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Echocardiography and NAFLD (non-alcoholic fatty liver disease)☆

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ABSTRACT

Non-alcoholic-fatty-liver-disease (NAFLD) is associated with atherosclerosis, increased cardiovascular risks and mortality. We investigated if, independently of insulin resistance, diet, physical activity and obesity, fatty liver involvement has any relationship with echocardiographic measurements in NAFLD.

Patients and methods: 660 NAFLD and 791 non-NAFLD subjects, referred to the same out-patients medical unit for lifestyle-nutritional prescription, were studied. Congestive heart failure, myocardial infarction, malignancies, diabetes mellitus, extreme obesity, underweight-bad-nourished subjects and renal insufficiency were exclusion criteria. Liver steatosis was assessed by Ultrasound-Bright-Liver-Score (BLS), left ventricular ejection fraction (LVEF), trans-mitral E/A doppler ratio (diastolic relaxation) and left ventricular myocardial mass (LVMM/m^2) by echocardiography. Doppler Renal artery Resistive Index (RRI), insulin resistance (HOMA) and lifestyle profile were also included in the clinical assessment.

Results: LVMM/m^2 is significantly greater in NAFLD, 101.62 ± 34.48 vs. 88.22 ± 25.61, $p < 0.0001$ both in men and in women. Ejection fraction is slightly smaller only in men with NAFLD; no significant difference was observed for the E/A ratio. BMI (30.42 ± 5.49 vs. 24.87 ± 3.81; $p < 0.0001$) and HOMA (2.90 ± 1.70 vs. 1.85 ± 1.25; p: 0.0001) were significantly greater in NAFLD patients. By Multiple-Linear-Regression, NAFLD and unhealthy dietary profile are associated also in lean non-diabetic subjects with lower systolic function, independently of BMI, dietary profile, physical activity, RRI and insulin resistance.

Conclusion: NAFLD may be a meaningful early clue suggestive of diminishing heart function, with similar determining factors. NAFLD is amenable to management and improvement by lifestyle change counseling, addressing a dual target: reducing fatty liver, which is easily monitored by ultrasound, and, independently, maintaining a normal heart function.

1. Introduction

NAFLD (non-alcoholic fatty liver disease) is prevalent in most populations and is not directly attributable to single specific factors [1]. Unhealthy lifestyle and obesity are commonly considered the most probable causes in patients who are non-diabetic and who do not abuse alcohol, even though lean individuals can also be involved [2], meaning that other dietary or non-dietary factors could also be implicated. An association of NAFLD with coronary artery disease is currently recognized [3], but the relationship, if any, of the severity of steatosis with heart dysfunction is not defined. Relationship of liver triglyceride content with liver function was reported, at least in diabetes type 2, and was associated with decreased myocardial perfusion, reduced glucose uptake and high-energy phosphate metabolism in conjunction with impaired whole-body insulin sensitivity [4]. The prognostic impact of cardio-hepatic interactions in heart failure was investigated mainly in advanced stages of the disease [5], and only a few reports dealing with small groups are available for NAFLD; most of them include diabetic patients, and this is an important confounding factor. Relationship of NAFLD severity with greater intrarenal arterial resistance [6], assessed by renal resistive index (RRI), was reported and this associated factor can have a further influence on heart function and anatomy. Several reports display increased coronary atherosclerotic burden in the presence of NAFLD [7–9]: the hypothesis that liver steatosis could be, per se, a true risk factor for heart disease cannot be discarded a priori, but this needs to be a focus for renewed research activity. Overall, NAFLD has the feature of a comprehensive morphological marker of pathological ectopic fat accumulation combined with a low-grade chronic inflammatory state affecting adipose tissue and also characterized almost

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universally by insulin resistance [10]. The investigations elucidating relationship of NAFLD with subclinical atherosclerosis are many and important [11–16], with the limitation of addressing almost exclusively to ultrasound anatomical aspects of carotid artery, as a paradigm of arterial atherosclerotic involvement. Heart function can be impaired both by atherosclerotic arterial flow decline, but also by changes of anatomy and physiology of myocardium. Intervention studies have reported significant improvement or disappearance of NAFLD after comprehensive counseling and behavioral changes [17–19]. The aim of this study is to investigate whether the severity of liver steatosis can predict a poorer heart function, assessed by the most basic echocardiography measurements, in non-diabetic NAFLD patients independently of insulin resistance, dietary profile, intra-renal arterial resistance and obesity.

2. Patients and methods

This is an observational study, reporting the association of some basic liver, heart and kidney artery flow ultrasound measurements with laboratory assays and with some comprehensive score describing lifestyle profile in healthy subjects, non-diabetic and with minimal alcohol habits. The criterion currently accepted for the definition of NAFLD is alcohol daily intake less than 20 g. These subjects were consecutively referred to the same out-patient public medical unit (day-hospital of the Internal Medicine Department, Non-invasive Diagnostic and Medical Therapy Unit, the University Hospital) for lifestyle-nutritional prescription plans for reducing overweight (BMI > 25 ≤ 30)-obesity (BMI > 30 ≤ 40) throughout January 2008–December 2014. A comprehensive ultrasound assessment (liver-abdomen, heart, thyroid and lung) was provided according to our current practice [1]. At last, 1451 patients, satisfying the criteria below detailed, 660 NAFLD and 791 non-NAFLD subjects (women 907, men 544), without relevant acute or chronic disease, as detailed below in the exclusion criteria, were respectively included. According to exclusion criteria 1256 further subjects, also referred to the clinic in the same period and potentially eligible, were also observed. They were assessed and managed with specific workups according to the respective diagnosis, but not included in this study due to the presence of diabetes (451/1256), of other isolated or concurrent exclusion criteria (780/1256), or to insufficient availability of laboratory or ultrasound data (75/1256). This group of subjects not included in the analysis of data is not further described in the following sections.

