
HDL cholesterol (mg/dL)	45.8 (0.5)	50.6 (1.2)	44.3 (0.6)	<0.001
UACR (mg/g)	108.2 (12.9)	115.1 (14.6)	93.9 (14.7)	0.325
Cigarette smoke (%)				0.438
Never	52.9 (2.6)	52.5 (4)	53 (3.3)	
Past	34.1 (2.2)	31.6 (4)	35 (3.2)	
Current	13 (1.5)	15.9 (2.4)	12.1 (1.5)	
Metabolic syndrome (%)	84.9 (2.1)	66.4 (5.3)	91.2 (8.8)	<0.001
CKD (%)	16.8 (1.8)	20.5 (3.2)	15.6 (1.9)	0.133
CVD (%)	22.3 (1.9)	21.5 (4.2)	22.6 (2.3)	0.839
LSM > 8 kPa	26.6 (2.2)	9.2 (1.5)	32.6 (2.7)	<0.001
QUICKI	0.30 (<0.1)	0.32 (<0.1)	0.29 (<0.1)	0.001
Insulin sensitivity (%)				<0.001
Q1	27.6 (2.4)	8.5 (1.8)	34.2 (2.7)	
Q2	22.5 (2.3)	17.2 (2)	24.3 (3)	
Q3	26.4 (2.3)	32.7 (3.5)	24.2 (2.7)	
Q4	23.5 (1.8)	41.6 (3.7)	17.3 (2.4)	
Diabetes drugs (%)	71.6 (1.7)	71 (3.9)	71.7 (1.9)	0.873
ACE-i/ARBs (%)	57.0 (2.7)	55.9 (4.7)	57.3 (2.6)	0.749
Beta-blockers (%)	28.8 (2.0)	27.0 (3.9)	29.4 (2.6)	0.648
Statins (%)	52.9 (3.3)	53.9 (4.3)	52.6 (3.9)	0.811

Data are weighted proportions for categorical variables and weighted means for continuous variables. For abbreviations, see the main text. Data shown in parentheses are standard errors.

Clinical and laboratory features of the studied population according to quartiles of IS are shown in Table 2. Participants with a lower IS (i.e., more insulin resistant, quartile 1) were significantly younger, had higher BMI and DBP, HbA1c levels, higher liver enzymes, a worse lipid profile and a much higher prevalence of both MASLD and significant liver fibrosis. Conversely, no significant differences were present in sex, race–ethnicity, cigarette smoke and comorbidities such as CKD and CVD.

Table 2. Features of the study participants segregated by quartiles of estimated insulin sensitivity.

