



ORIGINAL

Prevalence, impact and management of hypertension-mediated organ damage in type 2 diabetes patients



A.A. Romero-Secin^{a,b}, J. Díez-Espino^{b,c}, M.A. Prieto-Díaz^d, V. Pallares-Carratala^{e,*}, A. Barquilla-García^f, R.M. Micó-Pérez^g, J. Polo-García^h, S.M. Velilla-Zancadaⁱ, V. Martín-Sánchez^j, A. Segura-Fragoso^k, L. Ginel-Mendoza^l, V.M. Arce-Vazquez^m, S. Cinza-Sanjurjo^{n,o}

^a Specialist in Family and Community Medicine, Colloto Health Clinic, Principality of Asturias Health Service, Asturias, Spain

^b Fundacion redGEDAPS, Spain

^c Specialist in Family and Community Medicine, Tafalla Health Center, Tafalla, Navarrese Health Service, Navarra, Spain

^d Specialist in Family and Community Medicine, Vallobín-La Florida Health Center, Principality of Asturias Health Service, Asturias, Spain

^e Department of Medicine, Jaume I University, Castellon, Spain

^f Specialist in Family and Community Medicine, Trujillo Health Center, Extremadura Health Service, Cáceres, Spain

^g Specialist in Family and Community Medicine, Fontanars dels Alforins Health Center, Xàtiva-Ontinyent Department of Health, Valencia, Spain

^h Specialist in Family and Community Medicine, Casar de Cáceres Health Center, Extremadura Health Service, Cáceres, Spain

ⁱ Specialist in Family and Community Medicine, Joaquin Elizalde Health Center, Rioja Health Service, Logroño, La Rioja, Spain

^j Institute of Biomedicine (IBIOMED), University of León, Epidemiology and Public Health Networking Biomedical Research Centre (CIBERESP), León, Spain

^k Epidemiology Unit, Semergen Research Agency, Madrid, Spain

^l Specialist in Family and Community Medicine, Ciudad Jardín Health Center, Málaga, Spain

^m Centro de investigación en medicina molecular y enfermedades crónicas (CIMUS), Universidad de Santiago de Compostela, Galicia, Spain

ⁿ Specialist in Family and Community Medicine, Milladoiro Health Centre, Health Area of Santiago de Compostela, Health Research Institute of Santiago de Compostela (IDIS), A Coruña, Spain

^o Networking Biomedical Research, Centre-Cardiovascular Diseases (CIBERCV), Santiago de Compostela, Spain

Received 19 December 2023; accepted 16 February 2024

Available online 29 March 2024

KEYWORDS

Cardiovascular;
Diabetes;

Abstract

Objective: To determine the prevalence, impact and management of hypertension-mediated organ damage (HMOD) according to the presence of type 2 diabetes (T2DM).

* Corresponding author.

E-mail address: pallares.vic@gmail.com (V. Pallares-Carratala).

<https://doi.org/10.1016/j.semerg.2024.102220>

1138-3593/© 2024 Sociedad Española de Médicos de Atención Primaria (SEMERGEN). Published by Elsevier España, S.L.U. All rights reserved.

GLP-1 receptor agonists;
SGLT2 inhibitors;
Hypertension-mediated organ damage

Methods: IBERICAN is an ongoing multicenter, observational and prospective study, including outpatients aged 18–85 years who attended the Primary Care setting in Spain. In this study, the prevalence, impact and management of HMOD according to the presence of T2DM at baseline were analyzed.

Results: At baseline, 8066 patients (20.2% T2DM, 28.6% HMOD) were analyzed. Among patients with T2DM, 31.7% had hypertension, 29.8% dyslipidemia and 29.4% obesity and 49.3% had ≥ 1 HMOD, mainly high pulse pressure (29.6%), albuminuria (16.2%) and moderate renal impairment (13.6%). The presence of T2DM significantly increased the risk of having CV risk factors and HMOD. Among T2DM population, patients with HMOD had more dyslipidemia (78.2% vs 70.5%; $P=0.001$), hypertension (75.4% vs 66.4%; $P=0.001$), any CV disease (39.6% vs 16.1%; $P=0.001$) and received more drugs. Despite the majority of types of glucose-lowering agents were more frequently taken by those patients with HMOD, compared to the total T2DM population, the use of SGLT2 inhibitors and GLP-1 receptor agonists was marginal.

