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Classical and emergent cardiovascular disease risk factors in type 2 diabetics from the Vallecas area (DICARIVA study)

Factores de riesgo cardiovascular clásicos y emergentes en pacientes con Diabetes mellitus tipo 2 del Área de Vallecas (estudio DICARIVA)

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a major independent risk factor for cardiovascular disease (CVD) and a highly prevalent disease with a wide variety of associated metabolic disorders.

Objective: To describe features and prevalence of altered CVD risk factors in a T2DM population: *DI*abetes *CA*rdiovascular *RI*sk of *VA*llecas (DICARIVA) study.

Patients and methods: 735 adult Spanish patients of the Vallecas area with T2DM from the Infanta Leonor Hospital (Madrid, Spain) were included in the study. Age, disease time-evolution, anthropometric measurements, glycemia, HbA1c, lipid/lipoprotein profile, total cholesterol/high density lipoprotein cholesterol (HDL-cholesterol), low density lipoprotein cholesterol (LDL-cholesterol)/HDL-cholesterol and triglycerides/HDL-cholesterol ratios, triglycerides * glucose index (TyG), fibrinogen, *high sensitivity*-c reactive protein (hs-CRP) and microalbuminuria were assessed.

Results: Mean, standard deviations, and percentile distributions were obtained in males, females and the whole DMT2 population for classical and emergent CVD risk markers. Obesity was found in 45% of patients, while 60% had high cardiovascular risk according to waist circumference and conicity index. Total and LDL-cholesterol were at desirable and optimum levels, respectively, in 60% of patients. One third showed the conjoint presence of low HDL-cholesterol, high triglycerides and small and dense LDL. Increased levels of *hs-CRP*, hyperfibrinogenia and microalbuminuria were detected in 40%, 50% and 30% of patients, respectively. Age, body mass index, total cholesterol, hs-CRP and fibrinogen were higher while weight, conicity index, total cholesterol/HDL-cholesterol, LDL-cholesterol/HDL-cholesterol and triglycerides/HDL-cholesterol ratios, and microalbuminuria lower in women. According to TyG values 62% of patients suffered metabolic syndrome.

Conclusions: Altered anthropometric and metabolic CVD risk factors were highly prevalent in the DICARIVA study. The CVD marker cut-off points obtained in some

emergent markers seems relevant and would be employed for future early T2DM diagnoses strategy in order to reduce its high morbidity and mortality impact.

Key words: Type 2 diabetes mellitus. Cardiometabolic risk factors. Prevalences.

RESUMEN

Introducción: la diabetes mellitus tipo 2 (DMT2) es una enfermedad crónica con una amplia variedad de desórdenes metabólicos asociados.

Objetivos: describir las características y prevalencias de factores de riesgo cardiovascular alterados en el estudio *DI*abetes *CA*rdiovascular *RI*sk of *VA*llecas (DICARIVA).

Pacientes y métodos: 735 pacientes adultos españoles con DMT2 se incluyeron en el estudio. Se obtuvo información sobre parámetros antropométricos, glucemia, glycated haemoglobin A1c (HbA1c), perfil lipídico y lipoproteico, cocientes de riesgo colesterol total/HDL-colesterol, LDL-colesterol/HDL-colesterol, cociente molar triglicéridos/HDL, índice triglicéridos*glucosa (TyG), fibrinógeno, proteína C reactiva *ultrasensible* (Hs-CRP) y microalbuminuria.

Resultados: se calculó la media, desviación estándar y percentiles de los factores, clásicos y emergentes relacionados con el riesgo cardiovascular para hombres, mujeres y el total de la población de pacientes con DMT2 estudiados. El 45% de los pacientes tenía obesidad y el 60% riesgo cardiovascular elevado atendiendo al perímetro de cintura y al índice de conicidad. En un 60% de los pacientes, los niveles de colesterol total y LDL-colesterol estaban en valores deseables y óptimos, respectivamente. Sin embargo un tercio de los pacientes presentó conjuntamente bajos niveles de HDL-colesterol y elevados de triglicéridos y de LDL densas y pequeñas. Se detectaron niveles incrementados de Hs-CRP, hiperfibrinogenia y microalbuminuria en 40%, 50% and 30% de los pacientes, respectivamente. Las mujeres tenían más edad, índice de masa corporal, niveles de colesterol total, Hs-CRP y fibrinógeno, pero menos peso, índice de conicidad, cociente colesterol total/HDL-colesterol, LDL-colesterol/HDL-colesterol, cociente molar triglicéridos/HDL-colesterol y microalbuminuria que los hombres.

Conclusiones: en el estudio DICARIVA se detectó una elevada prevalencia de niveles alterados de marcadores antropométricos y de factores de riesgo cardiovascular. Los puntos de corte obtenidos en algunos de los factores de riesgo cardiovascular emergentes podrán emplearse en futuras estrategias diagnósticas que permitan reducir la alta morbimortalidad de esta patología.

Palabras clave: Diabetes mellitus tipo 2. Factores de riesgo cardiometabólicos. Prevalencias.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes (90-95%) (1). It is characterized by chronic hyperglycemia as a consequence of disorders on insulin action and insulin secretion as the predominant feature (1). Cardiovascular disease (CVD) is the leading cause of mortality in the developed countries in spite of the declining trend observed (2). In T2DM patients the risk of death from CVD is 2-5 times higher than in non-diabetic persons (3). In Spain 30% of mortality is due to CVD (2), being DM considered as an independent CVD risk factor (3). A recent study estimated that for every point increase in glycated haemoglobin (HbA1c), the relative risk of CVD increases by 18% (4).

