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LIPOTOXICITY AND MICROVASCULAR DISEASE: CONTRIBUTION TO MYOCARDIAL DAMAGE IN CLINICAL AND EXPERIMENTAL MODELS OF DIABETES

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1. Summary

Diabetes mellitus (DM) and heart failure (HF) are two multifaceted entities that involve high morbidity and mortality when both conditions coexist. The incidence of heart failure (HF) is increased in patients with type 1 (DM1) and type 2 (DM2) diabetes mellitus. This cardiomyopathy is called "diabetic cardiomyopathy" (CMD). There are no specific biomarkers available for early diagnosis or to predict their clinical evolution.

Objectives

1.- To analyze in a cohort of patients with chronic heart failure (with and without diabetes mellitus) outpatients the prognostic value (mortality and readmission for heart failure) of clinical, anthropometric and biochemical parameters, including the lipid profile.

2.- In patients with type 1 diabetes mellitus (DM1) without clinical heart failure, to analyze the association of myocardial dysfunction with clinical, anthropometric and biochemical parameters (lipoprotein profile analysis and lipidomic analysis) as well as the presence and degree of renal and retinal microvascular disease.

3. To analyze, in patients with type 2 diabetes mellitus (DM2) without clinical heart failure, the association of myocardial dysfunction (diastolic and / or systolic) with the following parameters: a) clinical, anthropometric, biochemical (including a profile analysis of serum lipoproteins and lipidoma), b) the presence and degree of microvascular disease (renal and retinal).

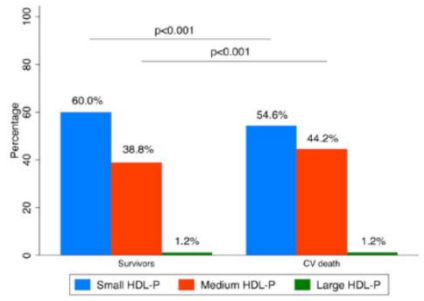
4.- In a subgroup of patients with DM2 with and without myocardial dysfunction, to analyze the association of clinical, anthropometric and biochemical parameters with the deposition of cardiac ectopic fat (epicardial and intramyocardial) as well as with microvascular disease.

2. Results obtained

Objective 1

A) *Analysis of the contribution of the advanced lipoprotein profile analyzed by nuclear magnetic resonance with spectroscopy on cardiovascular mortality in patients with a diagnosis of chronic heart failure*

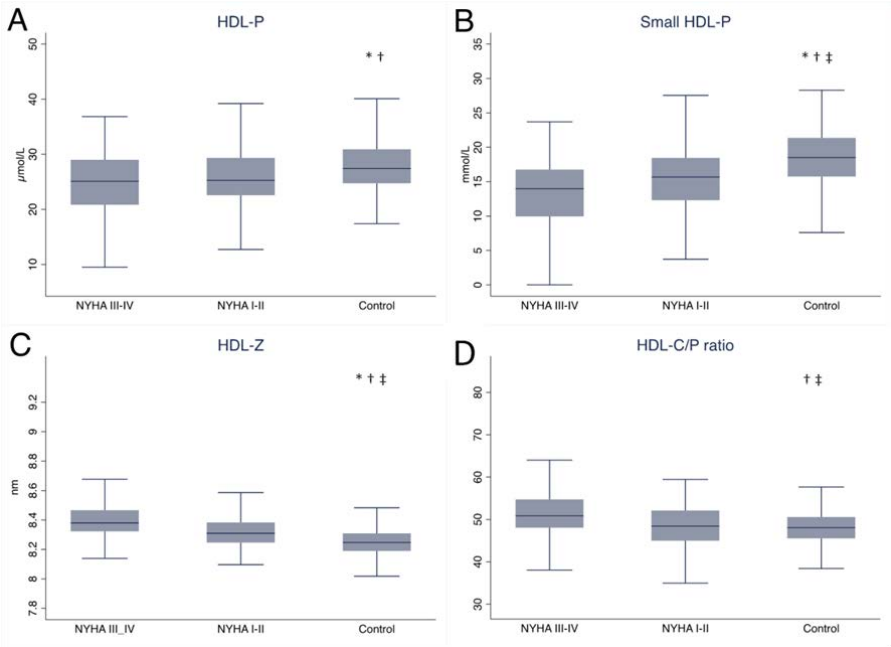
- 422 patients were included and followed up during a median of 4.1 (0–8) years. CV death occurred in 120 (30.5%) patients. Mean HDL-Sz was higher in CV dead as compared with survivors (8.39 nm vs. 8.31 nm, p< 0.001). This change in size was due to a reduction in the percentage of small HDL-P (54.6% vs. 60% for CV-death vs alive; p< 0.001). HDL-C/P ratio was higher in the CV-death group (51.0 vs. 48.3, p< 0.001). HDL-Sz and HDL-C/P ratio were significantly associated with CV death after multivariable regression analysis (HR 1.22 [95% CI 1.01–1.47], p= 0.041 and HR 1.04 [95% CI 1.01–1.07], p = 0.008 respectively). HDL-Sz and HDL-C/P ratio are independent predictors of CV death in chronic HF patients.



