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Heart valve calcification in patients with type 2 diabetes and nonalcoholic fatty liver disease

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ABSTRACT

Purpose. Aortic valve sclerosis (AVS) and mitral annulus calcification (MAC) are two powerful predictors of adverse cardiovascular outcomes in patients with type 2 diabetes, but the etiology of valvular calcification is uncertain. Nonalcoholic fatty liver disease (NAFLD) is an emerging cardiovascular risk factor and is very common in type 2 diabetes, but whether NAFLD is associated with valvular calcification in this group of patients is presently unknown.

Methods. We undertook a cross-sectional study of 247 consecutive type 2 diabetic outpatients with no previous history of heart failure, valvular heart diseases (aortic stenosis, mitral stenosis, moderate or severe aortic and mitral regurgitation) or hepatic diseases. Presence of MAC and AVS was detected by echocardiography. NAFLD was diagnosed by ultrasonography.

Results. Overall, 139 (56.3%) patients had no heart valve calcification (HVC-0), 65 (26.3%) patients had one valve affected (HVC-1) and 43 (17.4%) patients had both valves affected (HVC-2). 175 (70.8%) patients had NAFLD and the prevalence of this disease markedly increased in patients with HVC-2 compared with either HVC-1 or HVC-0 (86.1% *vs.* 83.1% *vs.* 60.4%, respectively; $p < 0.001$). NAFLD was significantly associated with AVS and/or MAC (unadjusted-odds ratio 3.51, 95% CI 1.89–6.51, $p < 0.001$). Adjustments for age, sex, waist circumference, smoking, blood pressure, hemoglobin A1c, LDL-cholesterol, kidney function parameters, medication use and echocardiographic variables did not appreciably weaken this association (adjusted-odds ratio 2.70, 95% CI 1.23–7.38, $p < 0.01$).

Conclusions. Our results show that NAFLD is an independent predictor of cardiac calcification in both the aortic and mitral valves in patients with type 2 diabetes.

Abbreviations: AVS, aortic valve sclerosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HVC, heart valve calcification; IHD, ischemic heart disease; IVRT, isovolumetric relaxation time; LV, left ventricular; MAC, mitral annulus calcification; NAFLD, nonalcoholic fatty liver disease; SAC, systemic arterial compliance; SVR, systemic vascular resistance.

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1. Introduction

Aortic valve sclerosis (AVS) is present in approximately 30% of adults >65 years of age [1,2]. For decades, this disease was thought to be a passive process of little or no clinical significance in which the valve degenerated with age in association with calcium accumulation. However, AVS shares histopathological and epidemiological features with coronary atherosclerosis [2], and large prospective studies have now documented that AVS is independently associated with increased cardiovascular mortality and morbidity both in the general population and in non-diabetic high-risk patient individuals [3–6]. Mitral annulus calcification (MAC) is common in the elderly (~15%) and is also now known to be associated with adverse cardiovascular outcomes [6–8]. Recently, we have also shown that the presence of AVS and MAC, singly or in combination, is very common in patients with type 2 diabetes (occurring in up to ~45% of patients), and AVS and MAC are associated with an increased risk of all-cause and cardiovascular mortality, independently of established risk factors [9]. Notably, we showed that the combined presence of AVS and MAC is more strongly associated with increased risk of all-cause and cardiovascular mortality than the presence of either AVS or MAC alone [9].

In parallel, nonalcoholic fatty liver disease (NAFLD) has emerged as a public health problem of epidemic proportions worldwide [10]. NAFLD is highly prevalent in people with type 2 diabetes (occurring in up to 70% of patients) [11–13], and is not only associated with liver-related mortality and morbidity, but is also associated with an increased risk of developing ischemic heart disease (IHD), abnormalities of myocardial function and structure, and cardiac arrhythmias (*e.g.*, atrial fibrillation) [14–16]. Preliminary evidence also suggests that NAFLD is associated with the presence of AVS, independently of established cardiovascular risk factors, in both non-diabetic and type 2 diabetic individuals [17,18]. However, to our knowledge, no studies have tested associations between NAFLD and MAC, or associations between NAFLD and AVS, to determine whether similar (or different) associations occur between NAFLD and AVS compared with NAFLD and MAC, in patients with or without type 2 diabetes. This issue is of clinical significance, because the aortic and mitral valves are different anatomically and are exposed to different intramyocardial pressure gradients during the cardiac cycle.

Thus, the aim of this study was to examine whether NAFLD is associated with AVS and MAC (singly or in combination) in a large sample of patients with type 2 diabetes.

2. Materials and Methods

2.1. Patients

We studied 247 white consecutive outpatients with type 2 diabetes, who regularly attended the diabetes clinics of the University of Verona and the "Sacro Cuore" Hospital of Negrar. Some data from a part of these patients (n = 180) reporting associations between NAFLD and AVS were published previously [18]. For the present analyses, we excluded patients with: (1) a prior history of chronic heart failure, heart valve diseases or prosthetic heart valves, atrial fibrillation, cancer and overt nephropathy; and (2) a prior history of cirrhosis of any etiology or other known causes of chronic liver diseases, including viral hepatitis, hemochromatosis and excessive alcohol intake (defined as >20 g/day for women and >30 g/day of alcohol intake for men, respectively). All women were postmenopausal and did not take hormonal replacement therapy.

The local Ethics Committee approved the study protocol. All participants gave their written informed consent for participation in this research.

2.2. Clinical and Laboratory Data

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Waist circumference was measured at the level of the umbilicus. Blood pressure was measured with a standard mercury sphygmomanometer (at the right upper arm using an appropriate cuff size). Information on alcohol consumption, smoking status and current use of medications was obtained from all patients via interviews during medical examinations.

Venous blood samples were drawn in the morning after an overnight fast. Serum liver enzymes, creatinine (measured using a Jaffé rate-blanked and compensated assay) and other biochemical blood measurements were determined using standard laboratory procedures (DAX 96; Bayer Diagnostics, Milan, Italy). Most participants had serum liver enzymes within the reference ranges in our laboratory, which for serum aminotransferases were 10 to 40 U/L for women and 10 to 50 U/L for men, respectively. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald equation. Hemoglobin A1c (HbA1c) was measured by an automated high-performance liquid chromatography analyzer (HA-8140; Menarini Diagnostics, Florence, Italy); the upper limit of normal for the laboratory was 5.6%. The glomerular filtration rate (eGFR) was estimated by the four-variable Modification of Diet in Renal Disease study equation [19]. Albuminuria was measured by an immuno-nephelometric method on a morning spot urine sample and expressed as the albumin-to-creatinine ratio; abnormal albuminuria was defined as an albumin-to-creatinine ratio ≥30 mg/g creatinine.

Presence of IHD was defined as a documented history of myocardial infarction, angina or coronary revascularization procedures. Presence of internal or common carotid artery stenoses was ascertained by echo-Doppler scanning. In all participants, the presence of microvascular complications, such as retinopathy (by fundoscopy after pupillary dilation), peripheral sensory neuropathy (by biothesiometer) and nephropathy (by eGFR and albuminuria measurements) was also recorded.

2.3. Echocardiography and Liver Ultrasonography

A 12-lead standard resting electrocardiogram and a transthoracic echocardiographic Doppler evaluation with spectral tissue Doppler analysis (Vivid 7, GE Vingmed, Horten, Norway) were performed within ~1 month of liver ultrasonography in all patients by two experienced cardiologists, who were

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