Lipoprotein Insulin Resistance Index Reflects Liver Fat Content in Patients With Nonalcoholic Fatty Liver Disease

Anusha Vittal,[1] Mark Shapses,[1] Bashar Sharma,[1,2] Disha Sharma,[1] Qian Sun,[3] Maureen Sampson,[3] Wilson Lee (ID) ,[1,4] Gil Ben Yakov (ID) ,[1] and Yaron Rotman (ID) [1]

The recently developed lipoprotein insulin resistance index (LP-IR) incorporates lipoprotein particle numbers and sizes and is considered to reflect both hepatic and peripheral IR. As tissue IR is a strong component of nonalcoholic fatty liver disease (NAFLD) pathogenesis, we aimed to assess the degree by which LP-IR associates with hepatic fat content. This was a single-center retrospective analysis of patients with NAFLD. LP-IR, the homeostasis model assessment of insulin resistance (HOMA-IR), and adipose tissue IR (Adipo-IR) were measured simultaneously. Liver fat content was estimated by FibroScan controlled attenuated parameter. Associations were assessed using Spearman's correlation and multivariate linear regression. The study included 61 patients. LP-IR was correlated with HOMA-IR (ρ = 0.30; P = 0.02), typically thought to reflect hepatic IR, but not with Adipo-IR (ρ = 0.15; P = 0.25). Liver fat content was significantly associated with Adipo-IR (ρ = 0.48; P < 0.001), LP-IR (ρ = 0.35; P = 0.005), and to a lesser degree with HOMA-IR (ρ = 0.25; P = 0.051). The association of liver fat with LP-IR was limited to patients without diabetes (ρ = 0.60; P < 0.0001), whereas no association was seen in those with diabetes. In a multivariate model, Adipo-IR, LP-IR, and diabetes were independently associated with liver fat and together explained 35% of the variability in liver fat. *Conclusion:* LP-IR is a reasonable measure of IR in non-diabetic patients with NAFLD and is associated with hepatic fat content. Although adipose tissue is the major contributor to liver fat, the additional contribution of nonadipose tissues can be easily estimated using LP-IR. (*Hepatology Communications* 2021;5:589-597).

Nonalcoholic fatty liver disease (NAFLD), the excess accumulation of triglycerides in the liver, is strongly associated with insulin resistance (IR).[1-5] Insulin action differs between target tissues (such as liver, adipose tissue, or muscle),[6-8] all of which may contribute to hepatic fat accumulation.[9] Importantly, muscle and liver IR lead to hyperinsulinemia and hyperglycemia, important drivers of hepatic *de novo* lipogenesis (DNL).[10-12] In addition, adipose tissue IR leads to persistent lipolysis and free fatty acid (FFA) release from the adipose tissue and excess availability of FFA to the liver.[2,13] In NAFLD, the sources of hepatic fat are adipose tissue (59%), DNL (26%), and dietary intake (15%)[9]; therefore, IR-associated processes contribute the majority of fat. IR is not distributed equally among tissues[5]; hence, the extent to which each tissue contributes to NAFLD varies. For example, Bril et al.[14] found that

Adipo-IR had a stronger association with intrahepatic triglyceride content (IHTC) compared to hepatic IR.

Although clamp and tracer studies are considered the gold standard for measuring IR,[15-17] IR is more commonly estimated using fasting serum-based indices.[18] The homeostatic model assessment of insulin resistance (HOMA-IR)[19] is the most commonly used IR index. HOMA-IR uses fasting serum glucose and insulin levels to estimate insulin sensitivity and pancreatic beta-cell function and primarily reflects hepatic IR.[20] Adipo-IR, the product of serum fasting FFA and insulin, reflects adipose tissue insulin sensitivity.[21] These indices have recently come under scrutiny, however, as it was shown that NAFLD is associated with impaired hepatic insulin clearance.[22] As a result, serum insulin levels may not accurately represent hepatic insulin exposure. Furthermore, fasting insulin levels are highly variable, even within an individual, and can introduce significant variability.[23]

The lipoprotein insulin resistance index (LP-IR) is a newly described IR index. Its calculation is based on nuclear magnetic resonance (NMR) spectroscopy-derived measures of lipoprotein particle size and quantity.[24] It was derived in a large cohort study of predominantly non-diabetic subjects and was found to be correlated with HOMA-IR and to be a predictor of incident diabetes.[25] Importantly, measured insulin is not included in the LP-IR calculation. Although not formally defined, LP-IR is believed to provide a systemic estimation of IR, reflecting the contributions of both hepatic and peripheral tissue insulin sensitivity.

