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Original Article

# Cholesterol control according to the presence of metabolic syndrome in coronary and diabetic patients. Relationship with non-alcoholic fatty liver disease

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ABSTRACT

*Background and aims:* Metabolic syndrome (MS) is an association of cardiovascular risk factors that increases the risk of coronary disease or type 2 diabetes mellitus (DM2), and has also been associated with the presence of liver steatosis (LS). In this study the relation of MS and LS with cholesterol control was analyzed in very high cardiovascular risk patients (coronary patients and/or DM2).
*Methods:* A cross-sectional epidemiological study including 6988 patients, from whom information was obtained on their characteristics, lipid profile and treatments.
*Results:* 4455 patients (65%) of the total study population had MS. Of MS criteria, high BP was the criterion most represented in the total population, while high TGs was the least. Within the total population, coronary patients showed a greater proportion of high BP, high TG and low HDL-c than those without coronary disease. Although no influence of MS was seen on the achievement of LDL-c targets (<70 mg/dL), the presence of high BP, high blood glucose and low HDL-c was related to poorer control of LDL-c. Finally, patients with MS showed a greater proportion of liver steatosis and this was associated in turn with poorer control of LDL-c.
*Conclusions:* The criteria for MS are closely related to cholesterol control. LS is more prevalent in patients with MS, and it is associated with poorer control of LDL-c. We should focus on the presence of MS in high and very high CV risk patients in order to improve their lipid control.


## 1. Introduction

Metabolic syndrome (MS) is a combination of cardiovascular risk factors that, according to the definition of the International Diabetes Federation (IDF), includes the presence of abdominal obesity (waist ≥ 94 cm in European men and ≥ 80 cm in European women) together with at least two more factors (blood glucose ≥ 100 mg/dL or known DM2, blood pressure (BP) ≥ 140/90, triglycerides ≥ 150 mg/dL, HDL-c < 40 mg/dL in men, <50 mg/dL in women) [1]. The presence of these criteria, and hence of MS, is associated with an increased risk of cardiovascular disease and/or type 2 diabetes mellitus (DM2) [2].

Studies conducted more recently in Spain determined that the prevalence of MS exceeds 30% of the adult population [3], though this prevalence increases strikingly when very high cardiovascular risk patients are studied, specifically those with an established diagnosis of coronary disease (50%) [2,4].

Cholesterol and low-density lipoprotein (LDL-c) values do not significantly increase in the case of dyslipidemia in MS. However, the particles have different properties, similar to those found in diabetic dyslipidemia, since they are small and dense, which confers on them a high atherogenic potential [5,6].

Liver steatosis (LS) or non-alcoholic fatty liver disease is considered the liver component of MS [7], and is currently the most common liver disease in Western countries [8]. The diagnosis is clearly related to the presence of MS criteria [7], but with regard to dyslipidemia, a relationship between LS and poorer control of LDL-c has not been observed in Spanish epidemiological studies [9,10].

The objective of the CODIMET study was to examine the prevalence of cardiovascular risk factors and MS in patients with coronary disease and/or DM2, as well as the control of lipid profile in these patient groups [11]. In this new analysis, the objective is to determine the prevalence and relationship of MS and each of its components on the control of

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LDL-c in patients at very high cardiovascular risk (<70 mg/dL) [12,13]. In addition, the relationship of MS and its criteria to prevalence of LS is analyzed, and the association of this with control of lipid profile.

## 2. Patients and methods

### 2.1. Study design

The CODIMET is an epidemiological, observational, cross-sectional, multicenter national study in which data were collected retrospectively in a period of less than 3 months from patient inclusion date or during the study visit. There was no modification of the treatment of patients and the study protocol was approved by the ethics committee of Hospital Clínico San Carlos in Madrid. A total of 874 specialists in cardiology, endocrinology, internal medicine, and family medicine participated in the study from 17 autonomous regions to obtain a uniform and representative distribution of the Spanish population. Details of the study methods have been previously described [11].

### 2.2. Patients

We selected patients of both sexes, over 18 years of age, who gave their written informed consent, with at least one episode documented in the medical history of acute myocardial infarction or angina pectoris (coronary group) or diagnosed with DM2 (diabetic group without coronary disease) or with both diagnoses (mixed group). Patients were recruited between June and November 2006.