Conclusions: In patients daily attended in primary care setting in Spain, one in five patients had T2DM and nearly half of these patients had HMOD. In patients with T2DM, the presence of HMOD was associated with a higher risk of CV risk factors and CV disease. Despite the very high CV risk, the use of glucose-lowering agents with proven CV benefit was markedly low.

© 2024 Sociedad Española de Médicos de Atención Primaria (SEMERGEN). Published by Elsevier España, S.L.U. All rights reserved.

PALABRAS CLAVE

Cardiovascular;
Diabetes;
Agonistas del receptor GLP-1;
Inhibidores de los SGLT2;
Daño orgánico mediado por hipertensión arterial

Prevalencia, impacto y manejo del daño orgánico mediado por la hipertensión en pacientes con diabetes tipo 2

Resumen

Objetivo: Determinar la prevalencia, impacto y manejo del daño orgánico mediado por hipertensión (HMOD) según la presencia de diabetes tipo 2 (DM2).

Métodos: IBERICAN es un estudio multicéntrico, observacional y prospectivo, que incluye pacientes entre 18 y 85 años que acuden a consultas de atención primaria en España. En este estudio se analizó la prevalencia, el impacto y el manejo de la HMOD según la presencia de DM2 al inicio del estudio.

Resultados: Se analizaron 8,066 pacientes (20,2% DM2, 28,6% HMOD). Entre los pacientes con DM2, el 31,7% tenía hipertensión, el 29,8% dislipidemia, el 29,4% obesidad y el 49,3% tenía ≥ 1 HMOD, principalmente presión de pulso elevada (29,6%), albuminuria (16,2%) e insuficiencia renal moderada (13,6%). La presencia de DM2 aumentó significativamente el riesgo de tener factores de riesgo cardiovasculares y HMOD. Entre la población con DM2, los pacientes con HMOD tenían más dislipidemia (78,2% frente a 70,5%; $p=0,001$), hipertensión (75,4% frente a 66,4%; $p=0,001$), cualquier enfermedad cardiovascular (39,6% frente a 16,1%; $p=0,001$) y recibieron más fármacos. A pesar de que los pacientes con HMOD tomaban con mayor frecuencia la mayoría de los tipos de agentes hipoglucemiantes, en comparación con la población total de DM2, el uso de inhibidores de SGLT2 y agonistas del receptor de GLP-1 fue marginal.

Conclusiones: En los pacientes atendidos diariamente en atención primaria en España, uno de cada 5 pacientes tenía DM2 y casi la mitad de estos pacientes tenían HMOD. En pacientes con DM2, la presencia de HMOD se asoció con un mayor riesgo de factores de riesgo cardiovasculares y enfermedad cardiovascular. A pesar del riesgo cardiovascular muy alto, el uso de agentes hipoglucemiantes con beneficio cardiovascular demostrado fue notablemente bajo.

© 2024 Sociedad Española de Médicos de Atención Primaria (SEMERGEN). Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Type 2 diabetes (T2DM) is a main health care problem in Spain.^{1,2} The Di@bet.es study showed a decade ago that the overall prevalence of DM adjusted for age and sex was around 14%, of which 6% had unknown DM.¹ However, data

from the IDF 2021 Diabetes Atlas showed that the number of people with DM in Spain had increased from 2.8 million in 2011 to 5.1 million in 2021.² In addition, total diabetes-related health expenditure in 2021 in Spain was huge, accounting for \$15.5 billion, \$3000 per person with DM.²