In NAFLD, alterations in lipid homeostasis cause marked changes in the lipoprotein profile that correlate with increasing IHTC.[26] NAFLD is generally associated with increased very low-density lipoprotein (VLDL), increased LDL, and decreased high-density lipoprotein (HDL),[26] believed to result from increased FFA availability and systemic alterations in protein expression.[26,27] This promotes elevated circulating lipids and dyslipidemia as in metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease.[2,4,28,29] To date, the degree to which LP-IR and its subcomponents correlate with hepatic steatosis, the hallmark of NAFLD pathophysiology, has not been assessed.

We aimed to evaluate the applicability of LP-IR to assess IR in patients with NAFLD and to determine whether LP-IR and other IR indices associate with liver fat content. Our data provide insight into the relative involvement of different tissues in NAFLD pathogenesis and lends evidence to our understanding of the relationship between lipoprotein metabolism and NAFLD development.

Participants and Methods

STUDY DESIGN AND SUBJECTS

This was a single-center retrospective study of subjects with NAFLD who were seen at the Liver Clinic of the National Institutes of Health (NIH) Clinical Center between January 2016 and December 2018. All subjects with evidence of steatosis by imaging or histology were included. Exclusion criteria included uncontrolled diabetes with hemoglobin A1c (HbA1C) >8, use of insulin or other antidiabetics except metformin, decompensated cirrhosis, human

ARTICLE INFORMATION:

From the [1]Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA; [2]Department of Medicine, State University of New York Upstate Medical University, Syracuse, NY, USA; [3]Department of Laboratory Medicine, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, MD, USA; [4]Department of Medicine, Medstar Baltimore Program, Baltimore, MD, USA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Yaron Rotman, M.D., M.Sc., FAASLD
Liver and Energy Metabolism Section, Liver Diseases Branch
NIDDK, NIH
10 Center Drive, Building 10, Room 10N248C, MSC 1800

Bethesda, MD 20892-1800
E-mail: rotmany@niddk.nih.gov
Tel.: +1-301-451-6553

immunodeficiency virus infection, excessive alcohol consumption, viral hepatitis, and evidence of other chronic liver diseases. Subjects with a past history of hepatitis C who achieved sustained virologic response (SVR) with treatment were eligible if 12 months had elapsed from the day of SVR. Use of lipid-lowering medications did not exclude subjects because patients with NAFLD are very likely to require them; instead, we controlled for their use in a prespecified analysis.

Subjects were followed in a standardized manner every 3-6 months with fasting blood tests, including liver enzymes, glucose, insulin, and HbA1C and annual plasma FFA. A lipoprotein profile by NMR (see below) was performed annually. Transient elastography (TE) with measurement of controlled attenuation parameter (CAP) using the FibroScan device (Echosens) was performed routinely on all subjects, at least annually.

Subjects were enrolled in a natural history study (Clinicaltrials.gov NCT00001971), which was approved by the Institutional Review Board. All subjects provided written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

CALCULATION OF IR INDICES

Lipoprotein analysis was performed by NMR spectroscopy (NIH Clinical Center Department of Laboratory Medicine), and the LP-IR index was calculated as described.[24] Briefly, the particle size and number of VLDL, LDL, and HDL were each assigned a score, and the sum of the six scores constituted the LP-IR. Values ranged from 0 (most insulin sensitive) to 100 (most insulin resistant). HOMA-IR was calculated as fasting insulin (μU/L) × fasting glucose (mg/dL)/22.5. Adipo-IR was calculated as fasting FFA (mmol/L) × fasting insulin concentration (pmol/L). LP-IR, HOMA-IR, and Adipo-IR were calculated from results obtained simultaneously from the same blood draw.