Besides the classic cardiovascular risk factors, others, called emergent factors, like C reactive protein (CRP), microalbuminuria and fibrinogen, have been associated to CVD. Currently, *high sensitivity* CRP (*hs*-CRP) is a major index of inflammatory activity and increased *hs*-CRP levels are found during atherosclerosis development (5). The triglyceride-glucose index (TyG) and the triglyceride/HDL-cholesterol ratio in turn, have been described as insulin resistance indicators (6). A good correlation between TyG and the homeostatic model assessment-insulin resistance (HOMA-IR) has been described (6). Thus, determining insulin resistance is becoming cheaper using TyG instead of the HOMA-IR.

Studies showing association between T2DM and CVD risk factors in a large and uniform population are scarce. Moreover previous cited markers are not usually included in the diagnosis or follow up of T2DM patients. The DICARIVA study was born to evaluate the cardiometabolic risk in a T2DM population, where emergent CVD risk factors, CRP,

microalbuminuria, fibrinogen, the triglyceride/HDL-cholesterol and TyG, together with classical CVD risk factors, were included.

The present paper aims to ascertain in a relatively ample sample of male and female T2DM patients: a) levels of classical and emergent CVD risk factors; b) CVD risk factors prevalence; and c) the existing gender differences. Getting all these would permit to design earlier diagnosis strategies and the planning of more accurate treatments in those patients.

METHODS

This observational, epidemiological and cross-sectional study was conducted in T2DM patients from the *DI*abetes *CA*rdiovascular *RI*sk of *VA*llecas (DICARIVA) study and diagnosed in the Diabetes and Cardiovascular risk office at the Endocrinology and Nutrition Service of the Infanta Leonor Universitary Hospital in Madrid, Spain. This hospital gives medical support to approximately 350,000 people belonging to two Madrid districts: Puente de Vallecas y Villa de Vallecas. The study sample comprises 735 T2DM patients managed by endocrinologist (334 men and 401 women) out of 1,032 patients from Vallecas area filed in the hospital endocrinology office. A flowchart of study participants of the DICARIVA study is shown in figure 1. Patients included were chosen from the office endocrinology file according to the following inclusion criteria: > 18 years old, written informed consent signed and DMT2 diagnosed. The exclusion criteria were < 18 years old and DMT1 diagnosed. The selection was made within a confidentiality framework in accordance with the Declaration of Helsinki guidelines. Written informed consent was obtained from all patients. Data of age, gender, lipids, lipoprotein-lipids, CVD ratios, systolic and diastolic blood pressures were available in all of them. Patients without any of this data were excluded from the study. As the DICARIVA study is a cross-sectional study the time framework was short (three months).

Anthropometry

Height was obtained using a stadiometer (Holtain© LTD., Dyfed, UK) with patient barefoot and wearing light clothing. The head was adjusted in a way that an imaginary line crossed the auditory canal and the lowest part of the socket (Frankfurt plane).

Body weight was obtained using an electronic weighing scale (SECA© alphaGmbH&Co., Igni, France). Body mass index was estimated using the formula body weight (kg)/height (meters) squared. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest using a flexible non-stretch measuring tape (Holtain, Dyfed, UK).

The Conicity Index (C_{index}) was estimated using the formula described by Valdez (7).

$$C_{index} = \frac{\text{Waist circumference (m)}}{0.109 \times \sqrt{\frac{\text{Body weight (kg)}}{\text{Height (m)}}}}$$

The C_{index} has been associated with central obesity, having a theoretically expected range of 1-1.73. The C_{index} is based on the estimate volume of the human body constructed to range between the shapes of a cylinder and a double cone assuming a constant body density.

The systolic and diastolic blood pressures were measured according to WHO guidelines (8) by trained personal after 10 minutes patients rest, with a mercury sphygmomanometer (Empire Riester©, Jungingen, Germany).

Laboratory measurements

Blood samples were collected from the antecubital vein after an overnight fast in the laboratory of the Hospital Infanta Leonor. Blood extraction sample was made by trained persons and the serum separated by centrifugation (Orto Arlesa 21; Madrid, Spain) at 3500 rpm for 20 minutes. Biochemical parameters were determined on serum in a Cobas Mira Plus of Roche biochemical autoanalyzer (Basel, Switzerland). Glucose, cholesterol, HDL-cholesterol and triglycerides were determined by enzymatic colorimetric methods (ELITech kits, Salon de Provenze, SEES, France). Low-density lipoprotein- (LDL-) cholesterol was calculated using the Friedewald et al formula (9) except for patients with triglyceride values ≥ 400 mg/dL in those the cLDL-Plus direct method was used (Hitachi 917 Roche Diagnostics©, Basel Switzerland).

Values of HbA1c were obtained by HPLC (Agilent 1100, Agilent technologies, Santa Clara, USA). Microalbuminuria by assessed by immunoturbidimetry (Wiener Laboratory, Rosario, Argentina) while fibrinogen was quantified by the von Clauss method (10) according to the National Committee for Clinical Laboratory Standards

procedure. *High sensitivity* c reactive protein levels were measured by immunoturbidimetry (Wiener Laboratory, Rosario, Argentina).

Finally, the TyG index, as an insulin resistance biomarker, was calculated according to the formula (11):

TyG = Ln [Plasma triglycerides (mg/dL) * Fasting plasma glucose (mg/dL)/2]

Where TyG is the triglycerides * glucose index.

An external quality control was applied following the Spanish Association of Pharmacy Analysts (AEFA) guidelines for clinic laboratories and clinical practice.

