Research Article

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Chronic HCV infection increases cardiac left ventricular mass index in normotensive patients

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Background & Aims: Left ventricular hypertrophy (LVH), is an independent predictor for cardiovascular events. We investigated if chronic hepatitis C virus (HCV) infection and the related insulin resistance (IR)/hyperinsulinemia could influence the increase of left ventricular mass (LVM).

Methods: We enrolled 260 outpatients matched for age, body mass index, gender, ethnicity: 52 with never-treated uncomplicated chronic HCV infection (HCV^+), 104 never-treated hypertensives (HT) and 104 healthy subjects (NT). LVM was calculated according to the Devereux formula and indexed for body surface area. The following laboratory parameters were measured: fasting plasma glucose and insulin, total, LDL- and HDL-cholesterol, triglyceride, creatinine, e-GFR-EPI, HOMA. Quantitative HCV-RNA was assessed by PCR.

Results: HCV^+ patients with respect to healthy normotensive subjects had an increased LVMI (100 ± 23 *vs.* 83 ± 15 g/m^2; $p < 0.0001$), similar to that observed in HT group (103 ± 25 g/m^2). Regarding biochemical variables, HCV^+ patients, in comparison with normotensive healthy subjects, had higher triglyceride, creatinine, fasting insulin and HOMA (3.2 ± 1.3 *vs.* 2.5 ± 1.0; $p < 0.0001$). At linear regression analysis, the correlation between LVMI and HOMA was similar in HT ($r = 0.528$, $p < 0.0001$) and HCV^+ ($r = 0.489$, $p < 0.0001$) groups. At multiple regression analysis, HOMA resulted the major determinant of LMVI in all groups, explaining respectively 21.8%, 27.8%, and 23.9% of its variation in NT, HT and HCV^+. At correlational analysis HCV-RNA and HOMA demonstrated a strong and linear relationship between them, explaining the 72.4% of their variation ($p = 0.022$).

Conclusions: We demonstrated a significant and direct correlation between HOMA and LVMI in patients with chronic HCV infection, similar to that observed in hypertensives.

Keywords: Chronic C hepatitis; Left ventricular mass; Insulin resistance; Cardiovascular risk; Hypertension.

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Abbreviations: LVH, left ventricular hypertrophy; HCV, hepatitis C virus; LVM, left ventricular mass; HOMA, homeostasis model assessment; LVMI, left ventricular mass index; IR, insulin resistance; T2DM, type-2 diabetes mellitus; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; CV, coefficient of variation.

Introduction

Hepatitis C virus (HCV) infection is one of the major causes associated with chronic liver disease, affecting over 3% of world population. The majority of these subjects (90%) progress to chronic hepatitis C inducing both liver fibrosis and cirrhosis [1]. In addition, there are several evidences demonstrating that HCV infection is associated with some metabolic alterations, such as insulin resistance (IR) and new onset of type-2 diabetes mellitus (T2DM). In fact, several epidemiological and experimental data clearly demonstrate that HCV, operating by different pathogenetic mechanisms, is able to alter glucose metabolism [2–10]. In keeping with this, IR is already increased in the early stages of HCV-related liver disease [3]. A possible explanation of this consists in the fact that HCV infection is able to alter glucose homeostasis through some direct and indirect mechanisms, leading to both hepatic and extra-hepatic IR [11,12].

Consequently, despite a favourable lipid profile, the cardiovascular risk of HCV^+ patients is moderately increased, as a consequence of the presence of subclinical atherosclerotic organ damage [6,13–16]. On the other hand, there are several evidences demonstrating that insulin signalling influences, through an interaction with the renin-angiotensin-aldosterone system [17–19], cardiac growth and the development of LVH [20–22] that is recognised as an independent predictor for cardiovascular events in such conditions as hypertension [23], diabetes [20], chronic kidney disease [24], as well as in general population [25].

