Growth Differentiation Factor 15, a New Prognostic Marker in Diabetic Cardiomyopathy

**El factor de diferenciación de crecimiento 15, un nuevo marcador pronóstico en la miocardiopatía diabética**

**To the Editor,**

The various clinical guidelines and consensus statements recommend a multifactorial approach to diabetes mellitus, acting on glycemia and the other associated risk factors to obtain the greatest possible reduction in macrovascular and microvascular morbidity and mortality. Diabetic cardiomyopathy (DCM) is usually asymptomatic in the initial stages. Growth differentiation factor 15 (GDF-15) is a cytokine secreted by macrophages and cardiac myocytes in response to oxidative stress and inflammation.

Our group recently described the usefulness of GDF-15 as a screening tool in the diagnosis of DCM in asymptomatic patients with type 2 diabetes mellitus. The study aimed to describe the prognostic value of GDF-15 at 1 year in a cohort of patients with DCM, evaluating the relationship between the levels of this biomarker and the combined primary endpoint of heart failure with hospital admission and/or angina with hospital admission.

The details of the study have previously been described. Briefly, the study prospectively included 213 asymptomatic patients with type 2 diabetes mellitus. Diabetic cardiomyopathy was defined, according to the criteria of the European Society of Cardiology and the European Association of Diabetes, as left ventricular diastolic dysfunction (tissue Doppler with an E/E' ratio ≥ 15) in the absence of hypertension, ischemic heart disease, or other structural heart disease. For the analysis, the outcomes at 365 days of the 45 patients who had DCM were studied, as was the relationship between DCM and GDF-15 concentration.

Continuous variables are expressed as mean ± standard deviation for those with a normal distribution or median [interquartile range] for those with an abnormal distribution. Categorical variables are expressed as number (percentage). Quantitative variables were compared using the Student t test or Mann-Whitney U test. The association between qualitative variables was determined using the Pearson chi-square test or Fisher exact test. Survival analysis was performed using Cox regression, with variables with a P-value < .02 on univariate analysis being included in the model. Risk proportionality assumption was evaluated by Schoenfeld residual analysis. The statistical analysis was performed with the SPSS program, version 20 (SPSS Inc., Chicago, Illinois, United States).

The study population characteristics are shown in the Table. The primary endpoint of the study occurred in 12 patients (26.7%). There were no statistically significant differences between the 2 groups in baseline characteristics (age, sex, left ventricular ejection fraction, hypercholesterolemia, and smoking), treatment, or laboratory data. Concentrations of GDF-15 were higher in patients with DCM who experienced a combined event than in those with no events (6458.9 pg/mL vs 4706 pg/mL; P = .007) (Figure). Combined events occurred at a mean time of 162 ± 89 days in the Cox survival analysis.
analysis, after adjustment for other covariables (treatment with insulin, mean GDF-15, and left ventricular ejection fraction), the variables shown to be independent predictors of the combined endpoint were mean GDF-15 level (hazard ratio = 4.96; 95% confidence interval, 1.24-19.77; \( P = .023 \)) and left ventricular ejection fraction (hazard ratio = 0.83; 95% confidence interval, 0.7-0.98; \( P = .031 \)). The discriminatory power of the model, determined using the C-statistic, was 0.826.

The originality of this study is that it demonstrates for the first time that high GDF-15 levels are associated with poor prognosis at 365 days in patients with DCM. Hyperglycemia activates signaling pathways mediated by reactive oxygen species, leading to the development of myocardial hypertrophy and fibrosis with ventricular stiffness and chamber dysfunction. Experimental studies have demonstrated that cardiac GDF-15 expression significantly increases after various forms of stress, including pressure overload.

Given that GDF-15 is produced by several other types of cells besides cardiac myocytes (endothelial cells, adipocytes, and macrophages), it is likely that this biomarker comprises information from several disease pathways, providing the pathophysiological information necessary in patients with DCM.\(^4\)

The main limitation of this study is its small sample size and low number of combined events and therefore it should be considered a hypothesis generator. We conclude that in patients with DCM, high GDF-15 values are associated with poor prognosis at 1 year. Randomized studies with larger sample sizes are needed to add more information on the value of this biomarker in predicting events.

**REFERENCES**

**Current Management of Hyperlipidemia in Patients Discharged With a Diagnosis of Acute Coronary Syndrome**

**Manejo actual de la hiperlipemía en pacientes dados de alta con el diagnóstico de síndrome coronario agudo**

To the Editor,

Current European\(^1\) and American\(^2\) guidelines on the management of hyperlipidemia concur on the advisability of intensive treatment of low-density lipoprotein cholesterol (LDL-C) in patients hospitalized with acute coronary syndrome (ACS).\(^3\) However, they differ in their recommendations on post-discharge treatment. European guidelines have a therapeutic goal of LDL-C level \(< 70\) mg/dL or a reduction of LDL-C > 50%. In contrast, American guidelines, based on the efficacy shown in clinical trials,\(^4\) propose statin treatment classified according to their intensity and the theoretical percentage reduction in LDL-C they confer. As such, statins are classified into 3 categories: high-intensity (LDL-C reduction > 50%), moderate-intensity (reduction 30%-50%), and low-intensity (reduction < 30%). According to American guidelines, patients with ACS who are younger than 75 years should receive high-intensity statin therapy, while those older than 75 years should receive moderate-intensity statins. There is little focus in the guidelines on the management of atherogenic dyslipidemia (AD), which is characterized by the association of low levels of high-density lipoprotein cholesterol and high triglyceride levels, with or without increased LDL-C concentrations. Atherogenic dyslipidemia represents the main cause of residual increased cardiovascular risk once target LDL-C levels have been achieved with statins,\(^5\) but it has been little studied in patients with ACS. Our objectives were to assess the degree of compliance with current recommendations on lipid-lowering therapy on discharge in patients with a diagnosis of ACS, and to evaluate the prevalence of AD, the variables associated with this metabolic abnormality, and its influence on clinical outcomes after discharge in these patients.