Cut-off points used

Tables I and II show the cut-off points used. These values were taken from consensus statements of different scientific associations (12-16) and the different data groups on anthropometric, biochemical parameters, lipid/lipoprotein profile and blood pressure originated. The adiposity markers were body mass index $\geq$ 30 kg/m^2, waist circumference $\geq$ 80 cm for women and $\geq$ 94 cm for men; regarding the C_{index}, and due to absence of established cut-off values, a value of > 1.30 (17,18) was adopted. We also selected the value 9.1 for TyG to classify patients with and without metabolic syndrome (6).

Statistical analyses

The sample representability was calculated according to the following formula

$$n = \frac{N * Z_{\alpha}^2 p * q}{d^2 * (N-1) + Z_{\alpha}^2 * p * q}$$

Where:

N = Total population (350,000)

Z_{α}^2= 1.962 (when 95% security was considered)

p = Expected prevalence (7% for T2DM = 0.07)

q = 1 - p (1-0.07 = 0.93)

d = accuracy (1.9% = 0.019).

Where n = 690

Thus, the sample of 735 T2DM studied in the Hospital Infanta Leonor can be considered representative of the total known number of T2DM of Vallecas at the level of 95% and for an error less than 1.9% considering a total of 350,000 persons in Vallecas. Similarly, the T2DM male and female populations studied were also representative of the total known number of T2DM males and females of Vallecas at the level of 95% and for an error less than 1.9%.

Data were described as mean ± SD, range, quartiles, and maximum and minimum values. Shapiro-Wilks and Kolmogorov-Smirnov tests were performed to assess normality distributions in all population and studied subgroups. Data groups were compared by the unpaired Student's *t* test, the Snedecor's *F* followed by the Student-Newman-Keuls *post hoc*, the Mann-Witney U test, the Kruskal-Wallis test and the chi-square test as appropriate. Statistical significance was set at $p < 0.05$ using the SPSS version 22.0 and the SAS version 9.2 statistical software packages.

RESULTS

Table III shows data about disease time-evolution, age and anthropometric data of the T2DM patients. The average disease duration was 11.4 years with lengthier evolution in women ($p = 0.03$). Twenty-five per cent of volunteers had > 17 years of T2DM evolution. Mean age was 65 years with 25% of patients being older than 75 years. Men were younger, heavier, and taller and showed higher C_{index} (all $p < 0.0001$) but lower body mass index ($p < 0.0001$).

Total and HDL-cholesterol levels were higher ($p < 0.0001$) in women. Men showed higher triglycerides/HDL-cholesterol ($p = 0.0012$), total cholesterol/HDL-cholesterol ($p < 0.0001$) and LDL-cholesterol/HDL-cholesterol ratios ($p < 0.0001$).

Table IV shows data of blood pressures, fasting glucose, glycated haemoglobin, TyG and other emergent CVD risk factors. Diastolic blood pressure were virtually lower in men ($p = 0.082$). Higher microalbuminuria ($p < 0.0001$) but lower *hs*-CRP ($p = 0.0006$) and fibrinogen ($p < 0.0001$) levels were present in men.

Table V gives information on the T2DM population regarding anthropometric markers classified according to the different scientific Societies criteria and the C_{index}. Gender-significant differences were observed for the body mass index, waist circumference and C_{index} population distribution (all, $p < 0.0001$). The obesity/overweight prevalence

also shows gender differences (33.5%/45.5% in males *vs.* 53.9%/28.2% in females). Thirty-three women suffered from morbid and extreme obesity. The prevalence of patients at very-high-CVD risk according to the waist circumference was much higher in women than men (78 vs 40%, respectively). A high prevalence of T2DM patients with ≥ 10 years evolution was found.

Table VI shows information on the different lipoprotein and diabetes control markers distribution in men and women. The values distribution within the cut-off points for total cholesterol (p = 0.0038), the triglyceride/HDL-cholesterol molar ratio (p = 0.007), the total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios (p = 0.014 and p = 0.003, respectively) were significantly different in both genders, with higher prevalence of elevated levels of these three ratios in males. Gender distribution differences were also observed for microalbuminuria (*P*=0.0006), *hs*-CRP (p = 0.009) and fibrinogen (p = 0.0009), HbA1c being at the borderline for statistical differences (p = 0.058). The prevalence of women at the highest range for *hs*-CRP and fibrinogen was higher while that of microalbuminuria lower.

More than 90% of DICARIVA study T2DM were treated with oral hypoglycemic drugs and or/insulin and 77% with hypotensive drugs, while 12% received insulin plus biguanides plus statins suggesting polymedication for diabetes treatment and its comorbidities.

DISCUSSION

The broad sample of male and female T2DM patients studied is one of the important strength of the DICARIVA study. Moreover, we collected or measured all the variables directly at the hospital. In addition to disease time-evolution and several classic CVD risk factors, information about emergent CVD risk factors as TyG, microalbuminuria, CRP, fibrinogen was obtained and the prevalence of altered levels in both gender-populations calculated and compared. Due to the information of cut-off points in CVD emergent markers in T2DM is relatively unknown, the Q3 values obtained has relevant importance and can be used in future studies. However, some limitations should be considered, e.g., we did not have direct information on nutritional habits; nonetheless, some measurements tested, such as body mass index, waist circumference, total cholesterol, LDL-cholesterol, are closely related to nutritional habits.

The average time of the T2DM evolution was 11.4 years, four years more than the observed by others (19). This disease time-evolution appeared not associated with higher values of the different markers studied. We do not have any clear hypotheses for those findings, as several aspects can be at work (familiar antecedents, drugs treatment, etc.).

