ORIGINAL RESEARCH

Hepatic Steatosis Index Is Associated with Type 1 Diabetes Complications

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is associated with an increased risk of complications in type 1 diabetes (T1DM) patients. To date, several biochemical indexes of NAFLD have been developed. Among these, hepatic steatosis index (HSI) strongly relates with the results of magnetic resonance.

Aim: The aim of the present study was to evaluate the possible association between HSI and complications in T1DM.

Methods: Medical records of patients with T1DM were evaluated. Macro- and micro-vascular complications were evaluated by a combination of instrumental (ECG, carotid artery echo-Doppler, fundus examination, vibration threshold at biothesiometry) and laboratory examination. HSI was calculated based on gender, body mass index and transaminases level.

Results: Of the 124 patients evaluated, 71 were free of complications and 53 had at least one complication. The prevalence of diabetes complications was: 27% for retinopathy, 15% for carotid atherosclerosis, 16% for neuropathy. HSI was directly correlated with age, disease duration, triglycerides, total daily insulin and inversely with HDL and eGFR. In logistic regression analysis, HSI was independently associated with diabetic complications.

Conclusion: These findings show that HSI is independently associated with the presence of complications in subjects with T1DM. This can be of clinical utility, allowing a better diagnostic classification of the patient and possibly guiding the therapeutic choice.

Keywords: fatty liver, type 1 diabetes, diabetes complications

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis, in absence of other causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders.[1] NAFLD is emerging as the most common chronic liver condition in Western Countries. It encompasses a spectrum of conditions starting from fatty liver, and it can progress to cirrhosis and hepatocellular carcinoma.[2] Several studies have reported increased prevalence of NAFLD in obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM). It has recently been suggested that NAFLD is also associated with type 1 diabetes (T1DM) and diabetic complications.[3]

Ultrasonography, computed tomography and magnetic resonance are currently used to evaluate NAFLD. In fact, using ultrasonography, Targher et al have demonstrated the independent association of NAFLD with increased incidence of chronic kidney disease, increased risk of incident cardiovascular disease, and increased incidence of distal symmetric polyneuropathy in patients with T1DM.[4–6]

Imaging methods to detect the presence of fatty liver, however, are time-consuming, expensive and often unavailable in daily routine. Furthermore, using computed tomography and magnetic resonance, patients are exposed to radiation. Therefore, surrogate markers of hepatic steatosis, mainly based on laboratory tests and anthropometric measurements, have been developed.[7–9] Among these Hepatic Steatosis Index (HSI) is a composite marker, computed by combining serum transaminase levels, body mass index, gender and presence of diabetes. This marker was recently validated against magnetic resonance in patients with T1DM, showing a sensitivity of 86% and specificity of 66%.[10]

To our knowledge, the possible association between HSI and T1DM complications has not been investigated, though it might be relevant to improve the clinical setting of these patients. We have therefore designed the present study with the aim of evaluating the possible association between NAFLD, estimated through HSI, and the presence of complications in patients with T1DM.

Participants and Methods
Subjects and Study Design

The present study is a cross-sectional study, conducted by analyzing the clinical records of patients with T1DM regularly followed at the university outpatient clinic. All patients were Caucasian. Routinely, all patients receive, once a year or more frequently if indicated, a complete assessment of diabetes micro- and macro-vascular complications such as retinopathy, nephropathy, neuropathy and vascular diseases. They also undergo blood withdrawal for the measurement of fasting plasma glucose, HbA1c, lipids, and transaminase. In addition, clinical and anthropometric parameters are recorded at each visit. Patients with T1DM have a dedicated clinic, and the blood and instrumental tests are performed following precise protocols. Therefore, all the measurements were part of a routine check-up. The identity of subjects was not revealed, and an identification number was used while analyzing data. For the aim of our study, we selected records of 1 year and collected information from the last available office visit during which all procedures to detect diabetic complications were performed. This is a retrospective analysis of data routinely registered in our hospital database in compliance with EU GDPR – European Union General Data Protection Regulation, therefore it does not need additional approval of an ethics committee.

Clinical Examination

Height and weight were measured by routine methods and used to calculate body mass index (BMI), as weight (in kilograms) was divided by height (in square meters). Waist circumference was also recorded. Information about smoking habit and ongoing treatment were also available in clinical records.

Hypertension was defined as systolic/diastolic blood pressure $\geq$ 140/90 mmHg and/or the use of antihypertensive agents. Subjects who smoked regularly during the previous 12 months were classified as smokers.