The presence of DM doubles the risk of developing CV disease.³ The recent 2023 European guidelines for the management of CV disease in patients with T2DM consider that patients with clinically established atherosclerotic CV disease, or severe hypertension-mediated organ damage (HMOD), or 10-year CV disease risk $\geq 20\%$ using SCORE2-Diabetes have a very high CV risk.⁴ In other words, having severe HMOD could be considered an equivalent of CV disease. As a result, it is mandatory to improve the prevention and early detection of complications of patients with T2D, such as HMOD, through and holistic management to reduce the CV burden of this population.⁴⁻⁶ European guidelines define severe HMOD as the presence of any of the following conditions: estimated glomerular filtration rate (eGFR) $< 45 \text{ mL/min/1.73 m}^2$ irrespective of albuminuria, eGFR $45\text{--}59 \text{ mL/min/1.73 m}^2$ and albuminuria – previously named as microalbuminuria – (urinary albumin-to-creatinine ratio [UACR] $30\text{--}300 \text{ mg/g}$), proteinuria (UACR $> 300 \text{ mg/g}$), or presence of microvascular disease in at least three different sites, such as albuminuria plus retinopathy plus neuropathy.^{4,7-9} Therefore, the search and identification of HMOD in patients with T2DM should be strengthened in clinical practice. In this context, it is important to ascertain the prevalence and impact of HMOD in real-life population with T2DM.

IBERICAN (Identificación de la población Española de Riesgo CV y reNal – Identification of the Spanish population at risk of CV and renal disease –) is currently determining in more than 8000 subjects attended in primary care in Spain, the prevalence of CV risk factors and the incidence of CV events, after 10 years of follow-up.¹⁰⁻¹⁴ In this study, the prevalence, impact and management of HMOD according to the presence of T2DM at baseline were analyzed.

Methods

IBERICAN¹⁰⁻¹⁴ is an ongoing epidemiological, multicenter, observational and prospective study, which has included outpatients aged 18–85 years who attended the Primary Care setting of the National Health System in Spain, regardless of the presence of CV risk factors or CV disease, and who agreed to participate in the study by giving their written informed consent, with a follow-up for at least 10 years. Patients that changed the habitual residence to another city or country within the first six years after inclusion, with terminal disease, a life expectancy less than five years, or manifest difficulties to be followed-up were excluded from the study. The study was approved by the Independent Ethics Committee of the University Hospital Clínico San Carlos (Madrid, Spain) and was registered at <https://clinicaltrials.gov> under the number NCT02261441.

Data were collected from the electronic medical history of patients, direct interview and medical examination and were entered into an electronic Case Report Form (CRF) specifically created for the study. Sociodemographic data, CV risk factors (hypertension, dyslipidemia, smoking, obesity, sedentary lifestyle), HMOD (pulse pressure $\geq 60 \text{ mmHg}$ in subjects > 65 years of age, ankle brachial index < 0.9 , albuminuria: UACR between 30 and 299 mg/g , eGFR [CDK-EPI] $30\text{--}59 \text{ mL/min}$, left ventricular hypertrophy), and vascular disease (ischemic heart disease, heart failure, stroke,

peripheral arterial disease and chronic kidney disease) were recorded. All variables were defined according to the 2013 European Society of Hypertension/European Society of Cardiology guidelines.¹⁵ Physical examination included blood pressure, heart rate, and body mass index. Data from a 12-lead electrocardiogram and blood and urine tests (glycaemia, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, creatinine, uric acid and UACR) performed according to clinical practice in the previous 6 months before inclusion were considered valid for the study. Total number of drugs, as well as the type of glucose-lowering agents (metformin, sulphonylureas, glinides, glitazones, dipeptidyl peptidase 4 [DPP-4] inhibitors, glucagon-like peptide 1 receptor agonists [GLP-1 RA], sodium-glucose cotransporter 2 [SGLT2] inhibitors, insulin and others) were also recorded. A good glycemic control was considered as $\text{HbA1c} \leq 7\%$.¹⁶ Obesity was defined as a body mass index $> 30 \text{ kg/m}^2$, and sedentarism as doing physical less than 30 min daily of physical activity or absence of activity.

Statistical analysis

Qualitative variables were defined by their absolute and relative frequencies, and continuous variables as mean and standard deviation. Statistical tests were performed according to the nature of the variables. To study the relationship between the categorical variables, the Chi-squared test was used (where more than 20% of the cells had an expected frequency of less than five, Fisher's exact test was performed). Student's *t*-test was used to compare continuous variables between groups. Multivariate analyses were performed to determine those factors associated with an increased risk of CV risk factors and HMOD according to the presence of T2DM and among patients with T2DM, those factors associated with an increased risk of CV risk factors and CV disease according to the presence of HMOD. All those variables that showed a *P*-value < 0.05 in the bivariate analysis were included as independent variables in the initial model. From the initial model, the non-significant variables were manually eliminated, until the final model was reached. All comparisons rejected the null hypothesis with an alpha error < 0.05 . IBM SPSS version 22.0 was used for data analyses.