ASSESSMENT OF LIVER FAT

Quantitative liver fat content was estimated by FibroScan CAP, performed within 3 months of LP-IR. The M or XL probe was used according to device indication. Because CAP has an upper limit of 400, we performed a sensitivity analysis limited to patients with CAP ≤390 (n = 57). Advanced fibrosis was defined by TE >10 kPa.

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION

	Entire cohort (N = 61)
Age, years	54.2 ± 13.1*
BMI, kg/m^2	31.9 ± 5.4*
Males, n (%)	36%
Race/ethnicity	
Caucasian, n (%)	26 (42.6%)
African American, n (%)	1 (4.1%)
Hispanic, n (%)	25 (40.9%)
Asian, n (%)	7 (11.4%)
Other, n (%)	2 (8.3%)
Diabetes, n (%)	24 (39%)
Advanced fibrosis, n (%)	15 (25%)
Statin use, n (%)	15 (25%)
AST, U/L	40 ± 30.7*
ALT, U/L	53 ± 56*
ALP, U/L	83 ± 25.9*
HbA1C, %	5.9 ± 0.8*
CAP, dB/m	318 ± 45.6*
TE, kPA	8.4 ± 5.8*
HOMA-IR	6.6 ± 3.6*
Adipo-IR	12 ± 9.4*
LP-IR	54.3 ± 13.4*

*Mean ± SD.
Abbreviations: BMI, body mass index; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

STATISTICAL ANALYSIS

Statistical analysis was performed using Prism version 8.1.1 (GraphPad Software, San Diego, CA) and SPSS Statistics (IBM). The Mann-Whitney test was used for two-group comparisons of continuous variables. The association of CAP with IR indices was determined using Spearman rank correlations. To assess the contributions of individual components of the LP-IR, we tested the association of each component with CAP, as well as that of modified LP-IR scores, in which one of the components was removed. Multivariate linear regression was used to model the contributions of combined IR indices to liver fat content with step-wise selection of independent variables. HOMA-IR and Adipo-IR were log transformed to decrease skewness. A two-sided $P < 0.05$ was considered statistically significant.

Results

Between January 2016 and December 2018, 93 subjects with NAFLD met the inclusion criteria, of whom

61 had available laboratory and FibroScan results (Supporting Fig. S1). Baseline characteristics are shown in Table 1. Mean CAP was 318 ± 46 dB/m with a range of 221-400 dB/m. The M and XL probes were used in 29 (47.5%) and 32 (52.5%) patients, respectively. Mean LP-IR, HOMA-IR, and Adipo-IR were 54.3 ± 13, 6.63 ± 3.56, and 12.0 ± 9.37, respectively.

Liver fat content, estimated by CAP, was significantly associated with LP-IR (ρ = 0.35; P = 0.005), Adipo-IR (ρ = 0.47; P < 0.001), and trended for association with HOMA-IR (ρ = 0.25; P = 0.051) (Fig. 1A-C). Not surprisingly, LP-IR and HOMA-IR were correlated with each other (ρ = 0.30; P = 0.018; Fig. 2A), while no association was found between LP-IR and Adipo-IR (ρ = 0.15; P = 0.24; Fig. 2B).

Adipo-IR has been validated in diabetes,[30] but LP-IR was studied predominantly in subjects without diabetes. Whether diabetes also impacts the validity of LP-IR remains unclear. Although IR is typically higher in diabetes, we noted an overlap in LP-IR values between those with and without diabetes (Supporting Fig. S2; Table 2), suggesting that LP-IR may not accurately reflect IR in individuals with diabetes. We therefore analyzed the association of LP-IR with CAP separately in the two groups. LP-IR correlated with steatosis only in subjects without diabetes (n = 37; ρ = 0.60; P < 0.001), while no correlation was seen in the diabetic group (n = 24; ρ = 0.12; P = 0.55; Fig. 3A,B). Similarly to LP-IR, the association of Adipo-IR with steatosis was limited to individuals without diabetes (ρ = 0.50; P < 0.001), while no significant correlation was seen in the diabetic group (ρ = 0.38; P = 0.06; Supporting Fig. S3A,B).