B) *Analysis of differences in lipoprotein profile between outpatients with chronic heart failure and a control group without heart failure.*

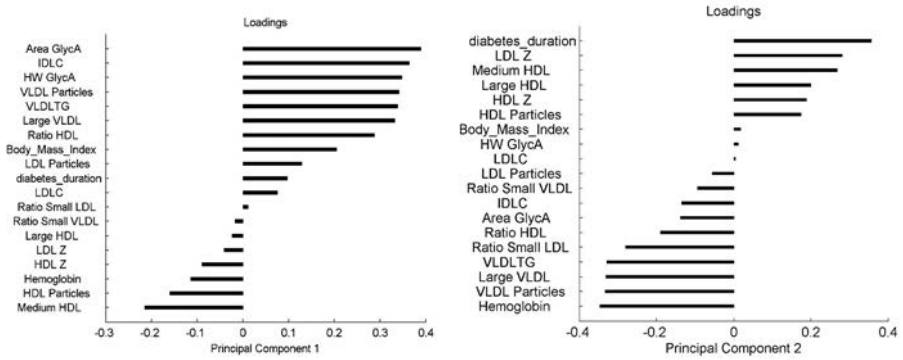
- The 429 included patients with chronic HF were compared with 428 matched controls. Patients with chronic HF presented with lower total cholesterol and lower mean LDL (1115 vs. 1352 nmol/L, p < 0.001) and HDL (25.7 vs. 27.9 μmol/L, p < 0.001). Mediating this difference were significantly lower small subfractions of LDL (635.4 vs. 792.2 nmol/L, p < 0.001) and HDL (15.2 vs. 18.6 μmol/L, p < 0.001). Mean VLDL, LDL, and HDL particle size was significantly higher in patients with HF vs. controls. All HDL-related differences from controls persisted after adjustment for New York Heart Association functional class or body mass index. We found strong negative correlations of known cardiac biomarkers (N-terminal pro-brain natriuretic peptide and ST2) with total and small LDL and HDL fractions and HDL particle size.

Comparison of differences in proportion of small, medium, and large subfractions of HDL particles in chronic HF as compared to controls. –P, particle concentration.



Objective 2

- A total of 304 DM1 subjects were analyzed from a cohort of Danish DM1 subjects (One thousand and one study) (54% women); n = 154 with subclinical myocardial dysfunction (SMD) (61.3 ± 11.7 years) and n = 150 without SMD (60.6 ± 11.1 years), matched by age, sex and HbA1c, all of them without known previous cardiovascular (CV) disease. All underwent a transthoracic echocardiogram and an NMR spectroscopy analysis of the advanced lipoprotein profile (Liposcale®) and the concentration of glycosylated proteins determined from the bonds between galactosamine, glucosamine and sialic acid bound to plasma proteins (GlycA). Of the 154 subjects with SMD, 146 presented diastolic dysfunction and 18 systolic. Compared to subjects without SMD, subjects with SMD have a longer duration of diabetes (p = 0.005), higher BMI (p = 0.013), higher serum NT-proBNP concentration (p = 0.001), higher systolic blood pressure (p <0.001), higher albuminuria (p <0.001) and higher percentage of advanced retinopathy (p <0.001). The supervised classification model identifies a specific molecular pattern associated with SMD, with an ability to discriminate diabetic patients with SMD from the rest of individuals without CV disease, in a modest but significant way in relation to chance (area under the ROC analysis curve 0.63, p <1.1801e-012). The PLS-DA showed that both the triglyceride-rich lipoproteins: VLDL (total VLDL particles, triglyceride content and large VLDL) and IDL (its cholesterol content), as well as the serum concentration of GlycA, significantly contribute to explain the presence of SMD.



