European Journal of Internal Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Fatty liver index is associated to pulse wave velocity in healthy subjects: Data from the Brisighella Heart Study

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ARTICLE INFO

Keywords:
Liver steatosis
NAFLD
NASH
Arterial stiffness
Population study

ABSTRACT

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is associated to increased risk of cardiovascular disease. Our aim was to evaluate association of indexes of fatty liver with arterial stiffness (AS).

Methods: We analyzed data of adult volunteers visited during the last Brisighella survey. We evaluated the Pulse Wave Velocity (PWV) and the following non-invasive indexes of liver steatosis: Fatty Liver Index (FLI), Lipid Accumulation Product (LAP), Hepatic Steatosis Index (HSI). We compared patients according to the risk of Non-Alcoholic Steatohepatitis (NASH): low-risk (BMI < 28 and no diabetes), intermediate-risk (BMI ≥ 28 or diabetes), high-risk (BMI ≥ 28 and diabetes). Multiple Linear Regression analysis was assessed for predictors of AS.

Results: We studied 1731 volunteers. In subjects with low metabolic risk, HSI (RR = 0.138, 95%CI 0.105–0.170, $p < 0.001$), FLI (RR = 0.024, 95%CI 0.016–0.032, $p < 0.001$), LAP (RR = 0.014, 95%CI 0.008–0.020, $p < 0.001$) and Serum Uric Acid (RR = 0.150, 95%CI 0.024–0.275, $p = 0.019$) were significant predictors of AS. HSI and FLI emerged as predictors of PWV in intermediate risk group (RR = 0.116, 95%CI 0.071–0.160, $p < 0.001$; RR = 0.010, 95%CI 0.001–0.020, $p = 0.041$). In volunteers with high risk, FLI and Uric Acid were related to PWV (RR = 0.049, 95%CI 0.011–0.087, $p = 0.013$; RR = 0.632, 95% CI 0.222–1.041, $p = 0.003$).

Conclusion: Fatty liver indirect indexes were associated to AS in subjects with different metabolic risk profiles.

1. Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common liver disorder in Western countries, affecting 17–46% of adults [1]. NAFLD is defined by the presence of histological steatosis in > 5% of hepatocytes (or by a proton density fat fraction > 5.6%) [2]. In the vast majority of cases, NAFLD should be considered the liver expression of metabolic syndrome. However, a liver pattern of NAFLD can be diagnosed in 7% of normal-weight people too [3]. Remarkably, NAFLD embodies a wide spectrum of diseases including fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) [4].

In general, subjects with fatty liver are at higher risk of developing type 2 diabetes and cardiovascular diseases, either because of the high prevalence of associated risk factors [i.e. obesity and insulin-resistance (IR)], but also independently, suggesting its specific role in the atherosclerotic disease [5,6]. Notably, the link between fatty liver, type 2 diabetes and cardiovascular diseases seems to be represented by IR. IR can induce pathological ectopic fat accumulation combined with a low-grade chronic inflammatory state, in turn resulting in abnormal glucose, altered fatty acid and lipoprotein metabolism, increased oxidative stress, deranged adipokine profile, hypercoagulability, endothelial dysfunction, accelerated progression of atherosclerosis and increased risk to develop cardiovascular risk [5].

In the clinical practice, the invasive nature of liver biopsy can limit

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https://doi.org/10.1016/j.ejim.2018.03.010
Received 11 September 2017; Received in revised form 6 February 2018; Accepted 19 March 2018

the diagnosis of liver steatosis. Consequently, non-invasive methods have been developed. For large scale screening studies, serum biomarkers should be preferred respect to imaging techniques, as availability and cost of imaging might affect the diagnostic feasibility [2]. Among the indirect indexes of liver steatosis, Fatty liver index (FLI), an algorithm based on waist circumference (WC), body mass index (BMI), and levels of triglyceride and γ-glutamyltransferase [6], represents one of the most interesting tool being able to predict metabolic, hepatic and cardiovascular outcomes [7,8].

Another index for screening of steatosis is the Lipid Accumulation Product (LAP) [9]. LAP, built for the assessment of cardiovascular risk, can be calculated by expressing waist enlargement as the measured WC that exceeded a sex-specific minimum value and then multiplying waist enlargement by the concentration of fasting triglycerides [10,8]. Fedchuk et al. [11] reported that FLI and LAP may be used to detect steatosis in patients for clinical and research purposes. In 2010, a further indirect index of steatosis was developed, the Hepatic Steatosis Index (HSI) [12]. HSI takes into account transaminases, BMI, and diabetes mellitus and it was validated in an internal cohort.

NAFLD was found to be an independent predictor of arterial stiffness (AS) faster progression, even after adjusting for other CVD risk factors [13]. Pulse wave velocity (PWV) is an excellent measure of AS and it is independently associated with increased CVD risk across several patient groups and even in the general population [14]. Sunbul et al. [15] demonstrated that in NAFLD patients, the liver fibrosis represents the major determinant of AS indirectly suggesting that NASH and not the “simple” NAFL can influence the AS itself. In fact, patients with NASH show higher cardiovascular risk than patients with NAFL [16,17] who seem to have an overall benign clinical course [18].

However, Yu et al. [19] showed that in Chinese non-obese, non-hypertensive, and non-diabetic young and middle-aged patients, fatty liver diagnosed by ultrasonography correlated with PWV.