	Q1	Q2	Q3	Q4	*p*-Val
N	271	271	271	271	
Age (years)	56.4 (1.3)	59.5 (1.4)	63.3 (0.6)	63.9 (1.4)	<0.001
Females (%)	41.3 (5.2)	47.6 (5.5)	48.9 (3.8)	45.5 (6.4)	0.707
Race–ethnicity (%)					0.129
NHW	61.9 (5)	51.4 (5.8)	64 (4.3)	55.7 (5.6)	
Hispanic	17.5 (3)	21.7 (2.8)	13.3 (2.4)	13.9 (3)	
NHB	11.7 (2.5)	15 (3.1)	12 (1.9)	13.5 (2.3)	
Other	9 (2)	11.9 (2.1)	10.6 (2.3)	16.9 (3.4)	
BMI (Kg/m^2)	39.1 (0.6)	34.4 (0.5)	31.9 (0.4)	27.6 (0.3)	<0.001
SBP (mmHg)	128.3 (1.7)	126.1 (1.9)	128.1 (1.3)	129.3 (1.7)	0.730
DBP (mmHg)	78.0 (1.1)	74.9 (0.9)	73.3 (1.0)	71.9 (1.3)	0.002
Diabetes duration (years)	8.2 (0.8)	9.0 (0.7)	9.8 (0.9)	10.7 (0.7)	0.043
HbA1c (%)	7.7 (0.1)	7.5 (0.2)	7.0 (0.1)	7.0 (0.1)	<0.001
AST (IU/L)	27.8 (1.5)	21.0 (1.1)	19.4 (1.2)	18.4 (0.5)	<0.001
ALT (IU/L)	35.2 (2.0)	24.1 (1.5)	20.1 (1.3)	17.9 (0.8)	<0.001
GGT (IU/L)	66.1 (4.0)	32.8 (0.9)	24.7 (1.1)	16.4 (0.6)	<0.001
Total cholesterol (mg/dL)	188.7 (4.1)	179.4 (3.7)	179.2 (3.9)	161.1 (5.2)	<0.001
Triglycerides (mg/dL)	267.3 (20.8)	213.5 (10.2)	159.5 (4.9)	119.0 (7.5)	<0.001
HDL cholesterol (mg/dL)	41.3 (0.7)	43.6 (1.2)	47.4 (0.8)	51.6 (1.5)	<0.001
UACR (mg/g)	290.8 (43.3)	59.7 (8.4)	35.3 (7.2)	21.1 (6.9)	<0.001
Metabolic syndrome (%)	96.8 (1.3)	94.3 (5.7)	85.5 (4.4)	61.9 (5.3)	<0.001
Cigarette smoke (%)					0.123
Never	43.2 (3.8)	47.5 (3.9)	59.3 (5.6)	60.1 (5.6)	
Past	42.6 (4)	38.4 (4.1)	30.5 (5.9)	26.4 (4.6)	
Current	14.2 (2.6)	14.1 (3.2)	10.2 (2.3)	13.4 (3.7)	
CKD (%)	17.2 (3.3)	17.4 (3.7)	17.4 (3.1)	17 (3.9)	1.000
CVD (%)	21.5 (3.3)	24.7 (3)	29.4 (5.7)	23.8 (3.9)	0.516
CAP > 274 dB/m (%)	92.1 (1.2)	80.4 (2.4)	68.3 (4.6)	54.7 (5.9)	<0.001
LSM > 8 kPa (%)	49.5 (3.8)	26.8 (4.1)	18.6 (3.2)	8.5 (2.9)	<0.001
QUICKI	0.28 (<0.1)	0.29 (<0.1)	0.31 (<0.1)	0.32(<0.1)	<0.001

Data are weighted proportions for categorical variables and weighted means for continuous variables. For abbreviations, see the main text. Data shown in parentheses are standard errors.

3.3. Association Between IS and MASLD/Liver Fibrosis

Figure 1 shows the results of a multivariable logistic regression model evaluating the association between included variables and the presence of MASLD and significant liver fibrosis (the outcome variables). As shown in the left panel, a higher waist circumference, non-Hispanic Asian ethnicity and a lower degree of IS (quartile 1 vs. quartile 4: OR 2.66, 95% CI 1.23–5.71) were associated with a higher prevalence of MASLD, while non-Hispanic Black participants were relatively protected from this outcome. Moreover, as shown in the right panel, a higher waist circumference and a lower degree of IS (quartile 1 vs. quartile 4: OR 3.30, 95% CI 1.45–7.51) were associated with a higher prevalence of significant liver fibrosis, while non-Hispanic Black participants were relatively protected from this outcome.

To evaluate the robustness of our findings, we performed subgroup analyses evaluating the association of IS with significant liver fibrosis. Results are depicted in Figure 2. As shown, lower IS was significantly associated with a higher prevalence of significant liver fibrosis independently of age (below or above 60 years), sex, and presence or absence of obesity. The numerosity of the subgroups was as follows: 578 males and 506 females, 439 non-obese and 645 obese participants, 423 participants younger than 60 and 661 older than 60.