Objectives 3 and 4

- The initial forecast of the project was to recruit 300 patients with DM2 from outpatient clinics. The inclusion criteria of patients with DM2 of the project (absence of insulin treatment, glycemic control with HbA1c between 6.5% and 8.5%, absence of a history of cardiovascular disease) made it difficult for these patients to be recruited in the outpatient consultations of the hospital. This patient profile is routinely visited by general practitioners in primary care centers. To do this, several sessions were held with different primary care centers of the hospital to request their collaboration in the recruitment of patients, since the patient profile that meets the inclusion criteria is seen mainly in primary care centers. These are subjects with type 2 diabetes mellitus in the earlier stages of their disease. The difficulty in including the number of patients initially planned in the study, accentuated by the COVID-19 epidemic, was the reason why we reconsidered conducting the study with a smaller number of patients. Finally, a smaller number of patients were included (n = 65). In these, a more complete cardiological imaging study was carried out than initially planned.

- A preliminary analysis was carried out in a group of 40 patients, out of the 65 patients that were recruited. The baseline characteristics of these patients with DM2 are as follows: age 63.6 years (46.6 to 75.1), 27 women and 38 men. According to the functional class of dyspnea from the New York Heart Association (NYHA) classification, 95% are class I and the remaining 5% are class II. The hemodynamic parameters of these patients show an average heart rate of 74 ± 9 beats per minute, a systolic pressure of 135 (97-171) mm Hg and a diastolic pressure of 81 (64-102) mmHg. They are all in sinus rhythm. The cardiac parameters obtained by echocardiography show, among other parameters, an average distance between the left atrium and the pulmonary atrium of 36.5 ± 4.8 mm, an E / A wave ratio of 0.8 ± 0.2, a wave

deceleration time e of 211.8 ± 43.3 ms, an overall e / e 'ratio of 8.1 ± 2.1, and a Tei index of 0.6 ± 0.1. An average value of the ejection fraction of the right ventricle of 56.2 ± 8.2% and of the left ventricle of 59.4 ± 6.4% was also found.

- The analysis of myocardial fat evaluated by magnetic resonance spectroscopy shows an average value in this cohort of 1.40 ± 1.99%. A correlation has been found between intramyocardial triglycerides and myocardial function (Tei Index) and the deceleration time of the E wave, regardless of the presence of other parameters such as age or arterial hypertension. The liver fat analysis showed an average value in this cohort of 14.37 ± 9.67%. No correlation between liver fat deposition and cardiac fat deposition was observed on MRI with spectroscopy (r = 0.092, p = 0.502). No correlation has been observed between serum concentrations of total cholesterol, HDL-C, and LDL-C or triglycerides with fat content in myocardial tissue. Neither with the liver fat content. Heart fat content correlates with right ventricular function (better FEVD and better RV strain) but instead with an increase in left atrial volume. The CT scan of the coronary arteries has shown the presence of coronary lesions in 79% of the cases, with a significant stenosis in 26% of the cases (DA 55%, Cx 17.5%, RCA 17.5% and LM 2.5%). 29% of patients present a retention pattern on MRI compatible with a probable cardiac microvascular lesion. All patients with significant coronary malignancy were tested for ischemia, and the result was negative for all of them. The percentage of liver fat content in the NMR spectroscopy showed a tendency to be higher in those patients with significant coronary artery disease compared to those without significant coronary disease (p = 0.061).

3. Relevance with possible future implications

Objective 1

The studies have shown that of all the lipoprotein subfractions that were analyzed, the one most related to the cardiovascular prognosis of patients with chronic heart failure as well as the degree of heart failure is that of HDL particles; specifically, with the number of HDL particles as well as with the cholesterol content per HDL particle. These findings indicate that future lines of research should focus on the mechanisms by which the HDL molecule is involved in the pathogenesis of heart failure and also on possible therapeutic options for heart failure related to the modification of the HDL molecule.

