INPLASY

Effect of non-alcoholic fatty liver disease on left ventricular mechanics in patients without overt cardiac disease: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

INTRODUCTION

*R*eview question / Objective What is the effect of NAFLD on LV-GLS in individuals without overt heart disease?

Rationale The possible association between liver fibrosis and MF, noninvasively assessed by LV-GLS, might clarify the mechanisms linking NAFLD and HFpEF, thus allowing the clinicians to adopt preventive strategies for HF occurrence.
Over the last few years, a fair number of echocardiographic studies have investigated the link between NAFLD and early cardiac remodeling by using conventional transthoracic echocardiography (TTE) implemented with two-dimensional (2D) STE analysis. These studies were primarily designed for assessing LV-GLS magnitude in NAFLD patients without overt cardiac disease, compared to healthy controls without NAFLD. However, they reported not univocal results. Accordingly, the present systematic review and meta-analysis has been designed to analyze the main findings of these studies and explore the main pathophysiological mechanisms underpinning the subclinical myocardial dysfunction in NAFLD patients without known heart disease.

Condition being studied Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis not related to a secondary cause of hepatic fat accumulation (PMID: 28714183). It represents the most common form of chronic liver disease worldwide, with a global prevalence of 30% (PMID: 36626630). NALFD is more frequently detected in the clinical practice due to the spread of unhealthy eating habits and sedentary lifestyle (PMID: 32799384), the rising obesity rate in rural areas (PMID: 31068725) and the population aging (PMID: 35790018).
Recent epidemiological studies have demonstrated that NAFLD is independently associated with increased risk of new-onset heart failure (HF) in healthy adults (PMID: 32345225). Notably, NAFLD patients have a higher risk to develop heart failure with preserved ejection fraction (HFpEF), also after adjustment for baseline

clinical and demographic factors (PMID: 34755544). The larger is the extent of liver fibrosis, the higher is the risk of coronary artery disease, adverse cardiac remodeling and cardiac arrhythmias (especially atrial fibrillation), which may precede and promote the HFpEF occurrence (PMID: 35027111).

This evidence highlights the importance of identifying an early marker of myocardial dysfunction in NAFLD patients without known heart disease.

METHODS

Search strategy Two independent reviewers (A.S. and M.L.) will perform an accurate search of all studies examining traditional echoDoppler variables by TTE and LV-GLS by STE, in NAFLD patients without overt cardiac disease, using PubMed, Embase and Scopus databases. The following terms will be included in the search strategy: "non-alcoholic fatty liver disease" OR "NAFLD" AND "echocardiography" OR "speckle tracking echocardiography" AND "cardiac function" OR "left ventricular mechanics" AND "left ventricular global longitudinal strain" OR "left ventricular strain" OR "LV-GLS". There will be no specific timeframe for the inclusion of echocardiographic studies. There will be no language restriction.

Participant or population All case-control studies evaluating both conventional echoDoppler parameters and LV-GLS in NAFLD patients without known heart disease vs. healthy individuals without NAFLD, regardless of their age, will be included in this systematic review and meta-analysis.

Intervention The primary endpoint is to quantify the effect of NAFLD on LV-GLS in individuals without overt cardiac disease.

Comparator Cohorts of healthy individuals without NAFLD.

Study designs to be included Case-control studies.

Eligibility criteria All case-control studies evaluating both conventional echoDoppler parameters and LV-GLS in NAFLD patients without known heart disease vs. healthy individuals without NAFLD, regardless of their age, were included in this systematic review and meta-analysis. Criteria of exclusion were the following: echocardiographic studies focused on patients affected by nonalcoholic steatohepatitis (NASH) or liver cirrhosis; echocardiographic studies conducted in NAFLD patients without LV-GLS assessment by STE, echocardiographic studies performed in NAFLD patients without controls, studies that measured myocardial strain parameters with imaging techniques different from 2D-STE analysis, and finally published documents different from clinical articles.

Information sources Two independent reviewers (A.S. and M.L.) will perform an accurate search of all studies examining traditional echoDoppler variables by TTE and LV-GLS by STE, in NAFLD patients without overt cardiac disease, using PubMed, Embase and Scopus databases.

Main outcome(s) The primary endpoint is to quantify the effect of NAFLD on LV-GLS in individuals without overt cardiac disease.

Additional outcome(s) No.

Data management Based on the aforementioned eligibility criteria, two reviewers (A.S. and M.L.) will screen the records and independently collect the following information concerning both NAFLD patients and healthy controls: (1) demographics (age and sex); (2) anthropometrics [body surface area (BSA), body mass index (BMI) and waist circumference (WC)]; (3) prevalence of the most relevant cardiovascular risk factors (hypertension, smoking, type 2 diabetes, dyslipidemia and obesity); (4) hemodynamics [heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP)]; (5) blood tests comprehensive of serum levels of transaminases and gamma-glutamyl transferase (GGT), glycometabolic parameters, estimated glomerular filtration rate (eGFR) (PMID: 10075613), lipid profile and C-reactive protein (CRP); 6) conventional TTE-derived echoDoppler indices of cardiac chambers cavity size and function; 7) LV-GLS magnitude and eventual additional data on left ventricular global strain rate (LV-GSR) and/or left atrial reservoir strain (LAS); finally, the current medical treatment.

Continuous data will be expressed as the median (range interquartile), whereas categorical variables as percentages (%).

Quality assessment / Risk of bias analysis The National Institutes of Health (NIH) Quality Assessment of Case-Control Studies will be used to assess the risk of bias (RoB) (PMID: 32111253). For each study, the quality rating will be independently estimated as "good", "fair", or "poor" by two authors (A.S. and G.L.N.). The level of agreement between the two raters will be quantified by the Cohen's Kappa coefficient (PMID: 23092060).

Strategy of data synthesis Continuous data will be expressed as the median (range interquartile), whereas categorical variables as percentages (%). The primary endpoint is to quantify the effect of NAFLD on LV-GLS in individuals without overt cardiac disease. Continuous data (LV-GLS) will be pooled as the standardized mean difference (SMD) comparing NAFLD cohorts with healthy controls. The overall SMD of LV-GLS will be calculated using the random-effect model, due to the high statistical heterogeneity among the included studies. The I-squared statistic (I2) will be used to quantify the proportion of total variation between studies. Begg's funnel plots and Egger's test will be used to assess potential publication bias. Meta-regression analysis will be performed to explore the relationship between LV-GLS and several potential confounders, such as age, male sex, BMI, SBP, fasting plasma glucose (FPG), total cholesterol, anti-hypertensive therapy and the ultrasound system used for STE analysis. Finally, a sensitivity analysis will be performed to evaluate the impact of removing each of the studies on the overall SMD of LV-GLS. The 95% confidence intervals (CIs) will be calculated and two-tailed p values less than 0.05 will be considered to be statistically significant. Comprehensive Meta-Analysis version 3.0 (Biostat, Englewood, NJ, USA) will be the software employed to perform the statistical analysis.

Subgroup analysis Not planned.

Sensitivity analysis A sensitivity analysis will be performed to evaluate the impact of removing each of the studies on the overall SMD of LV-GLS.

Language restriction No language restriction.

Country(ies) involved Italy.

Keywords NAFLD; left ventricular mechanics; LV-GLS; subclinical myocardial dysfunction.

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