As statin use affects lipoprotein profile, we examined its impact on the association between LP-IR and CAP and found an association in subjects who did not use statins (n = 46; ρ = 0.44; P = 0.002) but not in statin users (n = 15; ρ = 0.19; P = 0.49). However, most statin users were diabetic, which may have modified the association. No subjects were using fibrates or niacin. LP-IR correlated with steatosis in subjects without advanced fibrosis (n = 46; ρ = 0.44; P = 0.002) but not in subjects with advanced fibrosis (n = 15; ρ = 0.25; P = 0.36), although this could have been affected by the small number of subjects with advanced disease. A sensitivity analysis limited to subjects with CAP <390 (n = 57) showed similar results (ρ = 0.33; P = 0.01; Supporting Fig. S4).
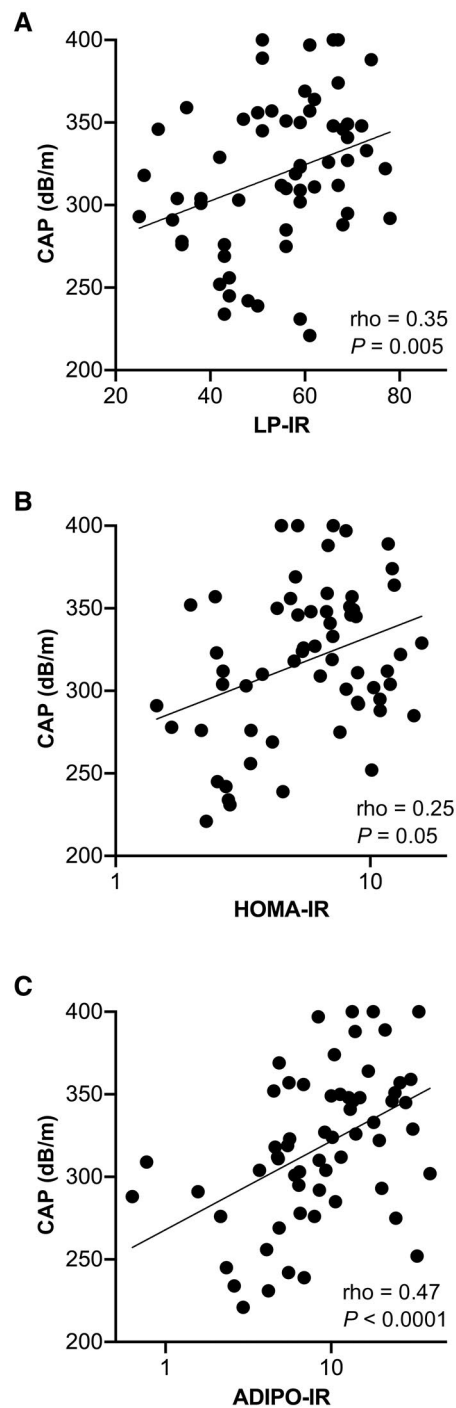

FIG. 1. Association of liver fat content with IR indices. Liver fat content measured by CAP was associated with (A) LP-IR, (B) HOMA-IR, and (C) Adipo-IR. Significance was assessed using Spearman correlation.