Objective 2

The variables of the metabolomic profile that best explain the presence of subclinical myocardial dysfunction (SMD) in subjects with DM1 without known CV disease are those related to triglyceride-rich pro-atherogenic lipoproteins (VLDL and IDL) and the pro-inflammatory biomarker GlycA. The results obtained point to a possible involvement in the pathophysiology of SMD of GlycA and triglyceride-rich lipoproteins. It will be necessary to investigate in the future the usefulness of these parameters as possible biomarkers of subclinical myocardial dysfunction in patients with DM1 and also to investigate the possible biological pathways involved in the possible relationship of triglyceride-rich lipoproteins and GlycA in the pathophysiology of myocardial dysfunction. In this regard, in the last two years, data have been available in the literature that point to the involvement of both triglyceride-rich lipoproteins and GlycA in the risk of heart failure in the general population without a history of diabetes mellitus.

Objectives 3 and 4

Intramyocardial fat deposition has been found to be related to myocardial function and structures. In the right ventricle the fat deposit has been associated with better ventricular function while in the left atrium it has been associated with a greater volume of it. The reasons for these findings are unknown. In the future, it will be necessary to investigate whether the consequences of intramyocardial fat deposition are different depending on its anatomical location in the myocardium. On the other hand, a non-negligible percentage of patients with significant coronary heart disease has been observed on coronary CT scan. This is a population of subjects with very good control of DM (average HbA1c of 6.7%) with an average LDL cholesterol figure of 112 mg / dl. This fact highlights the importance of achieving the control levels of c-LDL established by different scientific societies in patients with DM in order to prevent CV disease, even in those patients who have good metabolic control and no micro- or macrovascular complications associated with diabetes. Finally, the findings obtained point out that the fat content in the liver may be a marker of increased risk of significant coronary heart disease, even in asymptomatic subjects. This finding suggests, as the literature describes in recent years, that fatty liver in patients with diabetes would be a marker of an increased risk of CV disease. Therefore, in those patients with DM and fatty liver, achieving good control of all CV risk factors, including LDL cholesterol, would be vital.

4. Scientific bibliography generated

Objective 1

1.- Teis A, Cediel G, Amigó N, Julve J, Aranyó J, Andrés-Cordón J, Puig-Jové C, Castelblanco E, Gual-Capllonch F, Ferrer-Sistach E, Vallejo N, Juncà G, López-Ayerbe J, De Antonio M), Domingo M, Santiago-Vacas E, Codina P, Mauricio D, Lupón J, Alonso N, Bayes-Genis A. Particle size and cholesterol content of circulating HDL correlate with cardiovascular death in chronic heart failure. Sci Rep. 2021 Feb 4;11(1):3141. doi: 10.1038/s41598-021-82861-6.

2.- Puig-Jové C, Castelblanco E, Falguera M, Hernández M, Soldevila B, Julián MT, Teis A, Julve J, Barranco-Altirriba M, Franch-Nadal J, Puig-Domingo M, Ortega E, Amigó N, Alonso N, Mauricio D. Advanced lipoprotein profile in individuals with normal and impaired glucose metabolism. Rev Esp Cardiol (Engl Ed). 2021 Mar 27:S1885-5857(21)00073-6. English, Spanish. doi: 10.1016/j.rec.2021.02.006. Epub ahead of print. PMID: 33785266.

3.- Teis A, Castelblanco E; Cediel G, Amigó N, Julve J, Ribalta J,; Guardiola M; Franch J, Bermúdez-López M, Codina P, Lupón J, Mauricio D, Alonso N, Bayes-Genis A, MD. 1H-NMR spectroscopy lipoprotein profile in patients with chronic heart failure versus matched controls. Submitted a Rev Esp Cardiol (under review).

Objective 2

Puig-Jové C, Julve J, Amigó N, Andersen HU, Mauricio D, Rossing P, Alonso N. Contribution of the novel inflammatory biomarker GlycA and triglyceride-rich lipoproteins to the presence of subclinical myocardial dysfunction in patients with type 1 diabetes mellitus. Article prepared, awaiting submission.

Objectives 3 & 4

The results are currently being analysed and the article is in preparation.