THE RELATIONSHIP BETWEEN HEPATIC STEATOSIS, INFLAMMATION AND INSULIN RESISTANCE IN TYPE 2 DIABETES WITH METABOLIC IMBALANCE

Elena-Daniela Grigorescu[1], Mariana Floria[1,2], Cristina Mihaela Lăcătușu[1,3], Bogdan Mircea-Mihai[1,3], Ioana Crețu[1,4], Alina Delia Popa[1,3], Alina Onofriescu[1,3], Irina M. Jaba[1], Victoriția Șorodoc[1,5], Alexandr Ceasovschih[1,5], Laurențiu Șorodoc[1,5]
[1]"Grigore T. Popa" University of Medicine and Pharmacy Iași,
[2]3rd Medical Clinic, "St. Spiridon" Emergency Clinical Country Hospital Iaşi,
[3]Clinical Center for Diabetes, Nutrition and Metabolic Diseases Iași,
[4]Department Preventive Medicine and Interdisciplinarity,
[5]2nd Medical Clinic, "St. Spiridon" Emergency Clinical Hospital Iaşi
Correspondent author: Lecturer Dr. Victoriția Șorodoc, E-mail: vivisorodoc@yahoo.com

Abstract

Aim. *Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are in a bidirectional relationship. This prospective study focused on associations between parameters common to the pathogenesis of insulin resistance, inflammation and hepatic steatosis in T2DM patients with metabolic imbalance.*

Methods. *We used clinical data, insulin resistance and inflammation indices, and hepatic steatosis markers from 120 patients.*

Results. *The patients (44% men, mean age 58) had a mean body mass index (BMI) of 32 kg/m^2 and mean T2DM history of 6 years. With exceptions, significant correlations were found between metabolic, inflammatory and hepatic parameters.*

Conclusions. *In T2DM patients with poor glycemic control, hepatic steatosis correlates significantly with insulin resistance and inflammation. Increased prevalence and poor prognosis of these diseases together justify the need for NAFLD screening of diabetic patients.*

Keywords*: hepatic steatosis markers, type 2 diabetes, subclinical inflammation.*

Rezumat

Scop. *Între boala ficatului gras non-alcoolic (NAFLD) și diabetul zaharat de tip 2 (DZ2) relația este bidirecțională. În acest studiu prospectiv am analizat asocierea parametrilor căilor comune de patogeneză insulinorezistență-inflamație-steatoză hepatică la pacienții cu DZ2 dezechilibrați metabolic.*

Material și metodă. *Au fost utilizate date clinice, indici privind insulinorezistența și inflamația, respectiv markeri surogat ai steatozei hepatice de la 120 de pacienți.*

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Rezultate. *Pacienții (44% bărbați, vârsta medie 58 ani) au avut media indicelui de masă corporală de 32 kg/m² și 6 ani durata medie a DZ2. Cu excepții, observăm corelații semnificative între parametrii metabolici, inflamatori și hepatici.*

Concluzii. *La pacienții DZ2 cu control glicemic nesatisfăcător, markerii predictori ai steatozei hepatice se corelează semnificativ cu insulinorezistența și inflamația. Prevalența crescută și evoluția nefavorabilă a asocierii acestor afecțiuni justifică necesitatea screening-ului NAFLD în rândul pacienților cu diabet zaharat.*

Cuvinte cheie: *markeri hepatici ai steatozei, diabet zaharat tip 2, inflamație subclinică.*

Introduction

With a prevalence of 24% in 2018, non-alcoholic fatty liver disease (NAFLD) is contributing to the current pandemic surge of chronic illness. On one hand, NAFLD is a leading cause of liver disease in adults. On the other, its progression shares the main features of other noncommunicable diseases in the sense that it involves a wide spectrum of entities which are clinicohistopathologically distinct, from the uncomplicated hepatic steatosis to non-alcoholic steatohepatitis. These range from benign manifestations to the more severe cirrhosis and even hepatocarcinoma[1,2,3].

