Fatty liver index is a predictor of incident diabetes in patients with prediabetes: The PREDAPS study

Josep Franch-Nadal[1,2,3,4]*, Llorenç Caballeria[4,5,6], Manel Mata-Cases[1,2,3], Didac Mauricio[1,2,3,7], Carolina Giraldez-García[1,8,9], José Mancera[1,10], Albert Goday[1,11], Xavier Mundet-Tudurí[1,2,12]*, Enrique Regidor[1,9,13,14], for the PREDAPS Study Group¶

1 redGDPS Foundation, Madrid, Spain, 2 Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain, 3 Diabetes and Associated Metabolic Diseases Networking Biomedical Research Centre (CIBERDEM), Madrid, Spain, 4 Department of Medicine, University of Barcelona, Barcelona, Spain, 5 Liver and Digestive Diseases Networking Biomedical Research Centre (CIBEREHD), Madrid, Spain, 6 Unitat de Suport a la Recerca Barcelonès Nord, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain, 7 Department of Endocrinology and Nutrition, Health Sciences Research Institute & University Hospital Germans Trias i Pujol, Badalona, Spain, 8 Preventive Medicine Service, University Hospital Infanta Elena, Madrid, Spain, 9 Preventive Medicine, Public Health and History of Science Department, Complutense University of Madrid, Madrid, Spain, 10 Health Center Ciudad Jardín, Málaga, Spain, 11 Endocrinology Service, Hospital del Mar, Barcelona, Spain, 12 Autonomous University of Barcelona, Bellaterra, Spain, 13 Epidemiology and Public Health Networking Biomedical Research Centre (CIBERESP), Madrid, Spain, 14 Health Research Institute, Hospital Clínico San Carlos (IdISSC), Madrid, Spain

¶ Membership of the PREDAPS Study Group is provided in the Acknowledgments.
* 16274xmt@comb.cat (XM-T); josep.franch@gmail.com (JFN)

Abstract

Objectives

We evaluated the ability of the Fatty Liver Index (FLI), a surrogate marker of hepatic steatosis, to predict the development of type 2 diabetes (T2D) at 3 years follow-up in a Spanish cohort with prediabetes from a prospective observational study in primary care (PREDAPS).

Methods

FLI was calculated at baseline for 1,142 adult subjects with prediabetes attending primary care centers, and classified into three categories: FLI <30 (no steatosis), FLI 30–60 (intermediate) and FLI ≥60 (hepatic steatosis). We estimated the incidence rate of T2D in each FLI category at 3 years of follow-up. The association between FLI and incident T2D was calculated using Cox regression models adjusted for age, sex, educational level, family history of diabetes, lifestyles, hypertension, lipid profile and transaminases.

Results

The proportion of subjects with prediabetes and hepatic steatosis (FLI ≥60) at baseline was 55.7%. The incidence rate of T2D at 3 years follow-up was 1.3, 2.9 and 6.0 per 100 person-years for FLI<30, FLI 30->60 and FLI ≥60, respectively. The most significant variables increasing the risk of developing T2D were metabolic syndrome (hazard ratio [HR] = 3.02;

95% confidence interval [CI] = 2.14–4.26) and FLI ≥60 (HR = 4.52; 95%CI = 2.10–9.72). Moreover, FLI ≥60 was independently associated with T2D incidence: the HR was 4.97 (95% CI: 2.28–10.80) in the base regression model adjusted by sex, age and educational level, and 3.21 (95%CI: 1.45–7.09) in the fully adjusted model.

Conclusions

FLI may be considered an easy and valuable early indicator of high risk of incident T2D in patients with prediabetes attended in primary care, which could allow the adoption of effective measures needed to prevent and reduce the progression of the disease.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by free fatty acid and triglyceride infiltration of hepatocytes that is not the result of significant alcohol intake or secondary to established liver diseases. It is an entity that encompasses a wide spectrum of lesions ranging from simple steatosis to steatohepatitis, and can progress to liver cirrhosis or even hepatocellular carcinoma [1, 2]. The estimated overall worldwide prevalence of NAFLD in the general adult population is about 25% [3], and increases substantially up to 40%-70% in subjects with established type 2 diabetes (T2D) [4]. In Spain, the prevalence of NAFLD has been estimated to be 26% among the adult population [5]. In addition, several epidemiological studies have consistently shown that NAFLD is an independent risk factor for incident T2D [6], metabolic syndrome [7], and cardiovascular disease (CVD) [8]. Given the progressive nature of the disease and the risk of serious consequences, health care providers are strongly advised to screen for NAFLD in all patients with T2D and to be more proactive in their management [9].

Liver biopsy is the gold standard method to diagnose NAFLD, and as it is quantitative, is the only one way to distinguish between simple steatosis and steatohepatitis. However, it has important limitations: it is an invasive procedure that carries an inherent risk to the patient, it is costly, and it is subject to high interobserver and sampling variability [10]. For these reasons, non-invasive methods, including imaging techniques or serum markers, are increasingly being used [11]. Abdominal ultrasound imaging is the method of choice because it is widely available and inexpensive, but in spite of being sensitive to detect fat accumulation when more than 33% of hepatocytes are steatotic, it does not provide information on the degree of fibrosis [11]. Furthermore, single serological markers are suboptimal for diagnosing NAFLD. Therefore, different models that combine multiple clinical and biochemical parameters have been proposed: these indices are easily obtained in routine clinical practice, are readily applicable, and some have shown good diagnostic accuracy for detecting steatosis [11, 12]. The Fatty Liver Index (FLI) is a simple algorithm that combines measures of triglycerides, gamma glutamyl-transpeptidase (GGT), waist circumference and body mass index (BMI). FLI has an excellent discriminative ability to predict ultrasonographic fatty liver disease [13], and has been validated in both Asian and Western populations [14, 15]. FLI has been reported to correlate with insulin resistance, risk of coronary heart disease, risk of metabolic syndrome, early atherosclerosis, and rates of non-hepatic-related morbidity and mortality in nondiabetic subjects [16–19]. Finally, FLI also predicts incident hypertension in normotensive individuals [20], and further metabolic deterioration in women with previous gestational diabetes [21].

Two meta-analyses have reported that NAFLD diagnosed by either altered serum liver enzymes, radiological, or histological evidence increases the risk of developing T2D [7, 22],

and FLI-diagnosed NAFLD has also been found to be a good predictor of incident T2D [23–26]. In addition, different studies have reported that ultrasonography-diagnosed NAFLD predicts the occurrence of prediabetes [27–31]. However, the risk of progression to T2D in subjects with prediabetes has not been studied at large, and all available studies so far have been conducted in Asian populations: two of them used ultrasonography to diagnose NAFLD [28, 32], and only one used FLI [33]. The possibility of using FLI in subjects with prediabetes is of great interest because, based on epidemiological and clinical evidence, people at increased risk of developing T2D should be the target of primary prevention efforts [34]. The objective of the present study was to determine the FLI's ability to predict the development of T2D in a primary care European population with prediabetes.

Materials and methods

Study design and data source

This was a follow-up study of a cohort of 1,184 subjects with prediabetes and another cohort of 838 subjects without alterations in glucose metabolism participating in the PREDAPS (Primary Health Care on the Evolution of Patients with Prediabetes) Study [35]. Briefly, the PREDAPS is a prospective observational study that collected baseline data from patients aged 30–74 years attending primary care centers in Spain throughout 2012 that are currently under follow-up to 5 years. Patients were excluded if they had any of the following conditions: diabetes, terminal disease, pregnancy, major surgery or hospital admission in the preceding 3 months, or hematological diseases that could interfere with the HbA1c value.