Anthopometric parameters

In agreement with other studies conducted in T2DM patients (19) the anthropometric markers were clearly elevated. Patients showed lower weight, body mass index, waist circumference and height and higher disease evolution time than those included in the Rodriguez Bernardino et al. study (19). Weight, height, and waist circumference were higher in men but body mass index lower (19) and, as Tonding et al. (17) pointed out, lower C_{index} was found in females.

According to the waist circumference a similar value distribution was found in both sexes. However, according to their respective cut-points, central obesity, and thus, high CVD risk was more prevalent in women. However this risk would be ameliorated by other factors (e.g., estrogen, genetic, age) and would be assessed in future studies. According to body mass index, excess of fat mass (overweight and obesity) was present in 80% of the patients, in line with other findings (20), suggesting a cluster of obesity and T2DM. Elevated or very elevated waist circumference values were found in three out of four patients, this prevalence being much higher than that of non-diabetic Spanish population (21) suggesting that most of T2DM patients were at elevated CVD risk, as waist circumference shows a good predictive value for CVD risk. According to the C_{index}, the prevalence of patients at elevated CVD risk was larger than that observed by others (17), although the cut-off point selected in the present study (1.3) was slightly higher. A C_{index} of 1.18-1.2 has been suggested as a threshold for CVD risk and mortality increase by other investigators (18). If we compare the C_{index} with other methods of calculation of abdominal obesity we see that it brings some significant advantages over the most commonly used, waist circumference and body mass index. Regarding the first, conicity index prevents different interpretations according to race or ethnic group concerned and possible errors attributed to "eye of the beholder" (different persons measuring). Regarding the body mass index, it is not as specific as

the C_{index} rating visceral fat. In addition, some authors attribute to C_{index} better discriminating power of coronary risk (18). As C_{index} is directly related to abdominal fat distribution and, in turn to CVD risk, the Q3 values obtained in the study (1.39 in men and 1.37 in women) are proposed as cut-off points for future CVD risk in T2DM patients.

Lipid/lipoprotein profile, CVD risk ratios, TyG, and blood pressure

Although triglycerides and the triglycerides/HDL-cholesterol molar ratio showed elevated levels, total and LDL-cholesterol were relatively low both in men and women with 58% and 73% showing desirable or adequate values. The triglycerides/HDL-cholesterol molar ratio is indicative of LDL size and atherogenicity, being a relevant feature of diabetic dyslipemia (22). In T2DM the concentration of small LDL increases in spite of LDL-cholesterol one that remains normal or reduced; it means that LDL-cholesterol values could be misleading because they do not reflect the number of these atherogenic particles (22). In fact in the DICARIVA study, the prevalence of high LDL-cholesterol values was only 7.5%. Due to the relevance of the TG/HDLc molar ratio already commented the Q3 values obtained in the study (1.9 in men and 1.7 in women) are proposed as cut-off points for future CVD risk in T2DM patients.

CVD risk is elevated in T2DM (22) due to the presence of the Atherogenic Lipid Triad. The main features of this triad are: high levels of triglycerides, reduced value of HDL-cholesterol and elevated number of small dense and more oxidizable LDL particles (22). In spite of having relative low LDL-cholesterol levels, males presented triglycerides/HDL-cholesterol ratio higher than females suggesting a major CVD risk due to the increased presence of those more atherosclerotic LDL particles. The Atherogenic Lipid Triad was present in 18% of patients; almost 35% had reduced HDL-cholesterol levels, 36% presented hypertriglyceridemia, and 39% had elevated triglycerides/HDL-cholesterol ratio.

The total cholesterol/HDL-cholesterol ratio seems to be a better marker than LDL-cholesterol/HDL-cholesterol ratio, mainly if strong hypertriglyceridemia (> 400 mg/dL) is present and LDL-cholesterol levels have been calculated by Friedewald et al. formula (9). On the other hand, the association of CVD risk to elevated total cholesterol/HDL-cholesterol or LDL-cholesterol/HDL-cholesterol ratio increases dramatically in presence

of hipertriglyceridemia (22). Both total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios were similar to those found in other studies (23). Frequently CVD risk ratios are higher in males than in females in diabetic and non-diabetic populations. Hypercholesterolemia but not hypertriglyceridemia was more prevalent in women. Triglycerides levels are elevated during menopause, partially explaining the gender comparable triglyceride levels and prevalences of hypertriglyceridemia found in this study.

Females tended to have higher diastolic blood pressures. Blood pressure levels were, roughly, 4 mmHg lower than in other studies (19). Normal-high/moderate hypertension was found in 66% of patients while 2% presented severe hypertension, suggesting increased CVD risk. Rodríguez Bernardino et al. (19) reported that hypertension was present in 70.8% patients, probably related to the low antihypertensive treatment compliance as was reported in some cross-sectional studies in Spain. According to WHO, hypertension is responsible for, at least, 45% of deaths due to heart disease and 51% of deaths due to stroke (24).

More than 60% men and women presented metabolic syndrome according to the TyG values (6). These results agree with the high prevalence of obesity, hyperglycemia, dyslipemia and blood pressure observed in the DICARIVA study. As TyG has been recognized to be a good insulin resistance marker (11), and no significant differences were found for TyG between male and female, the Q3 values obtained for all studied patients (9.8) is proposed as cut-off points for future CVD risk and insulin resistance in T2DM patients.

Fasting plasma glucose, HbA1c, hs-CRP, microalbuminuria, and fibrinogen

Average fasting plasma glucose and HbA1c levels were far away from optimal values. The prevalence of T2DM patients with HbA1c $\geq$ 6.5% was 85%, suggesting a bad diabetes control and increased CVD risk (4,25) in a very high percentage of volunteers. HbA1c is considered a better indicator of future CVD event than fasting glycemia (25). Both fasting plasma glucose and HbA1c values were higher than in other studies (17,19), but lower than in other study in which similar disease time-evolution was reported (26).