The scientific literature already provides several assessment models which have been proven accurate – or at least promising - in establishing the diagnosis of hepatic steatosis using markers and indices based on clinical and biological parameters. Among these are the Fatty Liver Index (FLI), the NAFLD-Liver Fatty Score (FLS), and the Hepatic Steatosis Index (HSI). Given that the liver biopsy, currently the golden standard for diagnosing NAFLD, is invasive, costly and not without risk, the question is whether such models can provide sufficient accuracy and reliability for both the diagnostic stage and the subsequent follow up of histological developments[1,4].

From the point of view of prevention, as well as for the deeper understanding of the complex patho-physiological mechanisms involved, it makes sense to suspect NAFLD in all the patients who present with metabolic risk factors such as obesity, dyslipidemia, hypertension and insulin resistance[5,6]. Moreover, the bidirectional relationship between NAFLD and type 2 diabetes mellitus (T2DM) is widely accepted, and we know that

T2DM, too, is exacerbated by the same risk factors[7].

In addition, recent research has pointed to the progression from NAFLD toward NASH in tandem with the aggravation of pre-diabetes to full blown diabetes, and this should be taken into consideration when diagnosing a diabetic patient[3]. For instance, FLI has been found a valid predictor of diabetes in pre-diabetics within as few as 3 years. In the same study, elevated FLI values (>60) indicative of hepatic steatosis were concurrently strong independent predictors for the risk of developing diabetes (HR = 4.97)[8].

In light of the above, it is of both scientific and clinical interest to assess the extent to which the parameters and indices for insulin resistance, inflammation and hepatic steatosis correlate. This prospective study aims to investigate such associations and their implications in T2DM patients who are struggling to achieve glycemic control and are in a state of metabolic imbalance.

Materials and methods

The present study employs data obtained from 120 consenting diabetic outpatients with poor glycemic control, who were treated at a Clinical Center of Diabetes, Nutrition and Metabolic Diseases over the course of 20 months during 2016-2018. Their inclusion in the study cohort was based on age (30-75), diagnosis of type 2 diabetes unsatisfactorily managed with metformin and/or sulphonylurea. Patients with a known history of atherosclerotic cardiovascular disease (myocardial infarction, angina, coronary revascularization, signs of ischemia, stroke, transient ischemic attack and peripheral arterial disease), severe liver or kidney disease, acute pancreatitis, or major chronic infection were not considered. Also excluded from the research were smokers and female patients who were pregnant or seeking to procreate. The 84 patients selected for the study group were those whose ongoing therapy schemes required supplementing with a GLP-1 receptor agonist (15 patients), a DPP-4 inhibitor (69 patients), sulfonylurea or acarbose, according to the diabetologist's clinical judgment. The other 36 patients formed the control group (30%).

After obtaining informed consent in writing, the patients were asked to fill in a questionnaire with general demographic and medical information, including their history of diabetes, treatment and comorbidities, if any. They were then examined clinically; their weight, height, waist circumference were also measured and their BMIs calculated.

To profile the patients' lipids, glycemic levels, kidney and liver functions (AST, ALT, GGT), blood samples were collected in the morning, after overnight fasting. These were immediately centrifuged for 5 min at 3 000 G to collect insulin and C-peptide data. Chemiluminiscence (IMMULITE 1000) was used on the serum stored at -20°C in order to measure hsCRP, IL-6, insulin and C-peptide levels, while Ion-exchange high-performance liquid chromatography was used to measure HbA_{1c}.

Insulin resistance was assessed using the validated formulae *HOMA-IR = (glycemia à jeun in mg/dl × insulinemia à jeun in µU/ml) / 405*, *HOMA C-peptide = (glycemia à jeun in mg/dl /18 × C-peptide × 3.003) / 22.5 and index C-peptide = 20/[(C- peptide × 3,003) × (glicemia à jeun (mg/dl)/18)]* [9]. Also, for the liver steatosis prediction markers, we calculated the Fatty Liver Index (FLI), Hepatic Steatosis Index (HSI) and Non-Alcoholic Fatty Liver Disease-Liver Fat Score (NAFLD-LFS)

using online and mobile interfaces provided by MDCalc, a well known and widely used medical reference and e-tool [10-12].