Prediabetes was defined using the American Association of Diabetes criteria for prediabetes [36], namely fasting plasma glucose (FPG) levels between 100 and 125 mg/dl and/or HbA1c between 5.7% and 6.4% (39 and 46 mmol/mol) in the prior 6 months. Recruited subjects were subsequently monitored annually to determine the incidence of new cases of T2D, defined as basal plasma glucose level ≥126 mg/dl on two occasions, or HbA1c ≥6.5% (≥48 mmol/mol) on two occasions, or both at the same time [36].

The present study analyzed the relationship between FLI and various clinical and sociodemographic characteristics measured at baseline and the onset of T2D up to the third year of follow-up among the cohort of subjects with prediabetes and available information (N = 1,142).

Measures

Detailed information on the methodology of the study has been described elsewhere [35]. Clinical and demographic variables at baseline for this substudy included: age; sex; educational level; family history of diabetes; smoking status (classified as active smokers, ex-smokers, and never smokers), alcohol consumption (considering low-risk an intake ≤20 g/day in women and ≤40 g/day in men), physical activity (frequency and minutes per routine in the prior 2 weeks), sedentary lifestyle, defined as not following the World Health Organization recommendations on physical activity (i.e., at least 150 minutes a week of moderate aerobic activity, or 75 minutes a week of vigorous aerobic, or an equivalent combination of moderate and vigorous activities); and diet, based on the data collected on the frequency of consumption of fruits and vegetables, where subjects were classified into those who consumed those foods daily, and those who consumed them less frequently. Likewise, subjects were asked what they usually had for breakfast, and were divided into those who did not have breakfast or had an incomplete meal (only coffee, milk, chocolate, cocoa or yogurt), and those who had a proper breakfast.

During physical examination, height, weight, waist circumference and blood pressure were measured. Patients were classified with general obesity if their BMI was $\geq$30 kg/m^2 and with abdominal obesity if waist circumference was $\geq$102 cm in men and $\geq$88 cm in women. Hypertension was defined as systolic blood pressure (SBP) $\geq$140 mmHg, diastolic blood pressure (DBP) $\geq$90 mmHg, currently taking antihypertensive drugs or personal history of high blood pressure.

The following 12-hour fasting plasma determinations were measured: FPG, HbA1c, lipid profile (total cholesterol [TC], high-density lipoprotein [HDL], low-density lipoprotein [LDL] and triglycerides [TG]), GGT and transaminases (aspartate transaminase [AST] and alanine transaminase [ALT]). Hypercholesterolemia was defined as total serum cholesterol $\geq$250 mg/dL, low HDL as <40 mg/dL in men and <50 mg/dL in women, high LDL $\geq$100 mg/dL, and hypertriglyceridemia as serum TG $\geq$150 mg/dL. Liver enzymes were considered elevated when GGT $\geq$40 U/L, or either AST or ALT $\geq$35 U/L. Subjects were considered to have metabolic syndrome when they met three or more of the following criteria: waist circumference >102 cm in men or >88 cm in women; TG $\geq$150 mg/dl; blood pressure $\geq$130/85 mmHg; HDL <40 mg/dl in men or <50 mg/dl in women; and FPG between 110 and 126 mg/dL [37].

The FLI as an indicator of hepatic steatosis was calculated based on the measures of TG, GGT, BMI and waist circumference, using the formula described in the literature [13]. Moreover, and as it has been established, FLI values (ranging from 0 to 100) were classified into three categories: <30, 30–59, and $\geq$60 [13]. FLI values of <30 and $\geq$60 would rule out and confirm the presence of hepatic steatosis, respectively.

The study was approved by the Ethics Committee of Institut Hospital del Mar. All patient records and information was anonymized and de-identified prior to analysis.

Statistical analysis

We estimated the percentage and distribution of qualitative characteristics, and the mean of the quantitative characteristics for the three categories of FLI. Statistical significance was evaluated in the first case using the Chi-square test of heterogeneity, and in the second case with the analysis of variance (ANOVA) to test for differences between means. We calculated the incidence rate of diabetes per 100 person-years in each FLI category and then evaluated the association of the different baseline patient characteristics with the incidence of T2D. The measure of association was the hazard ratio (HR) and 95% confidence interval (CI) calculated by Cox regression models. We also estimated the degree to which the characteristics analyzed explained the association between FLI and the incidence of T2D. We first estimated a base model adjusted for age, sex and educational level, and then added the different characteristics to the baseline model, namely family history of diabetes, lifestyles, hypertension, lipid profile and transaminases. We did not include the variables involved in calculating the FLI (TG, GGT, BMI, and waist circumference). Patients who died (1.4%) and those who could not be followed up for 3 years (18.0%) were censored in the analysis, therefore they only contributed to the risk up to the date of death or loss to follow-up. We also conducted a sensitivity analysis excluding subjects with high-risk alcohol consumption. Finally, the extent to which FLI may be a better predictor of diabetes than insulin resistance is of interest. In the present study, fasting plasma insulin was not measured, although we estimated the predictive capacity of several surrogate markers that have shown high sensitivity and specificity for recognizing insulin resistance [38–45]. In particular, we analyzed the triglyceride glucose (TyG) index and various lipid ratios, namely the TG/HDL ratio, the total TC/HDL ratio, and the LDL/HDL ratio. Based on the value of each of these surrogate markers, subjects were stratified into tertiles. Statistical significance was established at a p-value <0.05. All analyses were conducted using the SPSS statistical package (version 20, SPSS, Chicago, Illinois, USA).

Results

Table 1 shows the sociodemographic and clinical characteristics collected at baseline according to FLI category. The proportion of subjects with prediabetes and hepatic steatosis (FLI

Table 1. Sociodemographic, lifestyle, and clinical characteristics of subjects with prediabetes at baseline, according to baseline FLI.

	Fatty Liver Index			
	<30	30–59	≥60	P-value
N (%)	187 (16.4)	319 (27.9)	636 (55.7)	
Gender, %				
Men	19.8	51.1	58.8	<0.001
Women	80.2	48.9	41.2	
Age, years, %				
30–49	16.0	12.2	17.1	0.020
50–64	57.8	48.9	48.0	
65–74	26.2	38.9	34.9	
Educational level, %				
Less than secondary	58.8	67.4	64.0	0.15
Secondary or higher	41.2	32.6	36.0	
Family history of diabetes, %	44.9	48.6	46.5	0.71
Smoking status, %				
Active smoker	15.0	12.5	19.3	<0.001
Ex-smoker	28.3	37.9	42.0	
Never smoked	56.7	49.5	38.7	
Alcohol consumption, %				
None	42.7	35.1	30.2	0.003
Low risk	48.1	55.2	54.3	
High risk or harmful	9.2	9.7	15.6	
Alcohol consumption (g/day), mean (SD)	9.0 (24.3)	13.1 (34)	20.4 (50.7)	0.002
Diet, %				
Daily consumption of fruits	84.5	78.1	75.8	0.04
Daily consumption of vegetables	65.8	58.0	53.9	0.015
Complete breakfast	89.8	87.1	85.2	0.25
Regular physical activity, %	58.3	61.4	51.1	0.007
Metabolic syndrome, %	8.6	21.0	56.3	<0.001
BMI (kg/m^2), mean (SD)	24.5 (2.4)	27.5 (2.3)	32.6 (4.2)	<0.001
Waist circumference (cm), mean (SD)	84.6 (7.3)	94.8 (6.4)	107.3 (9.6)	<0.001
FPG (mg/dL), mean (SD)	101.5 (11.7)	104.7 (10.7)	106.8 (9.9)	<0.001
HbA1c (%), mean (SD)	5.8 (0.3)	5.8 (0.3)	5.9 (0,3)	0.003
SBP (mmHg), mean (SD)	127.9 (14.8)	132.7 (14.7)	137.7 (16.3)	<0.001
DBP (mmHg), mean (SD)	77.0 (8.6)	79.7 (8.6)	82.9 (9.4)	<0.001
AST (U/L), mean (SD)	20.5 (7.4)	22.8 (9.3)	25.3 (11.3)	<0.001
ALT (U/L), mean (SD)	20.4 (9.6)	24.4 (11.3)	30.8 (18.0)	<0.001
GGT (U/L), mean (SD)	18.5 (8.6)	26.5 (14.8)	44.7 (41.3)	<0.001
Total cholesterol (mg/dL), mean (SD)	212.9 (35.6)	209.3 (39.7)	208.8 (37.6)	0.41
HDL cholesterol (mg/dL), mean (SD)	63.2 (16.1)	56.2 (13.2)	50.6 (13.0)	<0.001
LDL cholesterol (mg/dL), mean (SD)	132.8 (32.9)	129.7 (35.5)	126.9 (34.1)	0.10
Triglycerides (mg/dL), mean (SD)	85.2 (30.7)	117 (45.9)	156.4 (83.1)	<0.001