LP-IR is a composite score of six individual components. To determine which of the components was driving the association, we tested each component
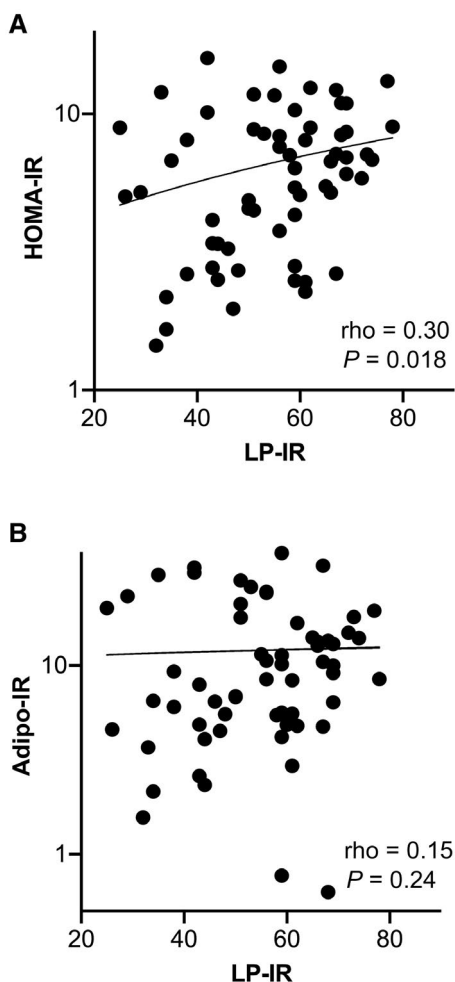
FIG. 2. Association of IR indices. Association of LP-IR with (A) HOMA-IR and (B) Adipo-IR. Significance was assessed with Spearman correlation.

TABLE 2. SUBJECT CHARACTERISTICS BY DIABETES STATUS

	With Diabetes (n = 24)	Without Diabetes (n = 37)	P Value[†]
Age, years	55.8 ± 10*	53.1 ± 14.8*	0.29
BMI, kg/m^2	6.5 ± 0.85*	31.5 ± 5.9*	0.26
Males, n (%)	7 (29.1%)	17 (40.5%)	0.42
Race			
Caucasian, n (%)	11 (45.8%)	15 (40.5%)	0.79
African American, n (%)	1 (4.1%)	0 (0%)	
Hispanic, n (%)	9 (37.5%)	16 (43%)	0.79
Asian, n (%)	1 (4.3%)	6 (16.2%)	
Other, n (%)	2 (8.3%)	0 (0%)	
Advanced fibrosis, n (%)	11 (45.8%)	4 (10.8%)	0.005
Statin use, n (%)	11 (45.8%)	4 (10.8%)	0.005
AST, U/L	42 ± 27)*	38 ± 33*	0.53
ALT, U/L	53 ± 40)*	53 ± 65*	0.95
HbA1C	6.5 ± 0.8*	5.5 ± 0.4*	0.001
CAP, dB/m	333 ± 40.5*	309 ± 46.9*	0.05
TE, kPA	10.5 ± 6.0*	7.0 ± 5.3*	0.005
HOMA-IR	8.2 ± 3.8*	5.6 ± 3.0*	0.008
Adipo-IR	13.4 ± 9.0*	11.1 ± 9.6*	0.21
LP-IR	52 ± 16.3*	56 ± 11.1*	0.36

*Mean ± SD.
[†]Mann-Whitney U for numeric values or χ^2 for proportions.
Abbreviations: BMI, body mass index; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

individually and also tested modified LP-IR scores where one lipoprotein component was left out. Of the individual components, only VLDL size (ρ = 0.31; P = 0.015) and VLDL particle number (ρ = 0.33; P = 0.01) were associated with CAP (Supporting Table S1). However, when individual components were removed, all models remained significant with similar correlation coefficients (Supporting Table S2).