### 2.3. Variables analyzed

The personal history of cardiovascular disease (myocardial infarction, angina pectoris) and of DM2 was recorded. The presence of MS was assessed according to the definition of the IDF [14]. Type 2 diabetes mellitus was defined on the basis of a prior medical diagnosis, fasting blood glucose ≥126 mg/dL as reflected by at least two of the last available laboratory test, or treatment with antidiabetic drugs and/or insulin. Waist circumference was obtained with the patient in a standing position by measurement at the midpoint between the iliac crest and the rib margin in the mid-axillary line. Arterial hypertension was defined by the presence of a previously documented diagnosis, need for antihypertensive treatment or the presence of a blood pressure ≥140/90 mm Hg (mean of 3 separate measurements). Lipid concentrations were obtained from the last available laboratory test in the 3 months prior to inclusion of the patient or at the study visit. The concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and fasting triglycerides (TG) were determined. These determinations were performed at the health centers where each physician practiced according to the standard laboratory test procedures of each center (routine clinical practice).

The indication of abdominal ultrasonography was performed at the discretion of the physician responsible for the patient and the diagnosis of LS was established depending on its result. The diagnosis was considered valid if the ultrasonographer of the corresponding center reported as such in their report.

### 2.4. Statistical analysis

With the initially planned sample size (3600 patients in each group), even under the least favorable mathematical conditions (percentage in the central qualitative variables of the study $p = q = 0.5$), and assuming 20% losses, with a 95% confidence level, estimations can be made with a maximum percentage error of ±1.8%.

Subsequently, statistical analysis was carried out using the GraphPad Prism (GraphPad Software, version 5, La Jolla, CA,USA) and SPSS® (SPSS Inc. version 18.0, Chicago, IL, USA). Categorical variables are reported as absolute values and percentages, while continuous variables are presented as medians with interquartile range. Kolmogorov–Smirnoff test was used to assess the variables distribution. Logarithmic transformation was performed for those variables without a normal distribution, but untransformed values are shown in the text and tables. Comparisons of prevalence between groups were made using the chi-square test or Fisher's exact test, as appropriate. Mean comparisons were performed using Student's *t* test or ANOVA. Statistical tests used a statistical significance level of 0.05.

## 3. Results

### 3.1. Prevalence of metabolic syndrome and its criteria

The clinical characteristics of the 6988 patients included in the study analysis are shown in Table 1 [11]. The total prevalence of MS according to IDF criteria was 65% (4550 patients). It was lower in those who only had DM2 (74%) or coronary heart disease (48%) than in those who had both disorders — mixed group — (76.8%, $p < 0.05$ for both comparisons) [11].

High BP was the most prevalent MS criterion in the total population, excluding high abdominal circumference, since it is a requirement for the diagnosis of MS according to IDF criteria, with greater prevalence in the mixed group than in the other two. Regarding the presence of hyperglycemia in the coronary group, the patients with MS had a greater proportion (double) than those without MS ($p < 0.0001$). Having raised TGs was the least represented criterion, and diabetic patients with no cardiovascular disease were those showing the lowest prevalence. Finally, low HDL-c had a higher prevalence in coronary patients with or without MS, regardless of the presence of DM2, compared to patients without coronary disease (Table 2).

Regarding the number of these criteria in the total population, coronary patients had a greater proportion with ≤3 criteria for MS compared to the other patient groups. On the other hand, being a diabetic was associated with a higher percentage of MS factors, regardless of the presence of coronary disease. Similar to the findings in the total study population, patients with MS and coronary disease met fewer criteria than diabetic patients, with or without coronary disease (Table 3).

### 3.2. Lipid fraction concentrations and cholesterol control

Patients with MS, by its definition, had higher TG and lower HDL-c values than patients without MS. Patients with DM2 but without cardiovascular disease showed higher HDL-c levels than those with coronary disease associated or not with DM2, regardless of the presence of MS. Furthermore, the highest levels of TG were seen in patients with diabetes and coronary disease compared to patients who had only DM2. The data for these values are shown in Table 4.

As regards the lipid profile not included in the MS criteria, higher values were observed for total cholesterol, LDL-c and non-HDL-C in patients with MS than in those without MS, and patients with coronary disease were those showing the greatest differences according to the presence of MS. For these three variables, patients with MS from the mixed group showed lower concentrations compared to the other groups (Table 4).

There were no significant differences in control of LDL-c (<70 mg/dL) in patients with MS versus those without. As seen in the total population, the proportion of patients with MS and LDL-c <70 mg/dL was greater in the mixed group compared to the other two groups (only coronary or only DM), with the poorest control in coronary patients. In respect to good control of non-HDL-c (<100 mg/dL), there was a similar trend in the differences between diagnostic groups, but in this case the proportion of patients with non-HDL-c <100 mg/dL was significantly smaller in patients with MS, with the greatest difference (15%) being observed in coronary patients. Predictably, the percentage of patients with levels