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma glutamyltranspeptidase; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; SD, standard deviation

https://doi.org/10.1371/journal.pone.0198327.t001

≥60), intermediate FLI (30–59), and no steatosis (FLI <30) was 55.7%, 27.9% and 16.4%, respectively. Subjects with FLI ≥60 were more frequently men, active smokers and high-risk drinkers, less frequently consumed fruits and vegetables daily, and exercised less regularly. Moreover, the frequency of metabolic syndrome was significantly higher in subjects with FLI ≥60 than in the other groups (56.3% vs. 8.6% in FLI < 30 and 21% in FLI 30–59; p<0.001), they also had higher rates of unfavorable body composition (higher BMI and waist circumference; p<0.001), adverse lipid profile (higher levels of TG and lower values of HDL cholesterol; p<0.001), and also higher blood pressure than the other FLI groups (p<0.001). Finally, subjects with FLI ≥60 also had higher glycemic levels (FPG and HbA1c; p<0.001 and p = 0.003, respectively), and their liver enzymes were more elevated than in the other groups (ALT, AST, and GGT; p<0.001).

Incidence of diabetes over 3 years and associated risk factors

Subjects were followed during an average of 2.83 years (SD = 0.87), and 107 out of the 1,142 initially assessed (9.4%) developed T2D at the end of follow-up. By FLI category, the proportion of participants who developed T2D was the highest among those with FLI ≥60 (n = 107; 16.8%), followed by those with FLI 30–59 (n = 27; 8.5%) and those with FLI <30 (n = 7; 3.7%). This corresponded to a T2D incidence rate of 1.3, 2.9 and 6.0 per 100 person-years in the categories FLI<30, FLI 30–59 and FLI ≥60, respectively.

Among all sociodemographic and lifestyle variables, only family history of T2D was found as a significant risk factor for incident diabetes, while daily consumption of fruit was the only significant protective factor (Table 2). Regarding clinical and biochemical parameters, the most significant variables increasing the risk of developing T2D were metabolic syndrome (HR = 3.02; 95%CI = 2.14–4.26) and FLI ≥60 (HR = 4.52; 95%CI = 2.10–9.72). Other individual risk factors moderately increasing the likelihood of progression were general obesity based on BMI, abdominal obesity based on waist circumference, presence of hypertension, high triglycerides, and elevated liver enzymes. Conversely, high levels of HDL cholesterol were protective against incident T2D.

FLI for the prediction of incident T2D in prediabetes

Multivariate models for the development of T2D at 3 years of follow-up in patients with prediabetes (Table 3) showed that the presence of FLI ≥60 was in all cases a significant independent risk factor. In the base model, adjusted for age, sex and educational level, the HR in the category FLI ≥60 with respect to FLI <30 was 4.97 (95%CI = 2.28–10.80). When the baseline model was adjusted by five other characteristics separately, the HR decreased slightly (HRs between 4.13 and 4.82). Adjustment for all the variables combined decreased the magnitude of the HR to 3.21 (95%CI = 1.45–7.09). In the sensitivity analysis restricted to subjects without high-risk alcohol consumption, the magnitude of the association increased: the HR for FLI ≥60 was 5.09 (95%CI = 2.20–11.76) in the base model, and 3.54 (95%CI = 1.51–8.31) in the fully adjusted model.

Finally, Table 4 shows the findings on the models for the risk of development of T2D at 3 years of follow-up in patients with prediabetes according to tertiles of surrogate markers for insulin resistance. After adjusting for all variables, the magnitude of the hazard ratios for all markers was lower than that observed with FLI.

Discussion

The results of the present prospective study conducted in Spain in a cohort of patients with prediabetes (PREDAPS study) showed that FLI-diagnosed hepatic steatosis is associated with a

Table 2. Bivariate analysis of baseline characteristics and incidence of diabetes in patients with prediabetes at 3 years follow-up.

Variable	HR (95%) CI
Gender	
Men	1.00
Women	1.01 (0.73–1.41)
Age	
30–49 years	1,00
50–64 years	0.93 (0.58–1.47)
65–74 years	0.94 (0.58–1.54)
Educational level	
Less than secondary	1.00
Secondary or higher	0.88 (0.62–1.25)
Family history of diabetes	
No	1.00
Yes	1.58 (1.13–2.21)
Tobacco consumption	
Smoker	1.00
Ex-smoker	1.49 (0.89–2.48)
Never smoker	1.16 (0.69–1.95)
Alcohol consumption	
None	1.00
Low risk	0.74 (0.52–1.07)
High risk or harmful	0.85 (0.51–1.43)
Daily consumption of fruits	
No	1.00
Yes	0.57 (0.40–0.81)
Daily consumption of vegetables	
No	1.00
Yes	1.04 (0.75–1.46)
Complete breakfast	
No	1.00
Yes	0.71 (0.46–1.09)
Regular physical activity	
No	1.00
Yes	0.74 (0.53–1.03)
BMI (kg/m^2)	
<30	1.00
≥30	1.80 (1.29–2.51)
Abdominal circumference (cm)	
<88 cm (women)/ <102 cm (men)	1.00
≥88 cm (women)/ ≥102 cm (men)	2.21 (1.44–3.38)
Blood pressure (mmHg)	
<140/90	1.00
≥140/90	1.58 (1.13–2.20)
Liver enzymes (U/L)	
AST ≤35	1.00
AST >35	2.18 (1.39–3.41)
ALT ≤35	1.00

(Continued)

Table 2. (Continued)

Variable	HR (95%) CI
ALT >35	1.93 (1.34–2.76)
GGT ≤40	1.00
GGT >40	1.66 (1.18–2.35)
Lipid profile (mg/dL)	
Total cholesterol <250	1.00
Total cholesterol ≥250	0.85 (0.51–1.42)
HDL cholesterol <40 (men)/ <50 (women)	1.00
HDL cholesterol ≥40 (men)/ ≥50 (women)	0.58 (0.41–0.82)
LDL cholesterol <100	1.00
LDL cholesterol ≥100	0.87 (0.58–1.30)
Triglycerides <150	1.00
Triglycerides ≥150	1.63 (1.16–2.30)
Metabolic syndrome	
No	1.00
Yes	3.02 (2.14–4.26)
Fatty liver index	
<30	1.00
30–60	2.22 (0.97–5.11)
≥60	4.52 (2.10–9.72)

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma glutamyltranspeptidase; HDL, high density lipoprotein; HR, hazard ratio; LDL, low density lipoprotein; SBP, systolic blood pressure

risk of developing T2D at 3 years of follow-up. Moreover, this association was independent of possible confounding factors such as family history of diabetes, lifestyle, hypertension, lipid profile and level of transaminases. The only available study performed so far to assess the incidence of T2D in subjects with prediabetes and NAFLD diagnosed through FLI was performed in a Japanese population [33]. However, new T2D was diagnosed based on self-administered questionnaires, and it is not clear whether the results could be as well applied to Western or Caucasian populations [33]. In our study, the diagnosis of T2D was based on basal plasma glucose or HbA1c values, and it is the first study evaluating the ability of the FLI to predict diabetes in subjects with prediabetes according to ADA criteria [36].