Results

Of the total of 8066 patients included in the IBERICAN study at baseline, 8056 (99.9%) were valid for the analysis. Of these, 20.2% had T2DM and 28.6% HMOD.

Among patients with T2DM, 35.6% had a sedentary lifestyle, 31.7% hypertension, 29.8% dyslipidemia, and 29.4% were obese. In addition, 49.3% had at least one HMOD, mainly high pulse pressure (29.6%), albuminuria (16.2%) and moderate renal impairment (13.6%) (Table 1). The prevalence of any HMOD was similar between men and women, but albuminuria was more common in men (20.6% vs 10.8%; $P < 0.001$) and moderate renal impairment in women (11.7% vs 16.1%; $P = 0.01$) (Table 2). Control of DM was numerically higher in patients with HMOD, but without significant statistical differences (74.4% vs 66.2%; $P = 0.81$), and time of evolution of DM was significantly greater in those patients

Table 1 Baseline clinical characteristics according to the presence of T2DM.

	T2DM (20.2%)	No T2DM (79.8%)	P
<i>Biodemographic data</i>			
Age, years	65.5 ± 10	55.9 ± 15	<0.001
Sex (male), %	55.5	42.9	<0.001
<i>Cardiovascular risk factors</i>			
Hypertension, %	31.7	9.6	0.001
Dyslipidemia, %	29.8	10.4	0.001
Obesity, %	29.4	15.3	0.001
Smoking, %	15.2	21.3	0.001
<i>HMOD</i>			
Any	49.3	23.5	<0.001
PP ^a , mmHg	29.6	13.5	<0.001
Albuminuria, %	16.2	5.5	<0.001
Moderate renal insufficiency ^b , %	13.6	5.7	<0.001
LVH, %	7.3	3.1	<0.001
ABI < 0.9, %	2.8	1.4	<0.001
<i>Physical examination</i>			
Waist circumference, cm	103.3 ± 15.0	94.7 ± 14.5	<0.001
BMI (kg/m ²)	30.5 ± 5.2	28.0 ± 5.4	<0.001
SBP (mmHg)	134.4 ± 15.8	127.63 ± 15.7	<0.001
DBP (mmHg)	76.9 ± 10.1	76.59 ± 10.3	0.271
HR (lpm)	74.7 ± 11.1	73.0 ± 10.8	<0.001
<i>Biochemical parameters</i>			
Glycemia (mg/dL)	137.6 ± 43.0	93.4 ± 13.2	<0.001
Total cholesterol (mg/dL)	177.2 ± 39.6	199.4 ± 38.4	<0.001
HDL cholesterol (mg/dL)	49.0 ± 14.1	56.5 ± 15.3	<0.001
LDL cholesterol (mg/dL)	100.9 ± 36.9	121.2 ± 34.1	<0.001
Triglycerides (mg/dL)	147.9 ± 87.8	118.8 ± 76.2	<0.001
Creatinine (mg/dL)	0.93 ± 0.5	0.85 ± 0.5	<0.001
UACR (mg/g)	1.2 ± 0.5	1.1 ± 0.3	<0.001
Uric acid	5.5 ± 1.5	5.2 ± 1.5	<0.001

ABI: ankle brachial index; BMI: body mass index; HR: heart rate; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; LVH: left ventricular hypertrophy; PP: pulse pressure; SBP: systolic blood pressure; T2DM: type 2 diabetes mellitus; HMOD: hypertension-mediated organ damage; UACR: urinary albumin-to-creatinine ratio.

^a PP: >60 mmHg in subjects > 65 years.

^b eGFR 30–60 mL/min/1.73 m².

Table 2 Prevalence of HMOD in patients with T2DM according to sex.

	Total	Men (55.7%)	Women (44.3%)	P
Any	49.3	48.8	49.9	0.688
PP ^a , mmHg	29.6	28.7	30.8	0.35
Albuminuria, %	16.2	20.6	10.8	<0.001
Moderate renal insufficiency ^b , %	13.6	11.7	16.1	0.01
LVH, %	7.3	7.4	7.1	0.77
ABI < 0.9, %	2.8	2.2	3.6	0.10

ABI: ankle brachial index; eGFR: estimated glomerular filtration rate; LVH: left ventricular hypertrophy; PP: pulse pressure; T2DM: type 2 diabetes mellitus; HMOD: hypertension-mediated organ damage.