The preliminary exclusion criteria were: (1) all patients with abnormal clinical, electrocardiography or echocardiography signs suggestive of moderate–severe congestive heart failure, previous myocardial infarction, idiopathic myocardiopathy, pericarditis; (2) any history of, or active malignancies; severe chronic liver disease, apart from the lone finding of bright liver; (3) abnormal aminotransferase levels at the beginning of this study, defined as alanine transaminase (ALT) > 30 IU/L in men and ALT > 19 IU/L in women; acute or chronic virus hepatitis were excluded by concurrent laboratory essays, as detailed below; (4) any history of diabetes mellitus (fasting glucose ≥126 mg/dL or HbA1c ≥ 6.5%); (5) extreme obesity (BMI ≥ 40) and underweight badnourished profile (BMI < 18.5 or serum albumin <3 g/dL); (6) acute and/or chronic infectious, rheumatic or autoimmune disease, (7) alcohol abuse (exceeding 20 g/day on a weekly base); [1] (8) renal insufficiency, i.e. glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 and/or proteinuria >0.10 g/day. GFR is assessed as estimated glomerular filtration rate (eGFR) by the modification of diet in renal disease (MDRD) formula in mL/min per 1.73 m^2, according to the Clinical Practice Guidelines for Chronic Kidney Disease KDOQI.

The severity of liver steatosis was assessed by ultrasound (US) Bright Liver Score (BLS), graded 0–3 [20] and previously validated by US-guided FNAB (Fine needle aspirate biopsy by 20 gauge Menghini's needles) [1,20]. GE echo color doppler machines (GE Logiq 5/Vivid7 Expert US manufactured by GE Medical Systems, Milwaukee, WI, USA), high resolution, with real-time convex, phased array and linear scan transducers, was used throughout this study. Left ventricular heart function was assessed by m-mode echocardiography as ejection fraction (LVEF), using the Teichholz methods; diastolic relaxation was assessed as transmitral E/A Doppler ratio and left ventricular hypertrophy evaluated according to the recommendations of the American Society of Echocardiography [21] for quantifying the left ventricular myocardial mass (LVMM/m^2). Left ventricular internal diameter was measured at end diastole, and calculated according to the following formula: 0.8(1.04(IVS þ LVDD þ PWT)3 – LVDD3) þ 0.6 g, 12 where IVS is interventricular septum thickness in diastole; PWT is posterior wall thickness in diastole; LVDD is left ventricular diameter in diastole. Routine laboratory tests included virus hepatitis (A, B and C virus: HAV, HBV, and HCV) and cancer biomarkers (Alpha-fetoprotein, CEA, Ca125, Ca 19-9, Ca15-3), thyroid hormones, thyroid-stimulating hormone (TSH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γGT), ferritin, total protein, and albumin. Renal color doppler echography is performed assessing intraparenchymal renal artery RRI (peak systolic velocity-end diastolic velocity/peak systolic velocity), as elsewhere detailed [6]. After recording pulse and blood pressure, the first measurement is the size of the left and right kidney. For orientation purposes, perfusion in the whole of the left and right kidneys is then checked using color doppler ultrasonography and the main trunk of the renal artery is displayed. Three measurements for each kidney are taken by pulsed doppler within 5 min near the interlobar artery. RRI is calculated as the average value of all measurements taken. The homoeostasis model-insulin resistance index (HOMA-IR) was used; insulin resistance is conventionally considered when HOMA-IR > 1.7, according to the likelihood ratios for 11-year cardiovascular disease prediction [22].

Mediterranean Diet Adherence Profile was assessed by the Adherence to Mediterranean Diet Score (AMDS) on the basis of a 1-week recall computerized questionnaire [1], using a pictogram-based method of visualizing dietary intake – descriptive also of the size of the single portion; pictograms includes also items for the quantification of sedentary habits, which is otherwise quantified by detailed physical activity reports (Baecke questionnaire) [17]. The Western Dietary Profile score, as a simplified paradigm of unhealthy diet, was assessed submitting a specific questionnaire, which is reported in appendix, below the Adherence to Mediterranean Diet Score (Appendix 2); also the Baecke's physical activity questionnaire, briefly described in appendix, was subsequently studied by statistical analysis. The questionnaire submitted for quantifying sun exposure score, was used mainly as an index of the open air activity; sleep habits and noise exposure questionnaires are routinely included within the context of a comprehensive lifestyle assessment, and detailed in Appendix 2; these three score were not used in the present statistical analysis. The regional ethics committee of the University Hospital of Catania approved this observational study (registration number 1151.15). Participants' consent was preliminarily obtained for privacy and for the analysis and use of personal anonymized data.

Statistical analysis: descriptive results of continuous variables are expressed as averages (±SD). Student's *t* test, univariate and multiple regression analysis were performed using SPSS 18.0 for Windows (SPSS, Chicago, IL).

3. Results

General characteristics of the studied population, are presented separately by gender in Table 1, women, and in Table 2, men. Overall, BMI was 27.4 ± 5.41; age 50.52 ± 10.05; differences between NAFLD vs. controls, not separately by gender, are reported in Appendix 3. According to BMI, the distribution in the overall population was: normal weight-slight overweight (n = 1039) i.e. BMI 20-30 (24.70 ± 2.81); obesity (n = 412) i.e. BMI >30 (34.19 ± 4.29).

According to the US detection of liver steatosis, NAFLD patients are comparable in terms of age (years 50.65 ± 10.16 vs. 50.41 ± 9.96; p: 0.641) to subjects of the normal liver imaging group. Differently, BMI