In the PREDAPS study, the baseline prevalence of hepatic steatosis (i.e., FLI ≥60) was 56%, which is higher than the 19% reported in the Japanese study [33], closer to the approximately 22–40% reported by studies with ultrasonography-diagnosed NAFLD [27, 28, 30, 46–49], and lower than the 75% observed in overweight and obese subjects in a study using magnetic resonance (MR) [50].

In a previous study conducted in France in subjects from the general population, the authors found that FLI ≥70 was associated with the development of T2D [23]. Our study shows that an FLI ≥60 can be a good predictor of T2D in subjects with impaired glucose metabolism. An important observation in the present study was that patients with FLI ≥60 had the most altered metabolic profile, with a high prevalence of metabolic syndrome and high values of each of its constituent components. These results are in line with the study of Nishi et al. conducted in Japanese subjects with prediabetes [33] and also with those of a large population-based study conducted in Italy in patients with established T2D [51]. These findings are not surprising if we take into account that the degree of liver fat content correlates

Table 3. Hazard ratios and 95% confidence intervals of multivariate models for the risk of incident T2D in patients with prediabetes at 3 years of follow-up according to FLI categories.

	Fatty Liver Index		
	<30	30–59	≥60
Incident T2D; unadjusted	1.00	2.22 (0.97–5.11)	4.52 (2.10–9.72)
Base model: Incident T2D adjusted for age, sex and educational level	1.00	2.40 (1.03–5.55)	4.97 (2.28–10.80)
Base model adjusted for family history of T2D	1.00	2.31 (1.00–5.36)	4.82 (2.22–10.48)
Base model adjusted for lifestyle*	1.00	2.26 (0.97–5.24)	4.63 (2.12–10.10)
Base model adjusted for hypertension	1.00	2.30 (0.99–5.34)	4.59 (2.10–10.03)
Base model adjusted for lipids (total and HDL cholesterol)	1.00	2.35 (1.01–5.44)	4.58 (2.09–10.01)
Base model adjusted for transaminases (AST, ALT)	1.00	2.22 (0.96–5.14)	4.13 (1.88–9.04)
Base model adjusted for family history of T2D, lifestyle* hypertension, lipids and transaminases			
All	1.00	1.96 (0.85–4.54)	3.21 (1.45–7.09)
Men	1.00	1.53 (0.43–5.40)	1.70 (0.50–5.74)
Women	1.00	1.73 (0.53–5.59)	4.95 (1.73–14.29)

*Includes tobacco consumption, alcohol intake, consumption of fruits and vegetables, breakfast and physical activity

T2D, type 2 diabetes mellitus; ALT, alanine transaminase; AST, aspartate transaminase; HDL, high density lipoprotein

with all components of metabolic syndrome [52]. This correlation can be attributed to the fact that both NAFLD and T2D share a series of common physiopathological mechanisms, including alterations in glucose and lipid metabolism, insulin resistance, and environmental and genetic factors [51, 53].

Another interesting finding was that patients with FLI≥60 had significantly higher mean levels of transaminases than the lower FLI groups, although over half of them exhibited normal values. It has been previously reported that a substantial number of patients with NAFLD, even in those with a more advanced stage of the disease, have normal transaminases [54–56]. This is important, since clinicians often rely on abnormal transaminases to identify patients with NAFLD, but it has been shown that an increase, even when levels are within the normal range, is an independent predictor of incident T2D and metabolic syndrome [57–59].

Only two previous studies conducted in Asian populations have assessed the risk of progression to T2D from prediabetes using ultrasonography to diagnose NAFLD. In one prospective study conducted in Japan, prediabetes was found as the strongest predictor for the development of T2D at 10-years follow-up, with a 6.4 fold-risk compared with subjects with normal glucose [28]. In another study, conducted in Korea, the risk for incident T2D at 5 years follow-up was enhanced by 9-fold only in subjects with NAFLD and concomitant impaired fasting glucose, but no increased risk of T2D was observed among those with NAFLD and normal glucose [30]. In our study, 9.4% of patients with prediabetes progressed to T2D during the 3-years follow-up, and the risk of progression was 3.21 times higher for subjects with FLI ≥60 than in those with FLI <30 in the fully adjusted model. This is in agreement

Table 4. Hazard ratios and 95% confidence intervals for the risk of incident T2D in patients with prediabetes at 3 years of follow-up according to tertiles of surrogate markers of insulin resistance.

Surrogate markers of insulin resistance	Bivariate analysis			Multivariate analysis[1]		
	HR	95% CI		HR	95% CI	
TyG Index						
1st tertile	1.00			1.00		
2nd tertile	1.24	0.71	2.16	1.00	0.56	1.78
3rd tertile	2.44	1.47	4.05	1.87	1.09	3.21
TG/HDL Ratio						
1st tertile	1.00			1.00		
2nd tertile	1.35	0.83	2.17	1.10	0.66	1.82
3rd tertile	1.95	1.25	3.04	1.59	0.94	2.68
TC/HDL Ratio						
1st tertile	1.00			1.00		
2nd tertile	1.40	0.89	2.20	1.26	0.78	2.02
3rd tertile	1.73	1.13	2.66	1.40	0.82	2.37
LDL/HDL Ratio						
1st tertile	1.00			1.00		
2nd tertile	1.20	0.78	1.85	1.07	0.69	1.68
3rd tertile	1.36	0.90	2.06	1.13	0.69	1.83

[1]Adjusted for age, sex and educational level, family history of T2D, tobacco consumption, alcohol intake, consumption of fruits and vegetables, breakfast and physical activity, hypertension, lipids and transaminases.

CI, confidence interval; HDL, high density lipoprotein; HR, hazard ratio; LDL, low density lipoprotein; TC, total cholesterol; triglyceride glucose index (TyG index)

with the results obtained in the only available and comparable study using FLI to diagnose NAFLD [33]. In the Nishi et al. Japanese study [33], 11.5% of men and 6% of women with prediabetes developed T2D during 3 years follow-up, and they observed similar risk figures after adjusting for almost the same variables as in our case (odds ratio 2.68 in men and 10.35 in women), although in our study the magnitude of HR was lower (1.70 in men and 4.95 in women).

FLI could be of use in routine clinical practice as an additional screening tool to identify those with prediabetes at high risk of progression that would benefit from early interventions [9, 60]. For instance, weight loss via energy restriction or physical activity have been shown to reduce liver fat and improve hepatic glucose metabolism within weeks [61, 62], and the resolution of fatty liver to significantly reduce the risk of T2D development to a level similar to individuals without NAFLD [63, 64]. Moreover, diabetes is an independent factor of NAFLD progression and of the development of cirrhosis [65–67], and a recent study showed that lipid-lowering therapy with statins correlates with improvement in the FLI score [19], and another one that long-term pioglitazone treatment in patients with prediabetes or T2D led to marked histologic improvements in hepatic steatosis, inflammation, and ballooning without worsening fibrosis [68]. Finally, NAFLD is an independent risk factor for the development of micro and macrovascular complications in patients with diabetes [69, 70], and statins have also been shown to substantially reduce cardiovascular morbidity and mortality by >50% compared with high-risk patients with normal liver structure and function [71].