The prevalence of microalbuminuria in the total population was high (36% in men and 25.5% in women) in line with other studies on T2DM patients (27). According to the HOPE study, global mortality, myocardial infarction, stroke or CVD mortality are higher in diabetic patients showing microalbuminuria (27). Any degree of microalbuminuria, persistent or clinic, has been associated with increased risk of CVD events.

The high prevalence found for elevated *hs*-CRP levels was in line with almost all scientific literature, although conclusions are not coincident in all of them. In concordance with Bruno et al. (28) *hs*-CRP levels suggest a higher inflammatory status in women. According to *hs*-CRP cut-off points two third of patients were at elevated or medium CVD risk (60.5% males and 70.3% females), confirming the association between T2DM and *hs*-CRP (29). Almost a half of the patients were at elevated CVD risk according to their fibrinogen levels. Higher hyperfibrinogenia in women has been also reported by others (30). The Q3 values obtained in the study for hs-CRP (4.3 mg/L in men and 5.8 mg/L in women) and for fibrinogen (441 mg/dL in men and 468 mg/dL in women) are proposed as cut-off points for future CVD risk in T2DM patients.

As commented, the presence of toxic habits was relatively frequent among the patients, suggesting the need to control and reduce alcohol and tobacco consumption and to increase physical activity in those T2DM patients. The high prevalence of altered markers contrasts with the relatively high drug consumption of these patients as most of them were treated with oral hypoglycemic drugs and or/insulin and with hypotensive drugs. This fact seems paradoxical but, as commented, it suggests low treatment compliance (19). The conjoin treatment with insulin plus biguanides plus statins in one tenth of DICARIVA participants suggests polymedication for diabetes and its comorbidities treatment.

In conclusion most of the classic and emergent CVD risk factors, particularly the Atherogenic Lipidic Triad, were altered in the DICARIVA study suggesting the presence of several metabolic disorders and CVD risk within this diabetic population. Significant differences by gender were found in some of the indicators but not in HbA1c. As the information of cut-off points in CVD emergent markers in T2DM is relatively unknown, the Q3 values obtained for C_{index}, TyG, hs-CRP, TG/HDLc molar ratio and fibrinogen are proposed to be included as tools for future studies in T2DM.

Therefore, early diagnoses strategy and T2DM drug treatment compliance follow up, together with lifestyle behavior control are needed to avoid or at least to decrease the high CVD risk found in these population.

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Table I. Cut-off points used for anthropometric values, blood pressures and lipid and lipoproteins

Parameter	*Scientific society*	*Level*	*Cut-off points*	
Body mass index (kg/m^2)	SEEDO	Thickness Normal weight Overweight Obesity	< 18.5 18.5-24.9 ≥ 25-29.9 ≥ 30	
Waist circumference (cm)	ATPIII	Normal High CVD risk Very high CVD risk	Men: < 95 Men: ≥ 95-101.9 Men: ≥ 102	Women: < 82 Women: ≥ 82-87.9 Women: ≥ 88
Conicity index	(17,18)	Low-normal Intermediate High	<1.3 ≥ 1.3-1.49 ≥ 1.5	
SBP/DPB (mmHg)	ESH/ESC	Normal High-normal/Grades 1, 2[+] Grade 3[+]	< 130/85 ≥ 130/85-179/109 ≥ 180/110	
Total cholesterol (mg/dL)	ATPIII	Desirable Borderline-high High	< 200 ≥ 200-239 ≥ 240	
HDL-c (mg/dL)	ATPIII	Low Intermediate High	Men: < 40 Men: ≥ 40-59 Men: ≥ 60	Women: < 50 Women: ≥ 50-59 Women: ≥ 60
LDL-c (mg/dL)	ATPIII	Optimal/good Borderline-high High	< 100 - ≤ 129 ≥ 130-159 ≥ 160 - ≥ 190	
Triglycerides (mg/dL)	ATPIII	Normal High	< 150 ≥ 150	
Triglycerides/HDL-c*		Normal High	< 1.33 ≥ 1.33	
Cholesterol/HDL-c	ATPIII	Normal Intermediate High	< 4.5 ≥ 4.5-4.99 ≥ 5.0	
LDL-c/HDL-c	ATPIII	Normal Intermediate High	< 3.0 ≥ 3.0-3.49 ≥ 3.5	

DPB: diastolic blood pressure; HDL-c: cholesterol transporter by high density lipoproteins; LDL-c: cholesterol transported by low density lipoproteins; SBP: systolic blood pressure; TyG index: tryglicerides * glucose index; [+]Hypertension; *Molar ratio. ATPIII (Adult Treatment Panel III) (13); ESH/ESC, European Society of Hypertension/European Society of Cardiology (14); SEEDO, Sociedad Española para el Estudio de la Obesidad (12). The cut-off points for the conicity index were selected from references of Tonding et al. (17) and Almeida et al. (18).