Patients at high risk of NASH (overweight and diabetic) show a well-described impaired cardiovascular profile. Indeed, in this subgroup, it is expected that indirect indexes of steatosis might correlate with AS. On the other hand, this association is at least doubtful in patients with intermediate or low metabolic risk.

Our aim was to evaluate the possible relationship between indirect indexes of fatty liver and AS in healthy adult subjects with different metabolic risk profiles.

2. Materials and methods

2.1. Study design

The Brisighella Heart Study is a longitudinal population study that is active since 1972. It works on a randomized sample representative of the population of Brisighella, a rural North-Italian village. The Institutional Ethics Board of the University Hospital of Bologna approved the protocol and all participants gave written informed consent to participate. The complete version of the protocol and the history of the study have been extensively described elsewhere [20,21].

In this study, laboratory and instrumental data of adult volunteers evaluated from 2004 to 2008 for primary prevention for cardiovascular disease were recorded. The exclusion criteria were the following: known arterial hypertension or ongoing treatment, known hyperlipidaemia or ongoing treatment, presence of causes of steatosis different from an altered metabolism such as alcohol use (> 30 or > 20 g/day for men and women, respectively), consumption of hepatotoxic medication or Hepatitis C virus infection (present or past). A full descriptive analysis of the investigated population sample was carried out. All available routine clinical and laboratory parameters have been sampled with standardized methods [22,23]. We conducted also a subanalysis dividing the cohort according to BMI and presence of type 2 diabetes, two consolidated predictors of NASH [24]. Indeed, we obtained the following three subgroups: a) low risk of NASH (BMI < 28 without type 2 diabetes), b) intermediate risk (BMI ≥ 28 or type 2 diabetes), and c) high risk (BMI ≥ 28 and type 2 diabetes).

2.2. Vascular parameters

AS was assessed using the Vicorder apparatus (Skidmore Medical Ltd), a validated cuff-based device that estimates central blood pressure using a brachial-to-aortic transfer function. Pulse wave velocity (PWV) represents an extensively used parameter for the indirect assessment of AS. PWV consists of the measurement of the pulse wave transmission through the arteries and is considered a reliable and early marker of AS and a predictor of cardiovascular risk [25].

The theoretical basis of PWV is elucidated with the equation of Moens–Korteweg [26], whereas in clinical practice, PWV is calculated as the length between 2 measurement sites divided by the time the pulse wave needs to cover that distance (m/s) [27].

The Vicorder apparatus records the radial pressure and, with a specific algorithm, is able to calculate the central blood pressure curve. PWV is calculated with a simultaneous measurement of carotid and femoral blood pressure. A small neck pad containing a photoplethysmographic detector is placed around the neck, and a normal cuff is positioned around the thigh of the patient. The distance between the suprasternal notch and the thigh cuff is measured with a measuring tape. This length represents the distance covered by the pulse wave in its carotid–femoral path and is used by the Vicorder apparatus to establish the PWV value [28,29]. The Vicorder system automatically adjusts the PWV measurement for heart rate and means artery pressure, as they are simultaneously recorded.

2.3. Non-invasive indexes of hepatic steatosis

The following non-invasive indexes of fatty liver were computed: 1) FLI [calculated as $e^{0.953 * \log e (\text{triglycerides}) + 0.139 * \text{BMI} + 0.718 * \log e (\text{gGT}) + 0.053 * (\text{waist circumference} - 15.745)} / (1 + e^{0.953 * \log e (\text{triglycerides}) + 0.139 * \text{BMI} + 0.718 * \log e (\text{gGT}) + 0.053 * \text{waist circumference} - 15.745)} * 100$] [8]. 2) LAP {calculated as [WC (cm) − 65] × TG (mmol/L) for men and [WC (cm) − 58] × TG (mmol/L) for women} [8]; 3) HSI [calculated as 8 × (GPT-ALT/GOT-AST ratio) + BMI (+2 if woman; +2 if T2D)] [14].

2.4. Statistical analyses

A physician trained in statistics encoded all samples into a dedicated database. Data are expressed as the mean [± standard deviation (sd)] or median (with range) as applicable. Confidence interval (CI) is presented where appropriate.

A full descriptive analysis was performed of all considered variables. The Kolmogorov–Smirnov normality test was performed for the continuous variables. The continuous variables were compared by ANOVA followed by the Tukey post hoc test. Non-normally distributed parameters were then log-transformed before continuing with further analyses. First, we carried out an age-adjusted and blood pressure-adjusted bivariate correlation for all the indirect indexes of steatosis and PWV. Then, we performed an age-adjusted and blood pressure-adjusted multiple linear regression analysis using PWV as dependent variable and gender, smoking habit, physical activity intensity, LDL-C, HDL-C, TG, apoB, apoAI, SUA, HSI, LAP and FLI as independent ones. This analysis was carried out including in the model only one fatty liver index and excluding the parameters used to calculate the single fatty liver index considered in the model itself, in order to avoid overfitting phenomena. The analysis was conducted firstly on the entire cohort and then was repeated by the predefined subgroups (low, intermediate and high-risk of NASH). A significance level of 0.05 was considered for every test. SPSS® software version 21.0 (MJ Norusis, Chicago, US) was used for all statistical analyses.