The database was compiled electronically and, apart from the general descriptive statistics, the following statistical analyses were conducted in SPSS 17.0 for Windows (SPSS Inc., Chicago): the t-test, Spearman correlations, linear regression, logistic regression and area under the ROC curve, at $p < 0.05$ statistical significance thresholds.

Results

The results hereby presented are part of initial patient assessment data collected in a still ongoing prospective research at doctoral level. The data were analyzed descriptively and comparatively, establishing the homogeneity of features across both the study and the control groups. This, then, may facilitate adequate highlighting of treatment effects onto the cardiac function and systemic chronic inflammation, as they are monitored and measured over time.

The cohort was comprised of 120 patients (of whom 44,3% men) with a mean history of T2DM of 6.04 ± 4.63 years. Their mean age was 58.16 ± 8.72, most patients (56.7%) being 50-65 years old, 20% younger than 50, and 23.3% older than 65. Also noteworthy is that 66.7% were obese and 29.2% overweight, as indicated by their mean BMI of 32.75±5.65 kg/m^2 and the mean abdominal circumference of 109,48±12.62 cm. These features are consistent with known patterns of obesity among T2DM patients worldwide.

Also, most patients had dyslipidemia and/or hypertension as pathological antecedents and comorbidities. Non-alcoholic hepatic steatosis was also noted in 15% of the cases, while only 15 patients suffered exclusively from type 2 diabetes mellitus. Treatment wise, 70% of the patients were undergoing monotherapy, of whom only 3 persons were on sulfonylurea, and the rest were taking metformin. The other 30% were prescribed a combination of oral metformin and sulfonylurea (23.3%) or metformin and acarbose.

With regard to the patients' metabolic, inflammatory and hepatic statuses, the mean values computed for the entire cohort may be summarized as follows:

- Metabolic status (including glycemic and lipid profile): glycemia = 171.60±43.24 mg/dl, HbA1c = 8.03±0.95%, total cholesterol = 195.04±47.49 mg/dl, LDL-cholesterol = 103.9±40.68 mg/dl, HDL-cholesterol = 56.97±15.09 mg/dl, triglycerides = 205.19±93.4 mg/dl, uric acid = 5.41±1.35 mg/dl
- Insulin resistance indices: HOMA-IR = 6.08±4.0, HOMA C-peptide =

Variables	Mean ± std. Dev.		p value
	Active group	Control group	
Age (years)	57.37±9.06	60±7.67	0.13
T2DM duration (years)	6.10±4.52	6.61±5.51	0.59
HbA1c (%)	8.05±0.86	7.97±1.15	0.69
Colesterol (mg/dl)	193±47.13	197.56±49.22	0.70
HDL-cholesterol (mg/dl)	55.02±14.24	61.52±16.23	**0.03**
LDL-cholesterol (mg/dl)	102.72±40.21	104.57±42.31	0.82
Triglycerides (mg/dl)	211.54±99.78	190.39±77.52	0.26
Uric acide (mg/dl)	5.39±1.43	5.46±1.18	0.79
Glycemia (mg/dl)	174.21±41.56	165.50±46.96	0.31
Insulin (µU/Ml)	15.48±9.55	11.59±6.49	**0.02**
C-peptide (ng/ml)	3.41±1.45	2.6±1.04	**0.04**
HOMA-IR	6.61±4.22	4.83±3.15	**0.02**
HOMA C-peptide	4.38±2.03	3.63±1.84	0.06
Index C-peptide	0.25±0.13	0.33±0.21	0.05
hsCRP (mg/l)	8.87±9.92	11.64±12.95	0.6
IL–6 (pg/ml)	2.88±1.88	4.58±7.78	0.82
AST (IU/L)	26.12±18.35	31.20±18.49	0.12
ALT (IU/L)	34.42±19.61	41.64±31.78	0.34
GGT (IU/L)	49±53.03	39.42±26.68	0.47
FLI	84.71±16.12	78.77±15.78	**0.01**
HSI	42.59±6.75	41.07±4.78	0.34
NAFLD-LFS	1.75±1.87	1.42±1.39	0.54

Table 1. *The baseline parameters in patients included in the study*

4.15±2.0, index C-peptide = 0.26±0.16

- Inflammation markers: on average, hsCRP = 9.69±10.49 mg/l, IL-6 = 3.39±4.57 pg/ml
- Routine liver function test results: AST = 27.64±18.46 U/L, ALT = 36.58±24.0 U/L, GGT = 46.19±46.76 U/L.
- Hepatic steatosis indices: FLI = 92.93±16.18, NAFLD-LFS = 1.65±1.74 and HSI = 42.13±6.24.