Table II. Cut-off points for glucose, glycated haemoglobin, triglyceride-glucose (TyG) index, *high sensitivity*-C reactive Protein (*hs*-CRP), microalbuminuria and fibrinogen

Parameter	*Scientific Entity*	*Level*	*Cut-off point*
Fasting glucose (mg/dL)	ADA	Normal Prediabetes Diabetes	< 100 ≥ 100-125.9 ≥ 126
Glycated haemoglobin (%)	ADA	Normal Prediabetes Diabetes	< 5.7 ≥ 5.7-6.49 ≥ 6.5
Tyg index	Unger et al (6)	Normal DM and no MS DM and MS	≤ 8.3 ≥ 8.3-9.09 ≥ 9.1
hs-CRP (mg/L)	AHA	Low CVD risk Intermediate CVD risk High CVD risk	≤ 1 > 1-2.99 ≥ 3
Microalbuminuria (mg/24 h)	ADA	Normal Microalbuminuria Clinic albuminuria	≤ 30 > 30-299 ≥ 300
Fibrinogen (mg/dL)		Normal High	< 400 ≥ 400

ADA: American Diabetes Association (15); AHA: American Heart Association (16); DM: diabetes mellitus; hs-CRP: high sensitivity C reactive protein; MS: metabolic syndrome; TyG index: tryglicerides * glucose index = Ln [fasting plasma triglycerides (mg/dL) * fasting plasma glucose (mg/dL)/2] (6).

Table III.

Anthropometric features in males, females type 2 diabetics from the DICARIVA study										
		N	*Mean*	*Standard deviation*	*Minimum*	*Maximum*	*Q1*	*Median*	*Q3*	*Gender p value*
Evolution (years)	Men	287	9.9	8.5	0	38	2	8	15	0.0001
	Women	350	12.7	10.0	0	48	4	11	18	
	All	637	11.5	9.5	0	48	3	10	17	
Age (years)	Men	334	62.6	14.5	18	92	55	65	73	< 0.0001
	Women	401	66.5	14.3	19	90	59.5	70	76.5	
	All	735	64.7	14.5	18	92	57	67	75	
Weight (kg)	Men	334	80.0	14.5	50	138.5	69.6	78.05	88	< 0.0001
	Women	401	73.7	15.9	36.8	135.2	62.5	71.4	82.4	
	All	735	76.5	15.6	36.8	138.5	65.7	75	86	
Height (cm)	Men	334	167.2	7.1	145	188	163	167	172	< 0.0001
	Women	401	153.4	6.8	134	180	149	153	158	
	All	735	159.7	9.8	134	188	152	159	166	
BMI (kg/m^2)	Men	334	28.6	4.6	16.61	47.32	25.4	28.19	31.2	< 0.0001
	Women	401	31.3	6.3	17.64	51.88	27.1	30.42	35,3	
	All	735	30.1	5.8	16.61	51.88	26	29.37	33.3	
Waist circumference	Men	327	100.4	12.3	70	141	92	100	108	0.12
(cm)	Women	392	98.5	13.5	64	143	90	99	107	

	All	719	99.4	13.0	64	143	91	99	108	
Conicity index	Men	327	1.3	0.08	1.1	1.62	1.28	1.33	1.39	< 0.0001
	Women	392	1.3	0.09	1.03	1.53	1.26	1.3	1.37	
	All	719	1.3	0.09	1.03	1.62	1.26	1.32	1.38	

N: sample size; P: probability; Q1 and Q3: 1 and 3 quartiles, respectively; HDL-cholesterol and LDL-cholesterol: cholesterol transported by high and low density lipoproteins respectively. *Triglycerides/HDL-cholesterol molar ratio. *p* value, significant differences between men and women.

Lipid/lipoprotein profile and blood pressure levels in males, females and total population

		N	*Mean*	*SD*	*Minimum*	*Maximum*	*Q1*	*Median*	*Q3*	*p value*
Total cholesterol	Men	334	188.3	40.1	61	337	162	184	214	< 0.0001
(mg/dL)	Women	401	201.9	46.9	94	610	174	198	222	
	All	735	195.7	44.4	61	610	168	193	220	
HDL-c	Men	334	48.2	12.3	23	99	39	46	56	< 0.0001
(mg/dL)	Women	401	56.5	14.4	26	129	46	54	66	
	All	735	52.7	14.1	23	129	43	51	61	
LDL-c	Men	334	109.3	32.1	30	238	88	108	129	0.11
(mg/dL)	Women	401	114.2	34.1	36	275	93	110	133	
	All	735	112	33.3	30	275	90	109	131	
Triglycerides	Men	334	155.2	108.5	33	943	89	128	184	0.78
(mg/dL)	Women	401	155	132.0	27	1931	90	120	189	
	All	735	155.1	121.8	27	1931	89	124	187	
TG/HDL-c*	Men	334	1.6	1.5	0.2	15.76	0.7	1.21	1.9	0.0012

	Women	401	1.4	1.3	0.14	11.22	0.6	0.96	1.7	
	All	735	1.5	1.4	0.14	15.76	0.7	1.05	1.8	
Cholesterol/HDL-c	Men	334	4.1	1.3	1.88	9.62	3.21	3.87	4.73	0.0001
	Women	401	3.8	1.2	1.67	10.58	2.88	3.52	4.40	
	All	735	3.92	1.2	1.67	10.58	3.03	3.71	4.57	
LDL-c/HDL-c	Men	334	2.39	0.87	0.69	5.21	1.73	2.21	2.97	<0.0001
	Women	401	2.14	0.82	0.54	5.19	1.53	1.99	2.58	
	All	735	2.25	0.85	0.54	5.21	1.62	2.11	2.73	

N: sample size; SD: standard deviations; P: probability for differences between men and women; Q1 and Q3: 1 and 3 quartiles, respectively; HDL-c and LDL-c: cholesterol transported by high and low density lipoproteins respectively. *TG/HDL-c: triglycerides/HDL-cholesterol molar ratio.