^a PP: >60 mmHg in subjects > 65 years.

^b eGFR 30–60 mL/min/1.73 m².

with HMOD (≥10 years: 47.3% vs 34.7%, ≥15 years: 21.8% vs 14.7%; $P < 0.001$).

With regard to the biochemical parameters in patients with T2DM, mean glycemia was 137.6 ± 43.0 mg/dL,

mean LDL cholesterol 100.9 ± 36.9 mg/dL, mean creatinine 0.9 ± 0.5 mg/dL and mean UACR 1.2 ± 0.5 mg/g (Table 1). Compared to patients without T2DM, patients with T2DM had more CV risk factors and HMOD (Table 1). The

Table 3 Risk of cardiovascular risk factors and HMOD in patients with T2DM (vs no T2DM).

	OR	95% CI
Cardiovascular risk factors		
Hypertension, %	4.36	3.86–4.94
Dyslipidemia, %	3.64	3.22–4.11
Obesity, %	2.31	2.07–2.58
Smoking, %	0.67	0.57–0.78
HMOD		
Any	2.42	2.22–2.63
PP ^a , mmHg	2.69	2.37–3.06
Albuminuria, %	3.34	2.81–3.95
Moderate renal insufficiency ^b , %	2.62	2.19–3.13
LVH, %	2.45	1.94–3.10
ABI < 0.9, %	2.08	1.45–2.98

ABI: ankle brachial index; CI: confidence interval; eGFR: estimated glomerular filtration rate; LVH: left ventricular hypertrophy; PP: pulse pressure; OR: Odds Ratio; T2DM: type 2 diabetes mellitus; HMOD: hypertension-mediated organ damage.

^a PP: >60 mmHg in subjects > 65 years.

^b eGFR 30–60 ml/min/1.73 m².

presence of T2DM significantly increased the risk of having CV risk factors (hypertension, dyslipidemia and obesity) and HMOD (any HMOD, including high pulse pressure, albuminuria, moderate renal disease, left ventricular hypertrophy and ankle brachial index < 0.9) (Table 3). Except in very elderly patients, the prevalence of HMOD increased with age, in both patients with and without T2DM (supplementary Fig. 1).

Among patients with T2DM, with regard to CV risk factors, patients with HMOD (vs no HMOD) had more dyslipidemia (78.2% vs 70.5%; $P=0.001$), hypertension (75.4% vs 66.4%; $P=0.001$), and sedentarism (38.6% vs 32.6%; $P=0.012$). The risk was particularly high for hypertension (OR 2.78; 95% CI 2.18–3.54). Regarding CV disease, the presence of any CV disease, ischemic heart disease, peripheral artery disease, atrial fibrillation, heart failure, and stroke was more frequent in those patients with HMOD compared to those

without HMOD, particularly peripheral artery disease (OR 4.77; 95% CI 3.12–7.31) and heart failure (OR 3.50; 95% CI 2.21–5.55) (Table 4).

The number of antidiabetic drugs taken by patients with T2DM according to the presence of HMOD is presented in Fig. 1. Those patients with HMOD received more drugs than those without HMOD (bitherapy: 32.8% vs 30.4%; 3 drugs 14.8% vs 12.4%; $P<0.001$). In the overall population with T2DM, the most common glucose-lowering agents prescribed were metformin (35%), dipeptidyl peptidase IV inhibitors (15%) and insulin (9%). Only 3% of patients were taking SGLT2 inhibitors and 2% GLP-1 RA. The majority of types of glucose-lowering agents were more frequently taken by those patients with HMOD, compared to the total T2DM population (Fig. 2).

Discussion

Our study showed that among patients daily attended in primary care setting in Spain, around one in five patients had T2DM and nearly half of these patients had also HMOD. In patients with T2DM, the presence of HMOD was associated with a higher risk of CV risk factors and CV disease. Despite this high CV risk, the use of glucose-lowering agents with proven CV benefit was markedly low.