The present study has both strengths and limitations that should be acknowledged. Among its strengths is its prospective design, which included measurement of a large variety of possible confounding factors. However, given the complex bidirectionality between NAFLD, insulin resistance and hyperglycemia, it is challenging to distinguish whether NAFLD is a cause or

a consequence of insulin resistance and T2D. With regard to limitations, it must be noted that the different parameters that make up the FLI are also risk factors for T2D, which could call into question whether NAFLD based on the FLI is an independent predictor for the presence of T2D.

Another limitation was that we diagnosed NAFLD with FLI instead of liver biopsy. On the one hand, FLI was found to be highly reliable in a European study when subsequently confirmed by abdominal ultrasound [15], although another population study, where the diagnosis was confirmed by magnetic resonance spectroscopy, found a more moderate diagnostic precision [12]. On the other hand, FLI does not give information on the severity of hepatic steatosis, and we could not assess whether the presence of more severe forms of the disease (i.e., fatty infiltration plus inflammation [NASH]) appears to afford a greater risk for incident T2D than simple steatosis, as previously described [72]. Moreover, patients with FLI ≥60 were more likely to report high-risk alcohol, and GGT, an analytical marker of alcohol consumption, was also higher than in the lower FLI groups. It is known that alcohol consumption, regardless of the amount, can cause hepatic steatosis. Thus, although we cannot rule out a possible classification bias, whereby fatty liver in some patients classified as having NAFLD was actually due to alcohol consumption, the results were unchanged when subjects with high-risk alcohol intake were excluded from the analysis. In addition, we relied on FPG and/or HbA1c to diagnose diabetes and prediabetes, and the lack of a 2-hour oral glucose tolerance test might have resulted in the inclusion of subjects with undiagnosed diabetes at baseline or underestimated the number of patients with incident T2D cases. Lastly, a potential weakness of the study is that we had no data on insulin resistance (i.e., HOMA-IR index or fasting insulin), which is strongly associated with NAFLD and may contribute to the development of T2D [32, 73]. However, we were instead able to calculate several surrogate markers of insulin resistance. The magnitude of HR that evaluated the relationship between these markers and development of T2D at 3 years of follow-up was lower than that the one obtained in subjects whose FLI was ≥60. On the other hand, although high values of FLI are associated with reduced insulin sensitivity [17, 26], fatty liver diagnosed as FLI ≥60 has been shown to be a predictor of incident diabetes independently of insulin resistance [24]. In addition, insulin resistance did not significantly contribute to reduce the risk when it was considered as a confounding factor [23, 26].

Conclusions

FLI should be considered an easy and valuable tool to be used in primary care routine clinical practice for early identification of significant liver disease in subjects with prediabetes and to stratify the risk of developing T2D. This way, those at the greatest risk could be carefully monitored so that effective interventions to prevent and reduce progression of the disease could be adopted.

Acknowledgments

Boente (CS Porriño, Pontevedra), Antonia Borras (CS Canal Salat, Baleares), Remei Bosch (EAP Girona 2, Girona), Mª Jesús Brito (CS La Matanza, Baleares), Pilar Buil (EAP Azpilagaña, Navarra), J. José Cabré (EAP Reus-1, Tarragona), Ainhoa Cambra (CS Arrabal, Zaragoza), Francisco Carbonell (CS Mislata, Valencia), Francisco Carramiñana (CS San Roque de Badajoz, Badajoz), Lourdes Carrillo (CS La Victoria de Acentejo, Santa Cruz de Tenerife), Ana Casorrán (CS Fuente de San Luís, Valencia), Rafael Colas (CS Santoña, Cantabria), Blanca Cordero (CS Sta. María de Benquerencia, Toledo), Xavier Cos (EAP Sant Martí de Provençals, Barcelona), Gabriel Cuatrecasas (CAP de Sarrià, Barcelona), Cristina De Castro (CS Sta. María de Benquerencia, Toledo), Manuel De la Flor (CS Ntra. Sra. de Gracia, Sevilla), Carlos De la Sen (Consultorio San Gabriel, Alicante), Rosa Mar De Miguel (EAP Pubillas Casas, Barcelona), A. María De Santiago (Unidad Docente de Atención Familiar y Comunitaria, Guadalajara), Mercedes Del Castillo (CS Andrés Mellado, Madrid), Javier Díez (CS Tafalla, Navarra), Mª Carmen Durán (CS Lavadores Vigo, Pontevedra), Patxi Ezkurra (CS Zumaia, Guipúzcoa), Paula Gabriel (EAP Badia del Vallès, Barcelona), Javier Gamarra (CS Medina del Campo Rural, Valladolid), Francisco García (CS Don Benito Este, Badajoz), Luis García-Giralda (CS Murcia Centro, Murcia), F. Javier García-Soidán (CS Porriño, Pontevedra), Mª Teresa Gijón (CS Los Yébenes, Madrid), Ángel Gómez (CS Lasarte, Guipúzcoa), María del Carmen Gómez (CS Vélez-Málaga Norte, Málaga), J. Carles González (Girona 3, Girona), María González (CS Alcantarilla Sangonera, Murcia), Esteban Granero (CS Vista Alegre Murcia, Murcia), Ángela Trinidad Gutiérrez (CS El Calero, Las Palmas), Félix Gutiérrez (CS Bombarda-Monsalud, Zaragoza), Luisa Gutiérrez (CS Beraun, Guipúzcoa), M. Ángel Gutiérrez (CS Ávila Sur Oeste, Ávila), Ana Mª Hernández (CS El Calero, Las Palmas), Mercedes Ibáñez (CS Vandel, Madrid), Rosario Iglesias (CS Lain Entralgo, Madrid), Dimas Igual (CAP Manuel Encinas, Cáceres), Jaime Innerárity (CS Hereza Leganes, Madrid), Yon Iriarte (CS Aizarnazabal-Getaria, Guipúzcua), Ángeles Jurado (CS Salvador Caballero, Granada), Rafael Llanes (Villanueva de la Cañada, Madrid), Flora López (EAP Martorell, Barcelona), Riánsares López (CS Artilleros, Madrid), Ángela Lorenzo (CS Alcalá de Guadaira, Madrid), Carmen Losada (UGC Adoratrices, Huelva), Ramón Macía (CS Roces Montevil, Asturias), Fernando Malo (CS Ares, A Coruña), Mª José Mansilla (CS Martín de Vargas, Madrid), Mª Teresa Marín (CS General Ricardos, Madrid), José Luís Martín (CS Salvador Caballero, Granada), F. Javier Martínez (CS Federica Monseny, Madrid), Juan Martínez (CS Yecla, Murcia), Rosario Martínez (CS Oñati, Guipúzcoa), Mª Soledad Mayayo (CS Martín de Vargas, Madrid), J. Javier Mediavilla (CS Burgos Rural, Burgos), Luís Mendo (CS Cadreita, Navarra), J. Manuel Millaruelo (CS Torrero La Paz, Zaragoza), Alicia Monzón (CS Vecindario, Las Palmas), Ana Moreno (CAP San Roque, Badajoz), Pedro Muñoz (Unidad Docente de Medicina Familiar y Comunitaria, Cantabria), Teresa Mur (CAP Terrasa Sud, Barcelona), Emma Navarro (CS Añaza, Santa Cruz de Tenerife), Jorge Navarro (CS Salvador Pau, Valencia), Pedro Nogales (CS Las Águilas, Madrid), J. Carlos Obaya (CS Chopera, Madrid), Francisco Javier Ortega (CS Campos-Lamprena, Zamora), Francisca Paniagua (CS Ciudad Jardín, Málaga), José Luis Pardo (CS Orihuela I, Alicante), Francisco Carlos Pérez (CS Martín de Vargas, Madrid), Pedro P. Pérez (CS Mallen, Sevilla), Neus Piulats (EAP Raval Sud, Barcelona), Raquel Plana (CS Ponteareas, Pontevedra), Nuria Porta (CAP Terrassa Sud, Barcelona), Santiago Poveda (CS Jumilla, Murcia), Luís Prieto (CS Cáceres-La Mejostilla, Cáceres), Ramón Pujol (EAP Tremp, Lleida), Jazmín Ripoll (CS Fuente de San Luis, Valencia), Antonio Rodríguez (EAP Anglès, Girona), J. José Rodríguez (CS Villaviciosa de Odón, Madrid), Mª Angeles Rollán (CS Los Yébenes, Madrid), Laura Romera (EAP Raval Nord, Barcelona), Pilar Roura (EAP Badia del Vallès, Barcelona), José Félix Rubio (CS Lasarte, Guipúzcua), Antonio Ruiz (CS Pinto, Madrid), Irene Ruiz (EAP La Torrassa, Barcelona), Manuel Antonio Ruiz (CS Agost, Alicante), Isabel Sáenz (CS Espronceda, Madrid), Julio Sagredo (CS Los Rosales, Madrid), Alejandro Salanova (CS Fuente de San