Table 1. is a summary of the baseline characteristics of the subjects included in the study and control groups. The Spearman correlation formula was employed to assess the relationship between the inflammation markers, insulin resistance and hepatic steatosis predictor markers. The results are summarized in Table 2 below.

The preliminary results with regard to the relationship between insulin resistance and inflammation in the same patients have already been presented in national congresses [13]; statistically significant correlations were noted between HOMA-IR and the inflammation markers IL-6 (r=0.22, p=0.012) and hsCRP (r=0.29, p=0.001). At the same time HOMA C-peptide correlated weakly only with hsCRP levels (r=0.22, p=0.01). We were also interested in establishing if the predictor markers for hepatic steatosis were influenced in any way by the degree of glycemic imbalance and severity of insulin resistance. The Kruskall Wallis test revealed that the difference between the average ranking for each of the 3 calculated markers reached the p <0.001 threshold of statistical significance for the degree of insulin resistance (HOMA-IR<2, 2-5, >5). This was not so when the variable used in the comparison were the degree of glycemic imbalance (HbA1c<7.5, 7.5-8, >8) (see table 3).

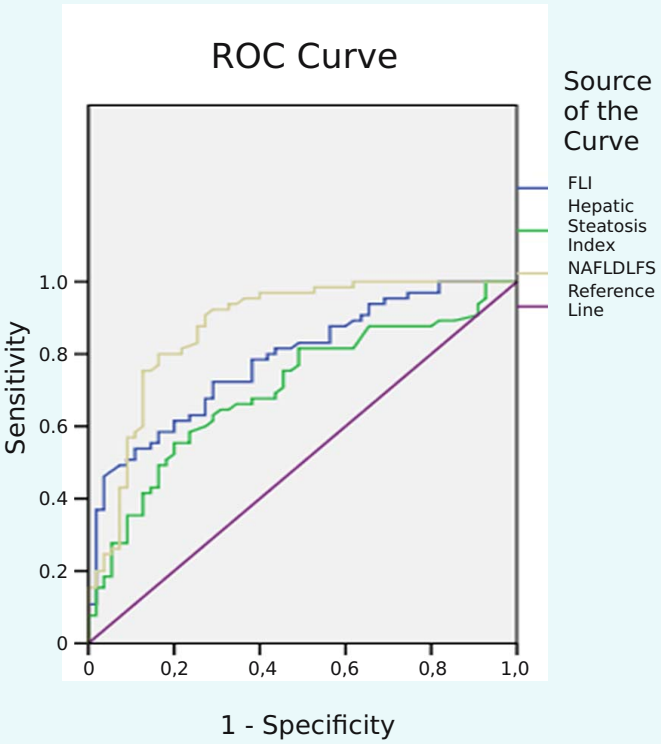

Figure 1. *AUROCs for diagnostic accuracy of severe insulin resistance*

Spearman correlations		HbA1c	IL-6	hsCRP	HOMA-IR	HOMA C-peptide	C-peptide INDEX
FLI	r	-0.04	0.19*	0.3**	0.53**	0.45**	-0.45**
	p	0.68	0.03	0.001	0.00	0.00	0.00
HSI	r	-0.08	0.18*	0.32*	0.35**	0.25*	-0.257*
	p	0.38	0.03	0.000	0.000	0.005	0.005
NAFLDLFS	r	-0.25	0.19*	0.29**	0.77**	0.55**	-0.55
	p	0.18	0.03	0.002	0.00	0.000	0.000

Table 2. *The correlations between hepatic steatosis, inflammation and insulin resistance markers*