Instrumental Examinations

Diabetic retinopathy was detected by fundus photography after mydriasis. Subjects were grouped according to the presence or absence of diabetic retinopathy. Retinopathy was defined as the presence of microaneurisms, hemorrhages, hard exudates, areas of revascularization, fibrous proliferation and/or laser scars.[11]

Standard ECG was performed and further cardiological examinations were done if necessary. Echo-Doppler examination of carotid arteries was performed to detect the presence of plaques or stenosis in extracranial tract of carotid arteries. The right and left common, internal and external carotid artery, and carotid bulb were studied with ultrasound in anterior, lateral and posterior approach using an echo Doppler (Philips HD 11XE, Royal Philips Electronics, the Netherlands) equipped with a 12-3-MHz linear probe. Plaque was defined as focal lesion encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-plus-media thickness (IMT) value or focal intima-plus-media thickening $\geq$ 1.5 mm. IMT was measured from the media–adventitia interface of the far wall to the intima–lumen interface of the far wall. Stenosis was defined as the presence of systolic blood flow velocity > 140 cm/s. IMT was measured offline by a dedicated software as elsewhere described.[12] Blood flow velocity was detected automatically by the instrument. Subjects were classified as with atherosclerosis if they had at least one plaque and/or stenosis in the examined carotid arteries and as without atherosclerosis if they had a normal echo-Doppler examination.

Sensorimotor polyneuropathy was defined as a combination of symptoms, signs and abnormality of nerve conduction. Based on national guidelines, abnormal nerve conduction was detected using a biothesiometer that generates vibrations in varying amplitudes. Vibration was

applied at the base of the first metatarsal, and at the distal plantar surface of great toe. Three readings in ascending and descending intensity using the staircase technique were recorded until the subject no longer feels the vibration. A threshold of 20 V is diagnostic for abnormal test.[13]

Laboratory Measurements

Fasting blood glucose (FBG) was measured by glucose-hexokines method (Roche, Basel, Switzerland), and HbA1c with a high-performance liquid chromatographer standardized and aligned to the DCCT/UKPDS (Menarini, Florence, Italy). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using the α-ketoglutarate reaction. Hepatic Steatosis Index has been calculated as: 8 x ALT/AST + BMI + 2 (if females) + 2 (if diabetes).

Serum creatinine was measured by an automated technique based on a Creatinine Jaffe` compensated method for serum and plasma (Roche Diagnostics) implemented in an autoanalyzer. All the assays were carried out according to the manufacturer's instructions. Estimated GFR was calculated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.

CKD was defined as eGFR<60 mL/min/1.73 m^2.

The presence of nephropathy was detected by urine analysis measuring the albumin/creatinine ratio. A value > 30 mg/g was used to diagnose incipient nephropathy and ≥300 mg/g overt nephropathy.[14]

Total cholesterol, HDL and LDL, and triglycerides were analyzed on Cobas 6000 (Roche Diagnostics, Basel, Switzerland), using an enzymatic (total cholesterol, HDL and LDL) or enzymatic-colorimetric (triglycerides) assay.

Statistical Analyses

Statistical analyses have been performed by PASW 18.0 (SPSS Inc., Chicago, IL, USA) for Windows. The normality of the distribution has been assessed by the Shapiro–Wilk test. Retinopathy, neuropathy, and nephropathy have been categorized into dichotomous variables (presence or absence of complication). ECG has been categorized as normal or abnormal. Carotid atherosclerosis has been defined as the presence or absence of plaque and/or stenosis. All studied continuous variables had normal distribution, except for triglycerides and disease duration. Student's *t*-test or Mann–Whitney test has been used, as appropriate, to test the differences between patients with and without complications. Pearson or Spearman correlation coefficient has been used, as appropriate, to test the

correlation between continuous variables. Logistic regression analysis has been performed to evaluate which variables were independently associated with diabetic complications. For the regression analysis, diabetic complications were grouped and used as dependent variables and all the variables that were significantly different from the *t*-test between the two groups with and without complications as independent variables. Statistical significance has been set at p<0.05 for each test.

Results

The records of 124 subjects with T1DM containing all the information needed for the present analyses were selected. Sixty-eight patients (55%) were men, and the mean age of the entire population was 37.0±11.3 years. Overall, the prevalence of diabetes complications was: 27% for retinopathy; 15% for carotid atherosclerosis; 16% for neuropathy. Positive test for microalbuminuria was found in 3 subjects. None of the subjects had IHD or chronic kidney disease. All subjects were on insulin treatment (CSII, continuous subcutaneous insulin injection or MDI multiple daily insulin injection) and only 14 were hypertensive.

In simple correlation analysis, HSI was directly correlated with age (r=0.24 p<0.01), disease duration (r=0.38 p<0.001), triglycerides (r=0.17 p=0.05), Total Daily Insulin (r=0.39 p<0.001) and inversely with HDL (r=−0.29 p<0.001) and eGFR (r=−0.22 p=0.01).