We retrospectively analyzed 856 consecutive patients discharged with a diagnosis of ACS: 506 (59.1%) had ST-segment elevation and 350 (40.9%) had no ST-segment elevation but had an objective sign of myocardial ischemia (dynamic changes in the ST-segment, raised troponin, or the presence of a coronary lesion identified as the cause of symptoms). Atherogenic dyslipidemia was defined as a high-density lipoprotein cholesterol level \(< 40\) mg/dL in men and \(< 50\) mg/dL in women, with triglyceride levels \(\geq 150\) mg/dL. We analyzed the baseline variables, the lipid profile during hospital admission and after discharge (median 3 months), and cardiac events—stroke or myocardial infarction—over a clinical follow-up of 12 months.

Statin therapy was prescribed in 830 patients (97%) (combined with ezetimibe in 10 patients and with fenofibrate in 18 patients). Ezetimibe alone was prescribed in 3 patients (0.4%), and fenofibrate alone in 2 (0.2%). Twenty-one patients (2.5%) received no lipid-lowering therapy. Of the 830 statin-treated patients, 570 (68.7%) received high-intensity (atorvastatin 80 mg in 77% and rosvastatin 20 mg in 23%), 247 (29.8%) received moderate-intensity, and 13 (1.6%) received lower-intensity statins.

The percentage of patients treated with high-intensity statins was 65.2% among those older than 75 years and was 89% in those younger than 75 years. Use of high-intensity statins was associated with a greater reduction in LDL-C levels after discharge and a higher percentage of patients achieving therapeutic goals. The incidence of myocardial infarction or stroke during follow-up was higher in patients treated with lower-intensity statins than in those receiving moderate- or high-intensity statins (Table 1).

On multivariate analysis, the only variables independently related to the incidence of myocardial infarction or stroke were diabetes (odds ratio = 2.3; \(P = .006\)) and use of lower-intensity statins compared with high-intensity statins (odds ratio = 7.0; \(P = .002\)). Achieving LDL-C therapeutic goals did not affect the incidence of these events during follow-up.

A total of 228 patients met the criteria for AD (26.5%). Compared with the non-AD group, patients with AD were younger (61.1 ± 11.4 years vs 65.8 ± 12.9 years; \(P < .001\)), had a higher prevalence of smoking (43.9% vs 36.0%; \(P = .036\)) and diabetes (39.9% vs 25.4%; \(P < .001\)), higher body mass index (29.5 ± 4.3 kg/m\(^2\) vs 28.4 ± 4.6 kg/m\(^2\); \(P = .004\)), and a higher ischemic risk score according to the Global Registry of Acute Coronary Events (GRACE: 150.3 ± 34.3 vs 139.2 ± 35.5; \(P < .001\)) (Table 2). At follow-up, a high percentage of patients in both groups achieved the therapeutic goals of LDL-C control. However, AD persisted in 46.9% of patients. Patients with AD had a higher incidence of stroke and myocardial infarction than patients without AD.

**Table 1** Baseline Patient Characteristics, Lipid Profile on Admission, and Events and Lipid Profile After Discharge, by Intensity of Statin Therapy Prescribed on Discharge

<table>
<thead>
<tr>
<th></th>
<th>High-intensity (n = 570)</th>
<th>Moderate-intensity (n = 247)</th>
<th>Lower-intensity (n = 13)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LDL-C(^a)</td>
<td>99.6 [76.2 to 123.6]</td>
<td>93.5 [72.7 to 117.2]</td>
<td>71 [63.4 to 121]</td>
<td>.047</td>
</tr>
<tr>
<td>HDL-C increase, %(^a)</td>
<td>5.1 [−9.7 to 22.5]</td>
<td>11.1 [−7.0 to 29.3]</td>
<td>12.0 [−2.0 to 25.8]</td>
<td>.022</td>
</tr>
<tr>
<td>TG reduction, %</td>
<td>13.6 [−15.2 to 33.3]</td>
<td>11.0 [−15 to 34]</td>
<td>−5 [−15.3 to 2.8]</td>
<td>.108</td>
</tr>
<tr>
<td>LDL-C reduction, %(^a)</td>
<td>27.9 [5.9 to 44.5]</td>
<td>17.2 [−1.2 to 38.3]</td>
<td>−1 [−15.5 to 22.6]</td>
<td>.001</td>
</tr>
<tr>
<td>LDL-C goal achieved(^b)</td>
<td>287 (50.4%)</td>
<td>94 (38.1%)</td>
<td>2 (15.4%)</td>
<td>.002</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>24 (4.2%)</td>
<td>11 (4.5%)</td>
<td>2 (15.4%)</td>
<td>.165</td>
</tr>
<tr>
<td>Stroke</td>
<td>10 (1.8%)</td>
<td>3 (1.2%)</td>
<td>2 (15.4%)</td>
<td>.025</td>
</tr>
</tbody>
</table>

\(^a\) Median [25th percentile to 75th percentile].

\(^b\) LDL-C < 70 mg/dL or reduction > 50% from baseline LDL-C.