Insulin resistance/ Glycemic control	Mean rank (Kruskall Wallis Test)					
	FLI	p	HSI	p	NAFLDLFS	p
HOMA-IR <2	27.94	<0.001	36.38	<0.001	26.27	<0.001
HOMA-IR = 2-5	48.12		52.18		37.26	
HOMA-IR >5	76.22		71.67		76.15	
HbA1c < 7.5	62.62	0.75	65.25	0.59	65.56	0.25
HbA1c = 7.5-8	61.96		58.73		54.16	
HbA1c > 8	57.30		57.91		54.93	

Table 3. *Difference of steatosis marker values depending on the insulin resistance and glycemic control*

The diagnostic performance of the indices was tested by the area under the receiver operating characteristic curve (AUROC). This showed that all three surrogate markers for hepatic steatosis also act as predictors of severe insulin resistance expressed as HOMA-IR>5.

In our study, the AUROC for FLI was 0.78 [95% CI (0.70, 0.86)]. For HSI it was 0.70 [95% CI (0.60, 0.79)], and for NAFLDLFS it was 0.87 [95% CI (0.81, 0.94].

Discussion

NAFLD is recognized as a public health problem of epidemic proportions, and its prevalence among T2DM patients reaches a staggering 56.8 – 70% [14-15]. The two medical conditions combined add to already elevated levels of cardiovascular risk in these patients. This substantiates our interest in the clinical and biological data we collected, with a view to unravelling the pathophysiological mechanisms of insulin resistance, subclinical inflammation and hepatic steatosis.

Overall, the baseline features of the patients included in our study as calculated by means of validated formulae point to metabolic imbalance, poor long-term glycemic control (HbA1c 8.03%), and substantial insulin resistance (HOMA-IR 6.08±4 and C-peptide 4,15±2; the significant difference for HOMA-IR at p=0.02 justifying incretinic therapy for the 64 patients whose values were >5). Also, regarding the lipid profile, the total cholesterol of 42.5% of patients exceeded 200 ml/dl and only 17.9% had their LDL-cholesterol under 70 ml/dl. At the same time, the triglycerides in two thirds of the patients were higher than 150 mg/dl.

The appropriate correlation formulae were selected in order to analyse any associations bearing statistical significance between the various parameters. Thus, we identified that insulin resistance levels expressed as HOMA-IR correlated significantly with the patients' HDL-cholesterol values (r=-0.24 at p=0.007). Similarly, HOMA C-peptide values correlated with the patients' triglycerides (r=0.19 at p=0.03) and with uric acid levels (r=0.28, p=0.001).

Although the coefficient points to only a weak positive correlation, it suggests that outpatients, too, may be resistant to insulin to a certain degree, even if this is not specifically measured in their case. The practical usefulness of this observation lies in providing more convincing explanations and increasing the patient's adherence to weight and lipid control measures. As a central feature of metabolic syndrome, insulin resistance accelerates multiple damaging processes (inflammation, thrombosis, oxidation) which, in turn, add to the level of cardiovascular risk [16].

The other element in the chain linking insulin resistance to cardiovascular risk is the presence of subclinical inflammation. We investigated it by assessing the serum levels of IL-6 and hsCRP, two markers of particular relevance in type 2 diabetic patients given how inflammatory cytokines alter cardiomyocytes as another form of chronic complication [17]. These intervene further by augmenting the effects of insulin resistance: the free fatty acids resulting from the activation of intracellular kinases lead to serine phosphorylation at the level of insulin receptors and, in this way, undermine the signalling pathway of insulin [18]. In light of these insights, the relationship between insulin resistance parameters and inflammatory markers fell within the scope of our analysis.

As discussed elsewhere, the degree to which our T2DM patients are subject to subtle inflammatory processes is of material clinical interest, given the wide-ranging damage that inflammation exerts on the body [19]. The hsCRP values recorded suggest that no less than 75% of the patients were at high risk of experiencing adverse cardiovascular events, as hsCRP > 3 mg/l in 88 cases and the median value of hsCRP was as high as 5.40 mg/l (interquartile range 8.92) even after excluding two extreme cases > 50 mg/l.