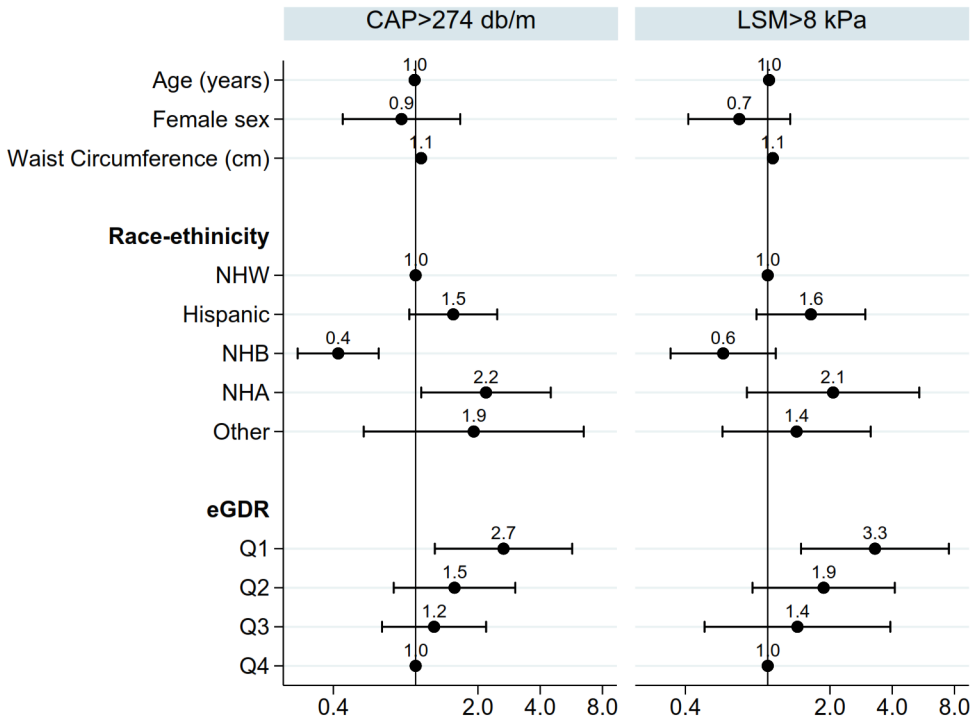

Figure 1. Multivariable logistic regression model showing odds ratios and 95% confidence intervals for both elevated controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) in the studied population. Abbreviations: NHW, non-Hispanic white; NHB, non-Hispanic Black; NHA, non-Hispanic Asian; eGDR, estimated glucose disposal rate.

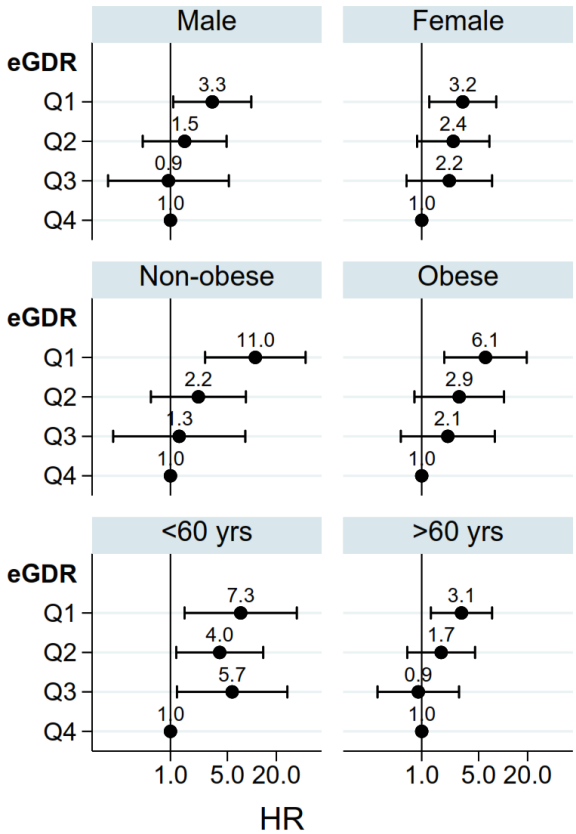

Figure 2. Odds ratios and 95% confidence intervals for elevated controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) in subgroups of the studied population.

Estimates were obtained with a multivariable logistic regression model adjusted for age, sex, race–ethnicity and waist circumference. Abbreviations: NHW, non-Hispanic white; NHB, non-Hispanic Black; NHA, non-Hispanic Asian; eGDR, estimated glucose disposal rate.

Finally, we found a good degree of correlation between eGDR and QUICKI (r = 0.503, $p < 0.001$), while we found no significant association between the eGDR estimated through the formula proposed by Williams et al. and both liver steatosis and fibrosis after adjustment for body weight.

4. Discussion

In this cross-sectional study conducted on a large and representative sample of patients with T2D from the United States population, several noteworthy findings emerged. Firstly, we confirmed a strikingly high prevalence of MASLD (~75%) and significant liver fibrosis (~25%) in this patient population. Secondly, our study revealed that a lower degree of IS estimated through a readily available score was associated with a higher prevalence not only of MASLD itself but also of significant liver fibrosis independently of potential confounders. Thirdly, the association was robust, and results were maintained when analyses were stratified according to age, sex and obesity.