Table IV. Blood pressure, diabetes control markers level, *high sensitivity* c reactive protein and fibrinogen in males and females

		N	**Mean**	**SD**	**Minimum**	**Maximum**	**Q1**	**Median**	**Q3**	**p value**
SBP (mmHg)	Men	334	134.8	16.1	90	190	120	135	140	0.10
	Women	401	137.0	17.2	90	200	120	140	145	
	All	735	136.0	16.7	90	200	120	140	145	
DBP (mmHg)	Men	334	75.4	9.7	50	100	70	80	80	0.08
	Women	401	76.9	9.6	50	105	70	80	80	
	All	735	76.2	9.7	50	105	70	80	80	
Fasting glucose	Men	334	181.7	65.0	41	400	136	172	224	0.73
(mg/dL)	Women	401	180.6	63.7	29	534	139	172	215	

	All	735	181.1	64.3	29	534	137	172	219	
Glycated haemoglobin)	Men	334	8.1	1.8	4.6	14,4	6.8	7.9	9.1	0.66
(%)	Women	401	8.1	1.5	4.7	13.2	7.1	7.8	8.9	
	All	735	8.1	1.6	4.6	14.4	6.9	7.9	9	
TyG index	Men	334	9.3	0.77	7.09	11.91	8.8	9.3	9.7	0.93
	Women	401	9.3	0.71	7.47	12.26	8.8	9.3	9.8	
	All	735	9.3	0.74	7.09	12.26	8.8	9.3	9.8	
Microalbuminuria*	Men	326	152.4	713	0	9600	10.5	18.8	46.8	< 0.0001
(mg/24 h)	Women	394	58.6	263	0	3839	7.2	14.05	30	
	All	720	101	519	0	9600	8.4	15.9	36.2	
hs-CRP	Men	334	3.7	7.7	0.1	108.2	0.5	1.6	4.3	0.0006
(mg/L)	Women	401	5.6	22.1	0.1	431	0.8	2.5	5.8	
	All	735	4.7	17.2	0.1	431	0.7	2	5.1	
Fibrinogen	Men	330	389.9	86.0	188	789	331	379.5	441	< 0.0001
(mg/dL)	Women	397	414.4	85.7	214	730	353	404	468	
	All	727	403.3	86.6	188	789	342	391	455	

N: sample size; SD: standard deviations; P: probability for differences between men and women; Q1 and Q3: 1 and 3 quartiles, respectively; DBP: diastolic blood pressure; *hs*-CRP: *high sensitivity c* reactive protein; SBP: systolic blood pressure; TyG: triglycerides *Glucose index.

Table V. Men, women and total population distribution according to disease time-evolution, body mass index, waist circumference and conicity index ranges

		Men		*Women*		*All*		
	Level	*N*	*%*	*N*	*%*	*N*	*%*	*p* (χ^2)
Time-evolution	0-< 5 years	96	33.4	91	26.0	187	29.4	0.030
	5-< 10 years	59	20.6	57	16.3	116	17.4	
	≥ 10 years	132	46.0	202	57.7	334	52.4	
BMI	Thickness/normal	70	20.96	72	17.96	142	19.32	< 0.0001
(kg/m^2)	Overweight	152	45.51	113	28.18	265	36.06	
	Obesity	112	33.54	216	53.87	328	44.62	
Waist circumference	Normal	121	37	51	13.01	172	23.92	< 0.0001
(cm)	High CVD risk	74	22.63	35	8.93	109	15.16	
	Very high CVD risk	132	40.37	306	78.06	438	60.92	
Conicity index	< 1.3	104	31.8	184	46.94	288	40.06	< 0.0001
	≥ 1.3-1.49	214	65.44	205	52.3	419	58.28	
	≥ 1.5	9	2.75	3	0.77	12	1.67	
Blood pressure	Normal	111	33,23	117	29.18	228	31.02	0.43
(mmHg)	Normal-high/							
	Grade 1, 2	217	64.97	274	68.33	491	66.8	

	Grade 3	6	1.8	10	2.49	16	2.18	

Cut-off point Levels from Scientific Societies detailed in table I. N: sample size; %: percentage of patients; p (χ^2): probability according to chi square test.

Table VI.

Men, women and total population distribution according to lipid/lipoprotein and TyG index cut-off points								
		Men		*Women*		*All*		*p* (χ^2)
	Level	*N*	*%*	*N*	*%*	*N*	*%*	
Total cholesterol (mg/dL)	Desirable	215	64.37	211	52.62	426	57.96	0.0038
	Borderline-high	89	26.65	133	33.17	222	30.2	
	High	30	8.98	57	14.21	87	11.84	
HDL-c (mg/dL)	Low	107	32.04	148	36.91	255	34.69	0.36
	Borderline-high	98	29.34	113	28.18	211	28.71	
	High	129	38.62	140	34.91	269	36.6	
LDL-c (mg/dL)	Optimal/Good	253	75.74	286	71.32	539	73.34	0.36
	Borderline-high	63	18.86	78	19.45	141	19.18	
	High	18	5.39	37	9.23	55	7.48	
Triglycerides (mg/dL)	Normal	211	63.17	256	63.84	467	63.54	0.85
	High	123	36.83	145	36.16	268	36.46	
Triglycerides/HDL-c	Normal	185	55.39	261	65.09	446	60.68	0.007
	High	149	44.61	140	34.91	289	39.32	
Cholesterol/HDL-c	Normal	226	67.66	309	77.06	535	72.79	0.014
	Intermediate	41	12.28	39	9.72	80	10.88	

	High	67	20.06	53	13.22	120	16.33	
LDL-c/HDL-c	Normal	251	75.15	341	85.04	592	80.54	0.003
	Intermediate	39	11.68	30	7.48	69	9.39	
	High	44	13.17	30	7.48	74	10.07	
TyG index	Normal	27	8.08	32	7.98	59	8.03	0.729
	DM & non-MS:	96	28.74	126	31.42	222	30.20	
	DM &MS	211	63.18	243	60.60	454	61.77	

Cut-off point levels from scientific societies detailed in tables I and II. N: sample size; %: percentage of patients; p (χ^2): probability according to chi square test.