The patients' BMIs correlated positively with their levels of hsCRP (r=0.33, p=0.00), as well as their IL-6 values (r=0.244, p=0.007). The same trend was noted when abdominal circumference was taken into consideration (r=0.403 at p=0.00, and r=0.206 at p=0.024, respectively). This reinforces the knowledge that abdominal weight surplus leads to adipose tissue dysfunction by increasing the flow of free fatty acids in the liver, the synthesis of inflammatory cytokines and a decrease in adiponectin. The potential consequences are twofold: on one hand, insulin resistance and the onset of diabetes mellitus per se, and, on the other, a build up of fat in the liver in the form of atherogenic dyslipidemia (elevated LDL-cholesterol and triglycerides, low HDL-cholesterol) and increased oxidative stress [7].

Also, we analyzed the levels of hsCRP in conjunction with the patients' BMI and learned that inflammation levels differ significantly between patients who are normal weight and those who are overweight (1.6 mg/l versus 9.01 mg/l, p =0.01) or obese groups (1.6 mg/l versus 10.52 mg/l, p <0.01). The fact that the significance threshold was not reached when comparing overweight and obese patients (p =0.48) demonstrates that any patient with a BMI > 25 kg/m^2 is likely to develop subclinical inflammation.

The evaluation of the subclinical inflammatory status based on the mean values of the 2 markers in relation to the patients' weight status (normal, overweight, obese) indicated the only statistically significant difference in the case of hsCRP (p =0.04).

Upon subgroup analysis, as between normal weight and overweight patients, we noted that the statistical significance threshold was reached for hsCRP (1.6±0.93 mg/l vs. 9.01±11.21 mg/l, p=0.001).

This was not seen in the case of IL-6, for which p=0.3 and the mean values for the patients with normal weight compared to the overweight ones were 2±0 pg/ml vs. 3.29±2.77 pg/ml. Also, while the results for normal weight vs obese patients were significant with regard to hsCRP (1.6 vs. 10.52, p=0.00), there was no statistical significance when comparing the overweight patients with either normal weight or obese, whatever the marker taken into

consideration (p=0.81 for IL-6, and p=0.48 for hsCRP). When assessing the patients' poor glycemic control (no exceptions to HbA1c >7) in conjunction with inflammation markers, HbA1c correlated positively with hsCRP (r = 0.18, p = 0.042), but less than in other studies [20]. HbA1c also correlated with IL-6 (r=0.41, p<0.001). These findings suggest that the link between glycemic imbalance and subclinical inflammation is not necessarily a strong one, but may require additional analyses to address potential confounding factors which may diminish the strength of the relationship (e.g. years of diabetes history, other comorbidities, age, gender, treatment). Also, note should be made that our cohort was made exclusively of diabetic subjects whereas other studies included non-diabetics as well as diabetics, which might explain the difference.

The average duration of disease progression was of 7 years, which is less than recorded by others [21,22]. The patient distribution based on their T2DM evolution (<5, 5-10, >10 years) reveals that the serum levels of the studied inflammation markers did not differ significantly. Glycemic imbalance is known to aggravate the degree of subclinical inflammation. However, our analysis of patient data indicative of moderate and poor glycemic control did not yield any statistically significant differences either.

Equally interesting is the significant positive correlation between inflammation and insulin resistance. By applying the insulin resistance grading scale HOMA-IR <2, 2-5, and >5 to the inflammation results, we found that both IL-6 and hsCRP levels accurately confirmed the presence of a higher degree of insulin resistance defined as HOMA-IR >5 for 64 subjects. The AUROC was 0.63 for IL-6 (CI: 0.53-0.74; p = 0.01) and 0.68 for hsCRP (CI: 0.58-0.78; p = 0.01). Given the inhibitive costs and poor availability of some biological markers profiling the metabolism of diabetic patients, the inclusion of hsCRP in routine tests could facilitate the early identification of insulin resistance in patients with no clinical signs of inflammation, and justify the subsequent prescription of medication to address the subtle build up of insulin resistance.

The vicious cycle between inflammation and insulin resistance in diabetic patients is further augmented by hepatic steatosis. Research has shown that being at high risk of developing T2DM also multiplies the risk of NAFLD fivefold[23]. Moreover, NAFLD is not necessarily a consequence, but rather one of the factors causing the metabolic syndrome or even type 2 diabetes mellitus, worsening its progression[5]. For instance, patients suffering from both T2DM and NAFLD struggle harder to achieve satisfactory glycemic control compared to diabetic persons without NAFLD[24].