Luis, Valencia), L. Gabriel Sánchez (CS Carballeda, Zamora), Manuel Sánchez (CS Vista Alegre Murcia, Murcia), J. Javier Sangrós (CS Torrero La Paz, Zaragoza), Gloria Sanz (CS San José centro, Zaragoza), Mateu Seguí (UBS Es Castell, Baleares), Rosario Serrano (CS Martín de Vargas, Madrid), Dulce Suárez (CS El Calero, Las Palmas), Eduard Tarragó (EAP Bellvitge, Barcelona), Jesús Torrecilla (CS Bombarda-Monsalud, Zaragoza), José Luís Torres (CS Rodríguez Paterna, La Rioja), Mercè Villaró (EAP Terrassa Sud, Barcelona).

Author Contributions

Conceptualization: Manel Mata-Cases, Didac Mauricio, Albert Goday, Xavier Mundet-Tudurí, Enrique Regidor.

Data curation: Manel Mata-Cases, José Mancera, Xavier Mundet-Tudurí.

Formal analysis: Josep Franch-Nadal, Carolina Giraldez-García, Enrique Regidor.

Investigation: Llorenç Caballeria, Didac Mauricio.

Project administration: Josep Franch-Nadal.

Supervision: Josep Franch-Nadal, Enrique Regidor.

Writing – original draft: Josep Franch-Nadal, Llorenç Caballeria, Manel Mata-Cases, Didac Mauricio, Carolina Giraldez-García, José Mancera, Albert Goday, Xavier Mundet-Tudurí, Enrique Regidor.

References

1. Bellentani S, Marino M. Epidemiology and natural history of non-alcoholic fatty liver disease (NAFLD). Ann Hepatol. 2009; 8 Suppl 1: S4–8. PMID: 19381118

2. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. Hepatology. 2010; 51(2): 679–89. https://doi.org/10.1002/hep.23280 PMID: 20041406

3. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016; 64(1): 73–84. https://doi.org/10.1002/hep.28431 PMID: 26707365

4. Anstee QM, Day CP. The genetics of NAFLD. Nat Rev Gastroenterol Hepatol. 2013; 10(11): 645–55. https://doi.org/10.1038/nrgastro.2013.182 PMID: 24061205

5. Caballeria L, Pera G, Auladell MA, Toran P, Munoz L, Miranda D, et al. Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. Eur J Gastroenterol Hepatol. 2010; 22(1): 24–32. https://doi.org/10.1097/MEG.0b013e32832fcdf0 PMID: 19730384

6. Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. Metabolism. 2016; 65(8): 1096–108. https://doi.org/10.1016/j.metabol.2016.01.001 PMID: 26856933

7. Ballestri S, Zona S, Targher G, Romagnoli D, Baldelli E, Nascimbeni F, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J Gastroenterol Hepatol. 2016; 31(5): 936–44. https://doi.org/10.1111/jgh.13264 PMID: 26667191

8. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013; 10(6): 330–44. https://doi.org/10.1038/nrgastro.2013.41 PMID: 23507799

9. Bril F, Cusi K. Management of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Call to Action. Diabetes Care. 2017; 40(3): 419–30. https://doi.org/10.2337/dc16-1787 PMID: 28223446

10. Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol. 2014; 20 (2): 475–85. https://doi.org/10.3748/wjg.v20.i2.475 PMID: 24574716

11. Papagianni M, Sofogianni A, Tziomalos K. Non-invasive methods for the diagnosis of nonalcoholic fatty liver disease. World J Hepatol. 2015; 7(4): 638–48. https://doi.org/10.4254/wjh.v7.i4.638 PMID: 25866601

12. Kahl S, Strassburger K, Nowotny B, Livingstone R, Kluppelholz B, Kessel K, et al. Comparison of liver fat indices for the diagnosis of hepatic steatosis and insulin resistance. PLoS ONE. 2014; 9(4): e94059. https://doi.org/10.1371/journal.pone.0094059 PMID: 24732091

13. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006; 6: 33. https://doi.org/10.1186/1471-230X-6-33 PMID: 17081293

14. Yang BL, Wu WC, Fang KC, Wang YC, Huo TI, Huang YH, et al. External validation of fatty liver index for identifying ultrasonographic fatty liver in a large-scale cross-sectional study in Taiwan. PLoS ONE. 2015; 10(3): e0120443. https://doi.org/10.1371/journal.pone.0120443 PMID: 25781622

15. Koehler EM, Schouten JN, Hansen BE, Hofman A, Stricker BH, Janssen HL. External validation of the fatty liver index for identifying nonalcoholic fatty liver disease in a population-based study. Clin Gastroenterol Hepatol. 2013; 11(9): 1201–4. https://doi.org/10.1016/j.cgh.2012.12.031 PMID: 23353640

16. Rogulj D, Konjevoda P, Milic M, Mladinic M, Domijan AM. Fatty liver index as an indicator of metabolic syndrome. Clin Biochem. 2012; 45(1–2): 68–71. https://doi.org/10.1016/j.clinbiochem.2011.10.014 PMID: 22056738

17. Gastaldelli A, Kozakova M, Hojlund K, Flyvbjerg A, Favuzzi A, Mitrakou A, et al. Fatty liver is associated with insulin resistance, risk of coronary heart disease, and early atherosclerosis in a large European population. Hepatology. 2009; 49(5): 1537–44. https://doi.org/10.1002/hep.22845 PMID: 19291789

18. Calori G, Lattuada G, Ragogna F, Garancini MP, Crosignani P, Villa M, et al. Fatty liver index and mortality: the Cremona study in the 15th year of follow-up. Hepatology. 2011; 54(1): 145–52. https://doi.org/10.1002/hep.24356 PMID: 21488080

19. Leutner M, Gobl C, Schlager O, Charwat-Resl S, Wielandner A, Howorka E, et al. The Fatty Liver Index (FLI) Relates to Diabetes-Specific Parameters and an Adverse Lipid Profile in a Cohort of Nondiabetic, Dyslipidemic Patients. J Am Coll Nutr. 2017; 36(4): 287–94. https://doi.org/10.1080/07315724.2016.1262802 PMID: 28506114

20. Bonnet F, Gastaldelli A, Pihan-Le Bars F, Natali A, Roussel R, Petrie J, et al. Gamma-glutamyltransferase, fatty liver index and hepatic insulin resistance are associated with incident hypertension in two longitudinal studies. J Hypertens. 2017; 35(3): 493–500. https://doi.org/10.1097/HJH.0000000000001204 PMID: 27984413