To determine the combined contribution of different IR indices to liver fat content, we performed a multivariate linear regression. Based on the distinct differences between subjects with and without diabetes in association with LP-IR and steatosis, diabetes status was included in this model. A model including LP-IR, Adipo-IR, and diabetes strongly associated with CAP (R = 0.59; P < 0.001), with independent and relatively similar contributions of the three components (Table 3) and was superior to a model based on Adipo-IR and diabetes alone (R = 0.50; P = 0.005 for the difference between models). A similar model based on HOMA-IR, Adipo-IR, and diabetes was not as associated with CAP (R = 0.505; P = 0.001) and was not superior to the model using Adipo-IR and diabetes alone (P = 0.5 for the comparison between models). We performed a similar analysis limited to those without diabetes where again LP-IR and Adipo-IR were independently associated with CAP (R = 0.65; P < 0.001), and the model was superior to the association with Adipo-IR alone (R = 0.47; P = 0.001 for the difference between models). Adjustment of the analyses for advanced fibrosis and statin use did not affect model accuracy.
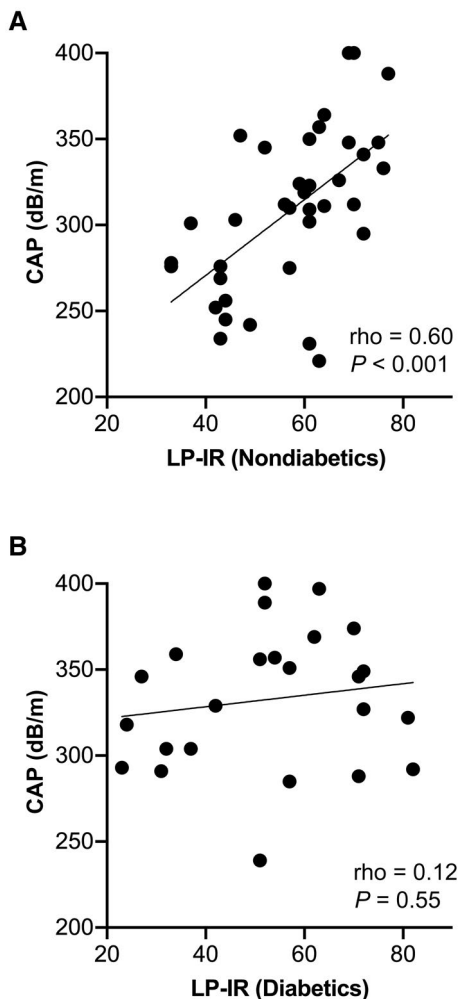
FIG. 3. Impact of diabetes. Association of liver fat content, measured by CAP, with LP-IR, assessed separately in subjects with NAFLD (A) with diabetes and (B) without diabetes. Significance assessed with Spearman correlation.

TABLE 3. MULTIVARIATE LINEAR REGRESSION FOR ASSOCIATION WITH CAP

Variable	Standardized β-coefficient	P Value
LP-IR	0.32	0.005
Adipo-IR (log)	0.39	0.001
Diabetes	0.26	0.021

Discussion

In this single-center retrospective study, we establish for the first time the utility of LP-IR in adult patients with NAFLD. We found LP-IR to correlate well with HOMA-IR, suggesting it is a reasonable measure of IR in NAFLD. We also found that LP-IR is associated with the degree of hepatic steatosis and that a model incorporating LP-IR, Adipo-IR, and diabetes strongly associates with liver fat content.

LP-IR has been validated as a measure of IR in a general nondiabetic population. However, its validity cannot be assumed in conditions that directly affect lipoprotein levels. NAFLD is known to be associated with alterations in plasma lipid species.[26,31,32] Furthermore, the kinetics of VLDL secretion and its size are closely related to liver fat content.[33,34] Therefore, it is important to validate LP-IR specifically in NAFLD. In this work, we show for the first time that in adult subjects with NAFLD, similar to the general population, LP-IR is correlated with HOMA-IR, which is typically considered a measure of hepatic insulin sensitivity.[19,35] This establishes LP-IR as an adequate measure of IR in NAFLD.

We found LP-IR to be correlated with liver fat content as estimated by CAP. The main components of the score that associated with steatosis are VLDL particle size and number, while LDL and HDL measures contribute to a lesser degree. The number and size of circulating VLDL particles reflect a balance between the kinetics of their secretion into the circulation from the liver and their extrahepatic metabolism and clearance.[34,36,37] Although VLDL secretion kinetics are associated with liver fat content, secretion reaches a plateau when IHTC is >10%.[33] Therefore, LP-IR likely represents a combination of hepatic IR and extrahepatic effects.