Men, women and total population distribution according to range of glucose, glycated haemoglobin, hs-C reactive protein and fibrinogen cut-off points

		Men		*Women*		*All*		*p* (χ^2)
	Level	*N*	*%*	*N*	*%*	*N*	*%*	
Fasting glucose	Normal	26	7.78	26	6.48	52	7.07	0.65
(mg/dL)	Prediabetes	41	12.28	44	10.97	85	11.56	
	Diabetes	267	79.94	331	82.54	598	81.36	
Glycated haemoglobin	Normal	21	6.29	11	2.74	32	4.35	0.058
(%)	Prediabetes ≥	38	11.38	43	10.72	81	11.02	
	diabetes	275	82.34	347	86.53	622	84.63	
hs-c reactive protein	Low CVD risk	132	39.52	119	29.68	251	34.15	0.009

(mg/L)	Medium CVD risk	90	26.95	104	25.94	194	26.39	
	High CVD risk ≥	112	33.54	178	44.39	290	39.46	
Microalbuminuria	Normal	208	64	291	74.62	499	69.79	0.0006
(mg/24 h)	Microalbuminuria	90	27.69	88	22.56	178	24.9	
	Clinic albuminuria	27	8.31	11	2.82	38	5.31	
Fibrinogen (mg/dL)	Normal	198	60	189	47.61	387	53.23	0.0009
	High	132	40	208	52.39	340	46.77	

Cut-off point Levels from Scientific Societies detailed in table II. N: sample size; %: percentage of patients; p (χ^2): probability according to chi square test.

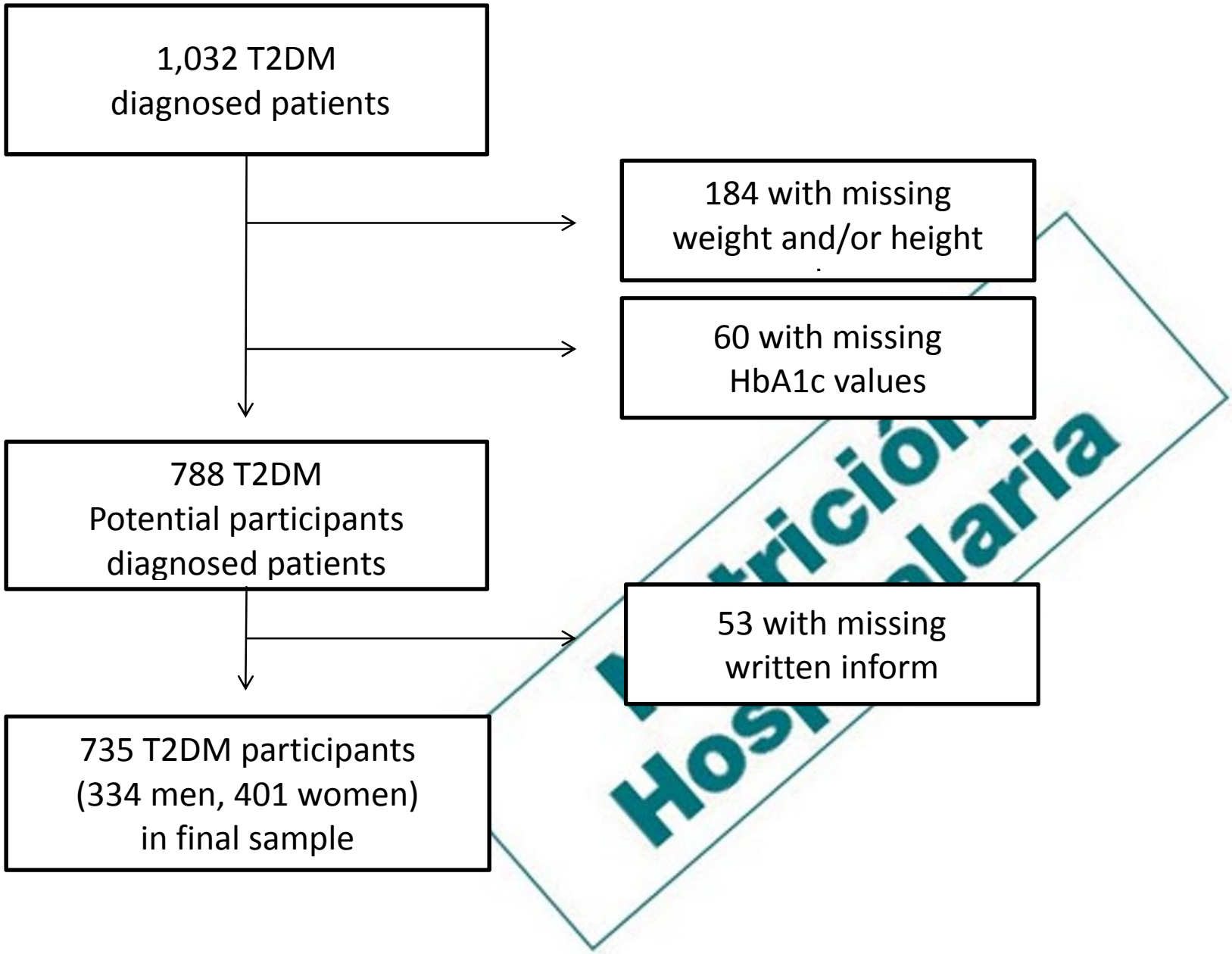

Figure 1. Flow chart of the DICARVA study.