21. Bozkurt L, Gobl CS, Tura A, Chmelik M, Prikoszovich T, Kosi L, et al. Fatty liver index predicts further metabolic deteriorations in women with previous gestational diabetes. PLoS ONE. 2012; 7(2): e32710. https://doi.org/10.1371/journal.pone.0032710 PMID: 22393439

22. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med. 2011; 43(8): 617–49. https://doi.org/10.3109/07853890.2010.518623 PMID: 21039302

23. Balkau B, Lange C, Vol S, Fumeron F, Bonnet F, Group Study DESIR. Nine-year incident diabetes is predicted by fatty liver indices: the French D.E.S.I.R. study. BMC Gastroenterol. 2010; 10: 56. https://doi.org/10.1186/1471-230X-10-56 PMID: 20529259

24. Jung CH, Lee WJ, Hwang JY, Yu JH, Shin MS, Lee MJ, et al. Assessment of the fatty liver index as an indicator of hepatic steatosis for predicting incident diabetes independently of insulin resistance in a Korean population. Diabet Med. 2013; 30(4): 428–35. https://doi.org/10.1111/dme.12104 PMID: 23278318

25. Jager S, Jacobs S, Kroger J, Stefan N, Fritsche A, Weikert C, et al. Association between the Fatty Liver Index and Risk of Type 2 Diabetes in the EPIC-Potsdam Study. PLoS ONE. 2015; 10(4): e0124749. https://doi.org/10.1371/journal.pone.0124749 PMID: 25902304

26. Yadav D, Choi E, Ahn SV, Koh SB, Sung KC, Kim JY, et al. Fatty liver index as a simple predictor of incident diabetes from the KoGES-ARIRANG study. Medicine (Baltimore). 2016; 95(31): e4447. https://doi.org/10.1097/MD.0000000000004447 PMID: 27495073

27. Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. Effects of nonalcoholic fatty liver disease on the development of metabolic disorders. J Gastroenterol Hepatol. 2007; 22(7): 1086–91. https://doi.org/10.1111/j.1440-1746.2006.04781.x PMID: 17608855

28. Arase Y, Suzuki F, Ikeda K, Kumada H, Tsuji H, Kobayashi T. Multivariate analysis of risk factors for the development of type 2 diabetes in nonalcoholic fatty liver disease. J Gastroenterol. 2009; 44(10): 1064–70. https://doi.org/10.1007/s00535-009-0091-1 PMID: 19533014

29. Yamada T, Fukatsu M, Suzuki S, Wada T, Yoshida T, Joh T. Fatty liver predicts impaired fasting glucose and type 2 diabetes mellitus in Japanese undergoing a health checkup. J Gastroenterol Hepatol. 2010; 25(2): 352–6. https://doi.org/10.1111/j.1440-1746.2009.05998.x PMID: 19817963

30. Bae JC, Rhee EJ, Lee WY, Park SE, Park CY, Oh KW, et al. Combined effect of nonalcoholic fatty liver disease and impaired fasting glucose on the development of type 2 diabetes: a 4-year retrospective

longitudinal study. Diabetes Care. 2011; 34(3): 727–9. https://doi.org/10.2337/dc10-1991 PMID: 21278140

31. Zelber-Sagi S, Lotan R, Shibolet O, Webb M, Buch A, Nitzan-Kaluski D, et al. Non-alcoholic fatty liver disease independently predicts prediabetes during a 7-year prospective follow-up. Liver Int. 2013; 33 (9): 1406–12. https://doi.org/10.1111/liv.12200 PMID: 23656177

32. Bae JC, Cho YK, Lee WY, Seo HI, Rhee EJ, Park SE, et al. Impact of nonalcoholic fatty liver disease on insulin resistance in relation to HbA1c levels in nondiabetic subjects. Am J Gastroenterol. 2010; 105 (11): 2389–95. https://doi.org/10.1038/ajg.2010.275 PMID: 20628364

33. Nishi T, Babazono A, Maeda T, Imatoh T, Une H. Evaluation of the fatty liver index as a predictor for the development of diabetes among insurance beneficiaries with prediabetes. J Diabetes Investig. 2015; 6 (3): 309–16. https://doi.org/10.1111/jdi.12290 PMID: 25969716

34. ADA. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care. 2016; 39(Supplement 1): S13–S22. https://doi.org/10.2337/dc16-S005 PMID: 26696675

35. Serrano R, Garcia-Soidan FJ, Diaz-Redondo A, Artola S, Franch J, Diez J, et al. [Cohort Study in Primary Health Care on the Evolution of Patients with Prediabetes (PREDAPS): basis and methodology]. Rev Esp Salud Publica. 2013; 87(2): 121–35. https://doi.org/10.4321/S1135-57272013000200003 PMID: 23775102

36. ADA. American Diabetes Association. Standards of Medical Care in Diabetes-2017: Summary of Revisions. Diabetes Care. 2017; 40(Suppl 1): S4–S5. https://doi.org/10.2337/dc17-S003 PMID: 27979887

37. Kahn R, Buse J, Ferrannini E, Stern M, American Diabetes A, European Association for the Study of D. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2005; 28(9): 2289–304. PMID: 16123508

38. Simental-Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metabolic syndrome and related disorders. 2008; 6(4): 299–304. Epub 2008/12/11. https://doi.org/10.1089/met.2008.0034 PMID: 19067533

39. Guerrero-Romero F, Simental-Mendia LE, Gonzalez-Ortiz M, Martinez-Abundis E, Ramos-Zavala MG, Hernandez-Gonzalez SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010; 95 (7): 3347–51. Epub 2010/05/21. https://doi.org/10.1210/jc.2010-0288 PMID: 20484475

40. Giannini C, Santoro N, Caprio S, Kim G, Lartaud D, Shaw M, et al. The triglyceride-to-HDL cholesterol ratio: association with insulin resistance in obese youths of different ethnic backgrounds. Diabetes Care. 2011; 34(8): 1869–74. Epub 2011/07/07. https://doi.org/10.2337/dc10-2234 PMID: 21730284

41. Mostafa SA, Davies MJ, Morris DH, Yates T, Srinivasan BT, Webb D, et al. The association of the triglyceride-to-HDL cholesterol ratio with insulin resistance in White European and South Asian men and women. PLoS ONE. 2012; 7(12): e50931. Epub 2012/12/20. https://doi.org/10.1371/journal.pone.0050931 PMID: 23251403

42. Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. Cardiovasc Diabetol. 2014; 13: 146. Epub 2014/10/20. https://doi.org/10.1186/s12933-014-0146-3 PMID: 25326814

43. Zhang L, Chen S, Deng A, Liu X, Liang Y, Shao X, et al. Association between lipid ratios and insulin resistance in a Chinese population. PLoS ONE. 2015; 10(1): e0116110. Epub 2015/01/31. https://doi.org/10.1371/journal.pone.0116110 PMID: 25635876

44. Er LK, Wu S, Chou HH, Hsu LA, Teng MS, Sun YC, et al. Triglyceride Glucose-Body Mass Index Is a Simple and Clinically Useful Surrogate Marker for Insulin Resistance in Nondiabetic Individuals. PLoS ONE. 2016; 11(3): e0149731. Epub 2016/03/02. https://doi.org/10.1371/journal.pone.0149731 PMID: 26930652

45. Lee DY, Lee ES, Kim JH, Park SE, Park CY, Oh KW, et al. Predictive Value of Triglyceride Glucose Index for the Risk of Incident Diabetes: A 4-Year Retrospective Longitudinal Study. PLoS ONE. 2016; 11(9): e0163465. Epub 2016/09/30. https://doi.org/10.1371/journal.pone.0163465 PMID: 27682598

46. Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, et al. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med. 2005; 22(9): 1141–5. https://doi.org/10.1111/j.1464-5491.2005.01582.x PMID: 16108839

47. Wong VW, Hui AY, Tsang SW, Chan JL, Wong GL, Chan AW, et al. Prevalence of undiagnosed diabetes and postchallenge hyperglycaemia in Chinese patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2006; 24(8): 1215–22. https://doi.org/10.1111/j.1365-2036.2006.03112.x PMID: 17014580

48. Singh SP, Singh A, Pati GK, Misr B, Misra D, Kar SK, et al. A Study of Prevalence of Diabetes and Prediabetes in Patients of Non-Alcoholic Fatty Liver Disease and the Impact of Diabetes on Liver Histology in Coastal Eastern India. Journal of Diabetes Mellitus. 2014; 4(4): 290–6.