Seventy-one patients (57%) were free of complications and 53 (43%) had at least one complication. Table 1 shows clinical and biochemical characteristics of subjects divided according to the presence or absence of any diabetic complications. Subjects with complications were significantly older, with longer disease duration and higher BMI compared to subjects without complications. They also had significantly higher transaminase levels and HSI.

To further investigate the association between HSI and diabetic complications, a logistic regression analysis was performed. Presence/absence of complications was used as dependent variable, while age, eGFR, disease duration, triglycerides, BMI and HSI were entered as predictors. The result of the logistic regression analysis is reported in Table 2. As displayed, variables independently associated with diabetic complications were age, triglycerides and HSI. Since BMI is part of the formula used to calculate HSI and to avoid possible collinearity between BMI and HSI, we performed other regression analyses with and without BMI as independent variable. These results confirmed that HSI is a stronger predictor than BMI.

Table 1 Characteristics of Patients with and Without Diabetes Complications

Variable	No Complications	Any Complication	P
Number	71	53	—
Age (years)	32.0 ± 9.6	43.0 ±10.0	<0.001
Male gender (n, (%))	34 (48)	34 (64)	NS
Disease duration (years)	12.2 ± 8.3	18.3 ± 11.0	0.001*
Blood glucose (mg/dL)	165 ± 71	174 ± 75	NS
BMI (kg/m^2)	23.5 ± 3.0	26.0 ± 4.4	<0.001
GOT (UI/L)	16 ± 5	20 ± 7	0.003
GPT (UI/L)	15 ± 6	21 ± 11	0.001
Glycated hemoglobin (%)	7.5 ± 1.1	8.0 ± 1.2	NS
Glycated hemoglobin (mmol/mol)	58 ± 8	64 ± 10	NS
HSI	34.0 ± 4.2	37.0 ± 5.5	0.001
HSI > 36 (n, (%))	23 (32)	26 (49)	0.06
Hypertension (n, (%))	5 (7)	9 (16)	NS
Smokers (n (%))	13 (18)	10 (18)	NS
Total cholesterol (mg/dL)	171 ± 32	175 ± 37	NS
HDL cholesterol (mg/dL)	64 ± 17	59 ± 17	NS
LDL cholesterol (mg/dL)	94 ± 27	99 ± 33	NS
Triglycerides (mg/dL)	63 ± 33	86 ± 40	0.001*
Creatinine (mg/dL)	0.71 ± 0.14	0.78 ± 0.15	0.01
TDI (Unit/day)	36 ± 16	42 ± 19	NS
eGFR CKD-EPI (mL/min)	117 ± 15	104 ± 15	< 0.001
Retinopathy (n, (%))	—	33 (62)	N/A
Carotid Atherosclerosis (n, (%))	—	19 (35)	N/A
Neuropathy (n, (%))	—	20 (37)	N/A
Nephropathy (n, (%))	—	3 (5)	N/A
IHD (n, (%))	—	0 (0)	N/A

Note: *Mann–Whitney test.
Abbreviations: BMI, body mass index; GOT, Glutamat Oxalacetat Transaminase; GPT, Glutamat Pyruvat Transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HIS, hepatic steatosis index; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; TDI, total daily insulin.

Table 2 Logistic Regression Analysis (Variables Entered)

Variable	B	Exp (B)	95% CI	P
Age (years)	0.096	1.101	1.050–1.149	<0.001
Triglycerides (mg/dL)	0.014	1.014	1.001–1.026	0.028
HSI	0.124	1.122	1.013–1.243	0.028

Notes: Variables not entered: BMI, eGFR, disease duration.
Abbreviation: HIS, hepatic steatosis index.

Discussion

The association between hepatic steatosis and diabetes mellitus has been well known for some years and has been demonstrated in numerous studies.[15] The aim of our analysis was to verify if a marker of hepatic steatosis, of simple calculation and therefore widely usable in the common clinical practice, was associated with the presence of the most common complications of diabetes, in patients with T1DM. The findings have clearly demonstrated that the Hepatic Steatosis Index is associated with complications, independently of patients' clinical characteristics and metabolic control.

The HSI was recently developed by Lee et al as a simple screening tool for the diagnosis of NAFLD.[9] The gold standard for the diagnosis of NAFLD remains liver biopsy, but ultrasound is the most widely used instrumental examination in clinical practice.[1,16] The ultrasound examination has numerous advantages but also several limits. It is, at least in part, dependent on the operator, it is time consuming, expensive and not always readily available. HSI has the great advantage of being extremely simple to calculate, using information that is available in clinical practice. National guidelines in fact suggest measurement of transaminases at least once a year in patients with diabetes.