At present, no information exists regarding a possible association between HCV infection and cardiac mass increase. Therefore, we designed the present study with the aim to investigate the effects of IR/hyperinsulinemia HCV-related on the development of cardiac hypertrophy in a group of subjects with a history of never-treated uncomplicated chronic HCV infection (HCV^+) in comparison with both never-treated hypertensives (HT) and healthy subjects (NT).

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Patients and methods

Study population

To test our hypothesis we designed a case-control study involving patients evaluated at the University Hospital of Catanzaro. We recruited 52 HCV$^+$ normotensive Caucasian outpatients (40 males and 12 females, mean age 48.73 ± 10.4 years). They were matched for age, body mass index and gender in a 1:2:2 ratio with 208 subjects participating to the CAtanzaro MEtabolic RIsk factors Study (CATAMERIS) [26], 104 never treated HT (77 males and 27 females, mean age 48.5 ± 9.7 years) and 104 NT (79 males and 25 females, mean age 48.8 ± 11.2 years). At the time of the first evaluation, both HCV$^+$ and hypertensive patients were untreated with antiviral therapy or antihypertensive drugs. Secondary forms of hypertension were excluded by systematic testing by a standard clinical protocol including renal ultrasound studies, computed tomography, renal scan, catecholamine, plasma renin activity and aldosterone measurements. Other exclusion criteria were T2DM detected by an oral glucose tolerance test, according to ADA guidelines; history or clinical evidence of angina, myocardial infarction, valvular heart disease, cardiomyopathy, heart failure or peripheral vascular disease; administration of any drugs interfering with glucose metabolism; kidney, thyroid, endocrine and advanced liver diseases, transplanted patients, history of malignant disease. We collected measurements of height and weight according to a standardised protocol, and body mass index was calculated as kilograms per square meter. The Ethical Committee approved the protocol and informed written consent was obtained from all participants. All the investigations were performed in accordance with the principles of the Declaration of Helsinki.

Blood pressure measurements

Readings of clinic blood pressure (BP) were obtained in the left arm of the supine patients, after 5 min of quiet rest, with a mercury sphygmomanometer. Minimum three BP readings were taken on three separate occasions at least 2 weeks apart. Systolic and diastolic BP was recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff sounds. Baseline BP values were the average of the last two of the three consecutive measurements obtained at intervals of 3 min. Patients with a clinic systolic BP (SBP) >140 mmHg and/or diastolic BP (DBP) >90 mmHg were defined as hypertensive.

Laboratory determinations

All laboratory measurements were performed after 12 h of fasting. Plasma glucose was determined immediately by the glucose oxidation method [Glucose analyzer, Beckman Coulter, Milan; intra-assay coefficient of variation (CV) 2.2%, inter-assay CV 3.8%]. Serum insulin was determined in duplicate by a highly specific radioimmunoassay using two monoclonal antibodies; intra-assay CV 2.1%, inter-assay CV 2.9%. IR was estimated by homeostasis model assessment ($HOMA_{IR}$) according to the following equation: HOMA = [insulin (μU/ml ∗ glucose (mmol/l)]/22.5 [27]. Total, low-density lipoprotein- (LDL), and high-density lipoprotein- (HDL) cholesterol and triglyceride concentrations were measured by enzymatic methods (Roche Diagnostics GmbH, Mannheim, Germany). Creatinine was measured by using Jaffe methodology. Values of estimated glomerular filtration rate (ml/min/1.73 m^2) were calculated by using the equation proposed by investigators in the chronic kidney disease epidemiology (CKD-EPI) collaboration [28]. Quantitative HCV-RNA was assayed by a real-time polymerase chain reaction (PCR) assay.