Interestingly, although LP-IR is associated with HOMA-IR, it shows no correlation with Adipo-IR. Given that Adipo-IR is a strong determinant of hepatic fat content,[14] we established a multivariate model incorporating LP-IR, Adipo-IR, and diabetes status. This model was strongly associated with liver fat content and demonstrates that integrating multiple organ systems involved in NAFLD is useful for understanding the pathogenesis of steatosis.

This is the first report to confirm the applicability of LP-IR as a measure of IR in NAFLD and to examine its association with liver fat content. Recently, Castillo-Leon et al.[38] evaluated the results of LP-IR testing in 76 pediatric patients with NAFLD but did not report on its association with steatosis. They identified a higher LP-IR in patients with nonalcoholic steatohepatitis (NASH) compared to those with nonalcoholic fatty liver

(NAFL), consistent with reports that effective lipo-protein synthesis is highly sensitive to hepatocellular dysfunction[27] and also with the findings of Fujita et al.[39] who found impairment in VLDL synthesis and export in patients with NASH but not in those with NAFL. They did not report on the association of LP-IR with other measures of IR or on its association with liver fat content. As the majority of the subjects in our study did not undergo liver biopsies, we could not confirm this association with NASH. Interestingly in our study, LP-IR was not associated with liver fat content in patients with advanced fibrosis, which, consistent with the results from Castillo-Leon et al.,[38] suggests LP-IR reflects multiple facets of NAFLD and not just steatosis.

Our study is significant in showing that LP-IR is a reasonable measure of IR in adult patients with NAFLD. It also highlights the contributions of periph-eral tissue IR in the development of steatosis, thereby strengthening our understanding of the systemic nature of NAFLD pathogenesis. The strengths of this study include a well-characterized patient cohort with pre-determined inclusion and exclusion criteria. CAP mea-surements, lipoprotein profile, and additional blood tests were collected prospectively on all subjects with NAFLD, minimizing selection bias. Furthermore, obtaining mea-sures for Adipo-IR, HOMA-IR, and LP-IR at the same time allowed us to compare and combine them in a reliable manner that is not always available when per-formed retrospectively. Another strength of our study is the use of CAP as a continuous rather than categorical variable in the correlation analyses.

Our study has several inherent limitations. First, we assessed liver fat content using FibroScan CAP and not by the gold standards of MR spectroscopy or pro-ton density fat fraction (PDFF).[40,41] Although CAP has imperfect sensitivity in detecting mild steatosis, it was shown to be closely and linearly associated with PDFF performed on the same day.[42] Several other studies have further demonstrated the strong correla-tion between CAP and PDFF.[43,44] Therefore, it is a useful tool in comparing the degree of liver fat con-tent among subjects. One of the limitations of CAP for fat quantitation is having a set maximal value of 400 dB/m, which limits the linearity of the assay at high-fat content. We therefore performed a sensitivity analysis limited to subjects with CAP <390 and found similar results. Second, our estimations of liver and adipose tissue IR are based on fasting HOMA-IR

and Adipo-IR, respectively, which are considered crude measurements of various types of IR and only surrogates for tissue-specific IR measurements using the gold standard of tracer and clamp studies. Third, we do not have histologic data from our patients and are unable to directly assess the association of LP-IR with histologic features. Finally, our sample size is moderate, limits the ability to perform more detailed multivariate analyses, and inherently suggests caution when interpreting subgroup analyses, such as associa-tion with diabetes or statin use.

In summary, we found LP-IR to be a reasonable measure of IR in NAFLD and demonstrated an asso-ciation between LP-IR and the degree of hepatic ste-atosis. These findings strengthen our understanding of the factors that contribute to steatosis in NAFLD and the important role peripheral tissue plays in its pathogenesis. Future studies should aim to validate these findings in a larger cohort and assess the validity of LP-IR in populations with diabetes.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1658/suppinfo.