The strict association between the degree of IS and liver steatosis and fibrosis is supported by several pieces of evidence. In a recent large epidemiologic study, the authors applied the cluster analysis suggested by Ahlqvist et al. [33] to patients newly diagnosed with T2D that were accurately phenotyped according to intrahepatic fat content and IS measured using the hyperinsulinemic clamp technique. It was shown that patients in the severe insulin resistance diabetes (SIRD) cluster (characterized by the lowest GDR) had the highest liver fat content, higher levels of triglycerides and a higher NAFLD fibrosis score (a non-invasive biomarker of liver fibrosis) [34]. These results are in line with our data. It should be stressed that in our study, 9 out of 10 patients in the lower IS quartile had elastographic evidence of steatosis, and, more importantly, half of them had an elevated LSM, indicative of potential significant liver fibrosis. In this sense, the IS score might be used not only to estimate the degree of IS and therefore potentially identify patients that might benefit from insulin-sensitizing agents, but also to help in the identification of patients with more severe forms of MASLD. A recent study performed in the NHANES population showed that a different score of insulin resistance, which was derived in a small cohort of patients with type 1 diabetes, was also associated with MASLD [35]. Our study differs as our biomarkers were derived in a larger population of patients with T2D and applied to a similar population, rather than to the general US population. Moreover, when we applied the mentioned biomarker in our population sample, it was not associated with either liver steatosis or fibrosis after adjustment for waist circumference. We speculate that the authors reported a significant association, which was not driven by insulin sensitivity itself but by BMI.

Recent guidelines recognize patients with T2D as a population that is particularly vulnerable from a liver-related standpoint and suggest active screening by the combined use of blood-based biomarkers (such as FIB-4) and VCTE for risk stratification [36,37]. Nonetheless, concordance between these biomarkers was shown to be frequently low, and the identification of new cost-effective strategies is still an unmet need in the field. Our data, although preliminary, suggest the use of the IS score as a potential first step to guide successive screening. Nonetheless, results need confirmation in other populations and in larger studies before a translation to clinical practice may be suggested.

Our study has several key strengths. It is a large-scale investigation involving a diverse U.S. adult population, representing different genders and ethnic backgrounds. The

substantial sample size provided strong statistical power, allowing for subgroup analyses and comprehensive multivariable assessments. Utilizing NHANES data enhances external validity, as the survey is designed to reflect the broader U.S. population. Moreover, clinical, laboratory, and anthropometric data were collected using standardized protocols, ensuring consistency and reliability.

Nonetheless, it is important to acknowledge several limitations. Firstly, the cross-sectional nature of our study does not allow us to evaluate temporal trends and therefore prove the existence of cause–effect relationships. Moreover, more detailed measurements of potential confounding factors such as physical activity, macronutrient intake and body fat distribution could not be retrieved in the NHANES database. Secondly, even though VCTE has been widely validated as an accurate measure of liver fibrosis, it cannot be considered a gold standard technique, as its performance is reduced in severely obese patients and in the setting of ascites, acute inflammation and congestion [38]. It should be stressed, however, that liver biopsy (the gold standard technique) is an invasive procedure, prone to both sampling variability and bleeding episodes, and therefore not applicable to a large population-based study [14,39]. Thirdly, certain variables such as smoking, alcohol use, and prevalent cardiovascular disease relied solely on self-reporting by participants. It is conceivable that some individuals were unaware of their condition.

Fourthly, while we excluded participants with significant alcohol consumption and viral hepatitis, data on less common liver disorders such as autoimmune liver diseases, hemochromatosis or drug-induced liver injury were not available. One can speculate that, given the general population setting in which the study took place, the number of individuals affected by these conditions is likely to be low and not compromise the overall findings.

5. Conclusions

In conclusion, our study shows that an IS score based on data that are routinely collected in diabetes clinics, as their measurement is recommended by clinical practice guidelines, is independently associated with both MASLD and significant liver fibrosis. These results, along with those related to its association with long-term mortality outcomes, make it a potentially useful tool to measure in clinical practice for both diagnostic and prognostic purposes.

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Informed Consent Statement: Written informed consent was obtained from all adult participants.

Data Availability Statement: The data that support the findings of this study are publicly available from the CDC website: https://wwwn.cdc.gov/nchs/nhanes/default.aspx (access on 10 April 2024).

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