Echocardiographic measurements

Tracings were taken 24–48 h after laboratory/clinical determinations with patients in a partial left decubitus position using a VIVID-7 Pro ultrasound machine (GE Technologies, Milwaukee, WI) with an annular phased array 2.5-MHz transducer. Echocardiographic readings were made in random order by the investigator, who had no knowledge of patients' BP and other clinical data. Only frames with optimal visualisation of cardiac structures were considered for reading. The mean values from at least five measurements of each parameter for each patient were computed. Having the same experienced sonographer (SM) performing all studies in a dimly lit and quiet room optimised the reproducibility of measurements. In our laboratory, the CVs were 3.85% for posterior wall thickness, 3.70% for interventricular septum thickness, 1.50% for left ventricular internal diameter, and 5.10% for LVM.

M-mode measurements

Tracings were recorded under two-dimensional guidance, and M-mode measurements were taken at the tip of the mitral valve or just below. Measurements of interventricular septum thickness, posterior wall thickness, and left ventricular internal diameter were made at end-diastole and end-systole. LVM was calculated using the Devereux equation [29] and normalised by body surface area [LVM index (LVMI)].

Statistical analysis

ANOVA for continuous clinical and biological data was performed to test the differences among groups, and the Bonferroni post-hoc test for multiple comparisons was further performed; for dichotomic variables we used the χ^2 test. Data are expressed as mean ± SD, and binary data as percent frequency. Correlation coefficients were calculated according to Pearson's method. The independent relationship between LVMI and HOMA was investigated by univariate and multiple linear regression analysis, in the whole study population and in the three groups separately. In the multivariate model we inserted only HOMA to avoid a possible collinearity with fasting glucose and insulin. To compare the effect of a fixed increase in HOMA (1 unit) on LVMI in NT, HT, and HCV$^+$ patients, we performed a covariance analysis, crude and adjusted for all variables significantly different among groups (Table 1). The effect of the patient's status, on HOMA-LVMI relationship, was assessed adding into the same linear regression model HOMA, patient's status (NT, HT, and HCV$^+$), the interaction term of these two variables, and all variables significantly different in the study groups. The estimated increase in LVMI, indicated by a fixed increase in HOMA, was then derived by the slope of the regression line of the HOMA-LVMI link fitted to the three study groups. The multiple linear regression analysis of LVMI in the three study groups separately was performed by a stepwise approach in order to construct parsimonious models. Differences were assumed to be significant at p <0.05. All calculations were done with a standard statistical package (SPSS for Windows version 16.0, Chicago, IL, USA).

Results

Study population

Clinical and laboratory characteristics of the study population are reported in Table 1. Notably, HCV$^+$ patients, with respect to healthy normotensive subjects, had an increased LVMI (100 ± 23 *vs.* 83 ± 15 g/m^2; p <0.0001), similar to that observed in HT group (103 ± 25 g/m^2) (Fig. 1). In addition, regarding biochemical variables, HCV$^+$ patients, in comparison with NT healthy subjects, had higher triglyceride, creatinine, fasting insulin and HOMA. Of interest, no differences were found in HOMA values between HT and HCV$^+$ (3.2 ± 1.3 *vs.* 3.3 ± 1.3; p = 0.651) patients. The mean value of HCV-RNA was 3868 ± 2963 × 10^3 (IU/ml) in HCV$^+$.

Correlational analysis

A linear regression analysis was performed to test the correlation between LMVI and different covariates in the whole study population and in the three groups (Table 2). LVMI, in the whole study population, was significantly correlated with SBP, DBP, pulse pressure, triglyceride, fasting insulin, HOMA, and inversely correlated with HDL-cholesterol. In HT and HCV$^+$ groups LVMI resulted statistically correlated with HOMA and fasting insulin. In addition, in the HT group, as expected, the other covariates correlated with LVMI were SBP, pulse pressure, creatinine and estimated glomerular filtration rate. In HCV$^+$ patients, instead, only viral load (r = 0.378; p = 0.003) and triglyceride were significantly correlated with cardiac mass. Finally, the correlational analysis between HCV-RNA and HOMA demonstrated a strong and linear