The cut-off values for the hepatic steatosis markers evaluated in our study are FLI > 60, HIS > 36 and NAFLD-LFS > -0.64. The first two were reached by 91% of the patients and the latter by 100%[10-12].

Findings reported in the literature with regard to the 3 markers predicting hepatic steatosis are promising, e.g. their association with abnormal insulin sensitiviy and secretion in 92 non-diabetics of normal weight[25], or how FLI values higher than 60 appeared to predict the risk of developing T2DM in Korean subjects monitored over a period of 2.6 years (HR = 2.84)[26]. Also, in another study enrolling type 1 diabetic patients, FLI was shown as a predictor of metabolic syndrome and liver fat content in 41 of 201 patients assessed using magnetic resonance, and in the case of those with confirmed hepatic steatosis, FLI was as high as 83.5 and HSI was 35.58[27].

The analysis of trends and patterns in our data revealed that hepatic steatosis predictor markers correlated positively with both inflammation markers and insulin resistance indices. The most significant of coefficients was that between HOMA-IR and NAFLD-LFS (r=0.77, p<0.001), possibly due to the fact that both formulae include plasma insulin values. In another study aiming to assess the performance and limitations of markers predicting hepating steatosis by comparing them with liver biopsy results in a cohort of 320 patients (of whom 41% with T2DM and 50% with metabolic syndrome), the three markers pointed reliably to the diagnosis of hepatic steatosis, but without facilitating accurate grading of severity [4]. For instance, moderate hepatic steatosis could not be told from the more severe one based on FLI and NAFLD-LFS values alone. Such a distinction, however, would be instrumental in addressing the harming effects of liver fat accumulation on the liver itself and on other organs.

With regard to the limits of research – ours as well as generally on this topic – the data featured in this study does not allow us to establish the relationship of causality in the observed associations. Predicting hepatic steatosis using the studied markers may be inexpensive and straightforward[28], but its reliability has yet to be confirmed by means of hepatic ultrasound. Although it requires specialized equipment and training, ultrasonography is currently a common method for diagnosing a fatty liver and, in addition, it allows for the semi-quantitative ultrasonographic scoring of mild, moredate and severe hepatic steatosis. For some of the 15% of patients diagnosed with hepatic steatosis in our study, this diagnosis was maintained based on prior medical records and altered transaminase levels.

Our position in favor of calculating these surrogate parameters for hepatic steatosis is also informed by situations when patients could suffer from underlying NAFLD without concurrently having abnormal levels of serum liver enzymes and/or ultrasound confirmation. Apart from screening applications, these markers could be used to research and/or diagnose hepatic steatosis (retrospectively) without having to resort to the liver ultrasound as routine examination.

Furthermore, diabetologists were proven to grossly underestimate the prevalence and severity of advanced fibrotic NAFLD in their diabetic patients (only 5% correctly chose the 50-75% interval).

Also, few reported using or intending to use non-invasive staging algorithms[29]. Such issues related to clinician perceptions and practices provide an interesting avenue for further research in conjunction with understanding the pathways by which NAFLD

contributes to chronic inflammation and insulin resistance, in order to optimally define therapeutic and preventative targets in diabetic patients with NAFLD[30].

Conclusion

A growing body of evidence helps establish NAFLD as a contributor to cardiovascular risk by increasing insulin resistance, atherogenic dyslipidemia and the release of proatherogenic mediators. Concurrently, it is becoming apparent that NAFLD diagnosis could be optimized further, since the full range of NSFLD histology has been found in patients with normal levels of aminotransferase and only mild liver dysfunction. In this context, our study highlights significant correlations between hepatic steatosis, insulin resistance and subclinical inflammation in T2DM patients with poor glycemic control. Given also the increased prevalence and unfavorable association of these conditions, our view is that the NAFLD screening of T2DM patients is necessary, as recommended in the EASL-EASD-EASO clinical guidelines from 2016.

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