49. Bansal A, Mourya S, Verma A, Khanam B, Bansal R. A Study of Prevalence of Diabetes and Prediabetes in Patients with Non Alcoholic Fatty Liver Disease and Impact of Diabetes on Liver Histology. Journal of Clinical and Experimental Hepatology. 2016; 6: S23. https://doi.org/10.1016/j.jceh.2016.06.043

50. Ortiz-Lopez C, Lomonaco R, Orsak B, Finch J, Chang Z, Kochunov VG, et al. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). Diabetes Care. 2012; 35(4): 873–8. https://doi.org/10.2337/dc11-1849 PMID: 22374640

51. Forlani G, Giorda C, Manti R, Mazzella N, De Cosmo S, Rossi MC, et al. The Burden of NAFLD and Its Characteristics in a Nationwide Population with Type 2 Diabetes. J Diabetes Res. 2016; 2016: 2931985. https://doi.org/10.1155/2016/2931985 PMID: 27123461

52. Lonardo A, Ballestri S, Marchesini G, Angulo P, Loria P. Nonalcoholic fatty liver disease: a precursor of the metabolic syndrome. Dig Liver Dis. 2015; 47(3): 181–90. https://doi.org/10.1016/j.dld.2014.09.020 PMID: 25739820

53. Saponaro C, Gaggini M, Gastaldelli A. Nonalcoholic fatty liver disease and type 2 diabetes: common pathophysiologic mechanisms. Curr Diab Rep. 2015; 15(6): 607. https://doi.org/10.1007/s11892-015-0607-4 PMID: 25894944

54. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002; 137(1): 1–10. PMID: 12093239

55. Fracanzani AL, Valenti L, Bugianesi E, Andreoletti M, Colli A, Vanni E, et al. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. Hepatology. 2008; 48(3): 792–8. https://doi.org/10.1002/hep.22429 PMID: 18752331

56. Portillo-Sanchez P, Bril F, Maximos M, Lomonaco R, Biernacki D, Orsak B, et al. High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels. J Clin Endocrinol Metab. 2015; 100(6): 2231–8. https://doi.org/10.1210/jc.2015-1966 PMID: 25885947

57. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, et al. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. Diabetologia. 2003; 46(3): 359–64. https://doi.org/10.1007/s00125-003-1036-5 PMID: 12687334

58. Goessling W, Massaro JM, Vasan RS, D'Agostino RB Sr., Ellison RC, Fox CS. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. Gastroenterology. 2008; 135(6): 1935–44, 44 e1. https://doi.org/10.1053/j.gastro.2008.09.018 PMID: 19010326

59. Ryu S, Chang Y, Woo HY, Yoo SH, Choi NK, Lee WY, et al. Longitudinal increase in gamma-glutamyltransferase within the reference interval predicts metabolic syndrome in middle-aged Korean men. Metabolism. 2010; 59(5): 683–9. https://doi.org/10.1016/j.metabol.2009.08.024 PMID: 19922966

60. Mata-Cases M, Artola S, Escalada J, Ezkurra-Loyola P, Ferrer-Garcia JC, Fornos JA, et al. Consensus on the detection and management of prediabetes. Consensus and Clinical Guidelines Working Group of the Spanish Diabetes Society. Rev Clin Esp. 2015; 215(2): 117–29. https://doi.org/10.1016/j.rce.2014.10.012 PMID: 25553948

61. Sato F, Tamura Y, Watada H, Kumashiro N, Igarashi Y, Uchino H, et al. Effects of diet-induced moderate weight reduction on intrahepatic and intramyocellular triglycerides and glucose metabolism in obese subjects. J Clin Endocrinol Metab. 2007; 92(8): 3326–9. https://doi.org/10.1210/jc.2006-2384 PMID: 17519317

62. Viljanen AP, Iozzo P, Borra R, Kankaanpaa M, Karmi A, Lautamaki R, et al. Effect of weight loss on liver free fatty acid uptake and hepatic insulin resistance. J Clin Endocrinol Metab. 2009; 94(1): 50–5. https://doi.org/10.1210/jc.2008-1689 PMID: 18957499

63. Sung KC, Wild SH, Byrne CD. Resolution of fatty liver and risk of incident diabetes. J Clin Endocrinol Metab. 2013; 98(9): 3637–43. https://doi.org/10.1210/jc.2013-1519 PMID: 23873989

64. Yamazaki H, Tsuboya T, Tsuji K, Dohke M, Maguchi H. Independent Association Between Improvement of Nonalcoholic Fatty Liver Disease and Reduced Incidence of Type 2 Diabetes. Diabetes Care. 2015; 38(9): 1673–9. https://doi.org/10.2337/dc15-0140 PMID: 26156527

65. Berkowitz SA, Krumme AA, Avorn J, Brennan T, Matlin OS, Spettell CM, et al. Initial choice of oral glucose-lowering medication for diabetes mellitus: a patient-centered comparative effectiveness study. JAMA Intern Med. 2014; 174(12): 1955–62. https://doi.org/10.1001/jamainternmed.2014.5294 PMID: 25347323

66. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol. 2015; 62(5): 1148–55. https://doi.org/10.1016/j.jhep.2014.11.034 PMID: 25477264

67. Bril F, Cusi K. Nonalcoholic Fatty Liver Disease: The New Complication of Type 2 Diabetes Mellitus. Endocrinol Metab Clin North Am. 2016; 45(4): 765–81. https://doi.org/10.1016/j.ecl.2016.06.005 PMID: 27823604

68. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med. 2016; 165(5): 305–15. https://doi.org/10.7326/M15-1774 PMID: 27322798

69. Targher G, Bertolini L, Chonchol M, Rodella S, Zoppini G, Lippi G, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and retinopathy in type 1 diabetic patients. Diabetologia. 2010; 53(7): 1341–8. https://doi.org/10.1007/s00125-010-1720-1 PMID: 20369224

70. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol. 2016; 65(3): 589–600. https://doi.org/10.1016/j.jhep.2016.05.013 PMID: 27212244

71. Athyros VG, Alexandrides TK, Bilianou H, Cholongitas E, Doumas M, Ganotakis ES, et al. The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An Expert Panel Statement. Metabolism—Clinical and Experimental. 71: 17–32. https://doi.org/10.1016/j.metabol.2017.02.014 PMID: 28521870

72. Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006; 44(4): 865–73. https://doi.org/10.1002/hep.21327 PMID: 17006923

73. Sinn DH, Gwak GY, Park HN, Kim JE, Min YW, Kim KM, et al. Ultrasonographically detected non-alcoholic fatty liver disease is an independent predictor for identifying patients with insulin resistance in non-obese, non-diabetic middle-aged Asian adults. Am J Gastroenterol. 2012; 107(4): 561–7. https://doi.org/10.1038/ajg.2011.400 PMID: 22108448