In literature, the data about the relationship among type 1 diabetes, diabetic complications and hepatic steatosis are

not unequivocal. For example, Petit et al did not find any association between type 1 diabetes and increased prevalence of hepatic steatosis.[17] Similar results were obtained also in other studies, demonstrating liver fat content lower in type 1 diabetes than type 2 diabetes.[18,19] In the present work, the prevalence of hepatic steatosis, defined as HSI > 36, was 37.1% in the entire population but reached 49% in subjects with complications and 32% in those without complications. This prevalence is halfway between that reported in children and in adults with T1DM. Al-Hussaini et al found liver steatosis in 21% of 106 children studied by ultrasound. They reported that liver fat accumulation associated with poor glycemic control and improved after improvement of glycemic control.[20] Another study carried out in 692 Egyptian children with T1DM reported a prevalence of 4.5% of abnormal liver hyperechogenicity and/or hepatomegaly.[21] In adults with T1DM, the reported prevalence of hepatic steatosis is higher than in children. Targher et al found hepatic steatosis, diagnosed by ultrasound, in 53.1% of the 343 adult patients with T1DM. The striking difference between adults and children could be due to the duration of diabetes and likely body weight.

Several hypotheses have been formulated to try to explain the excessive accumulation of fat in the liver of patients with T1DM. Some authors have suggested that an alteration in the synthesis of lipoproteins could predispose to the accumulation of triglycerides in the hepatocytes. In addition, the accumulation of fat in the liver could be fostered by hyperglycemia through the passage of glucose from blood to hepatocytes via GLUT2, and subsequent conversion of glucose into fat.[22] Another proposed mechanism involves atypical lipoprotein function that could be responsible for an insufficient triglyceride secretion from the liver by VLDL. Moreover, transcription factors of hepatic metabolism such as ChREBP and SREBP-1c are activated by hyperglycemia and promote hepatic lipogenesis.[22] However, regardless of the pathogenic mechanisms, hepatic steatosis when present is associated with poor metabolic control and chronic diabetes complications.[4,6] The findings of our study confirm that the presence of hepatic steatosis is associated, independently of other variables, with diabetic complications.

Our data, as well as those present in the literature, do not allow to understand if the presence of fatty liver is the consequence or cause of a poor glycemic control. It is possible that poor metabolic control favors the accumulation of fat in the liver, and this then worsens the metabolic

control itself. Furthermore, oxidative stress, systemic inflammation, and endothelial dysfunction might represent the common soil causing hepatic steatosis and vascular, kidney or neurological complications in diabetes.[23,24] It has also been reported that fatty liver releases multiple inflammatory cytokines able to induce systemic inflammation and enhance oxidative stress, which could contribute to the development of the kidney and vascular damage.[23] Regardless of this, the presence of fatty liver modifies the clinical picture, requiring greater attention and closer glycemic control. In this context, the availability of a simple and reliable marker of fatty liver, virtually always available on the basis of routine hemato-chemical tests, can be of great help in clinical practice. Our findings strongly support the utility of HSI in the framing of patients with T1DM. In this regard, it seems interesting that the association between HSI and Total Daily Insulin which could reflect increased hepatic resistance to insulin in patients with T1DM, thus suggesting possible therapeutic adjustments.

The present study has several limitations that reduce the possibility of understanding some pathophysiological steps, but do not undermine, in our opinion, the main finding. Thus, the retrospective nature of the study does not allow to establish whether a direct cause and effect relationship exists between HSI and diabetic complications or HSI simply represents a biomarker of complications. We think that HSI might have a clinical utility to select those T1DM subjects needing more intensive complications screening and follow-up. Furthermore, it would have been preferable to also have a liver imaging study to confirm the actual presence and magnitude of fatty liver. Unfortunately, this information was not available, but again HSI might be used to select individuals for liver ultrasonography in daily practice. Measures of plasma cytokines, adipokines or lipoprotein are lacking, and so it is difficult to explore the role of systemic inflammation as cause linking hepatic steatosis and diabetic complications. Last but not least, the two groups of patients, with and without complications, were significantly different for clinical characteristics, namely age, BMI and disease duration. While the total number of selected subjects does not allow the formation of two perfectly matched groups, we believe that the applied statistical analyses have markedly reduced the impact of these differences.

In conclusion, the results of the present study show that a marker of hepatic steatosis, namely HSI, readily available in clinical practice is associated with the presence of

complications in subjects with T1DM. This can be of clinical utility, allowing a better clinical portrait of the patient and possibly guiding the therapeutic choice.

Disclosure

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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