Different studies, such as ENRICA, DARIOS, ESCARVAL, or FRESCO, among others, have analyzed CV risk factors or CV disease in Spain. Unfortunately, these studies are outdated, not reflecting the current epidemiology of T2DM, have focused on particular populations or some risk factors in isolation, or have analyzed only specific regions of Spain.^{17–21} By contrast, IBERICAN is currently analyzing the distribution of CV risk factors and the incidence of CV disease in adult population attended in primary care throughout Spain. Therefore, IBERICAN is a large nationwide study, in which more than 500 investigators have included more than 8000 patients, making this study representative of the Spanish population attended in primary care setting.²²

In our study, 20% of patients had T2DM. In these patients, around one third had hypertension, and 30% dyslipidemia and obesity. As expected, the presence of CV risk factors

Table 4 Prevalence and risk of cardiovascular risk factors and HMOD in patients with T2DM according to the presence of HMOD.

	HMOD	NO HMOD	OR	95% CI	P
Cardiovascular risk factors					
Dyslipidemia, %	78.2	70.5	1.5	1.20–1.88	0.001
Hypertension, %	75.4	66.4	2.78	2.18–3.54	0.001
Obesity, %	52.5	49.8	1.11	0.91–1.35	0.289
Sedentarism, %	38.6	32.6	1.3	1.06–1.60	0.012
Smoking, %	11.2	15.2	0.7	0.53–0.94	0.018
Cardiovascular disease					
Any cardiovascular disease, %	39.6	16.1	3.43	2.71–4.34	0.001
Ischemic heart disease, %	17.2	7.8	2.43	1.78–3.33	0.001
Peripheral artery disease, %	14.5	3.4	4.77	3.12–7.31	0.001
Atrial fibrillation, %	13.9	5.4	2.83	1.96–4.07	0.001
Heart failure, %	10.0	3.1	3.50	2.21–5.55	0.001
Stroke, %	9.1	3.1	3.16	1.98–5.04	0.001

CI: confidence interval; OR: odds ratio; T2DM: type 2 diabetes mellitus; HMOD: hypertension-mediated organ damage.

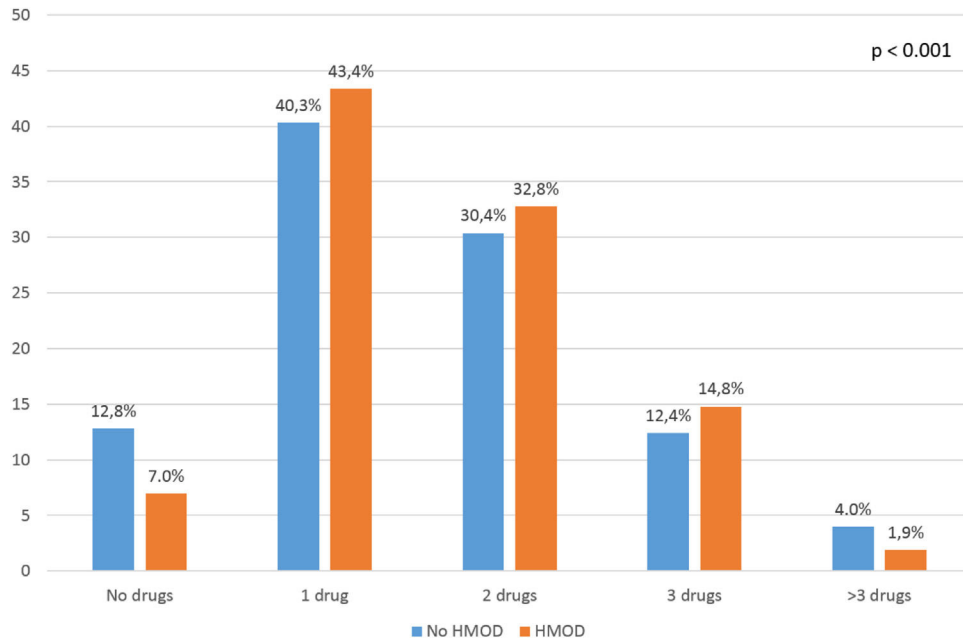


Figure 1 Number of antidiabetic drugs taken by patients with T2DM according to the presence of HMOD. T2DM: type 2 diabetes mellitus; HMOD: hypertension-mediated organ damage.

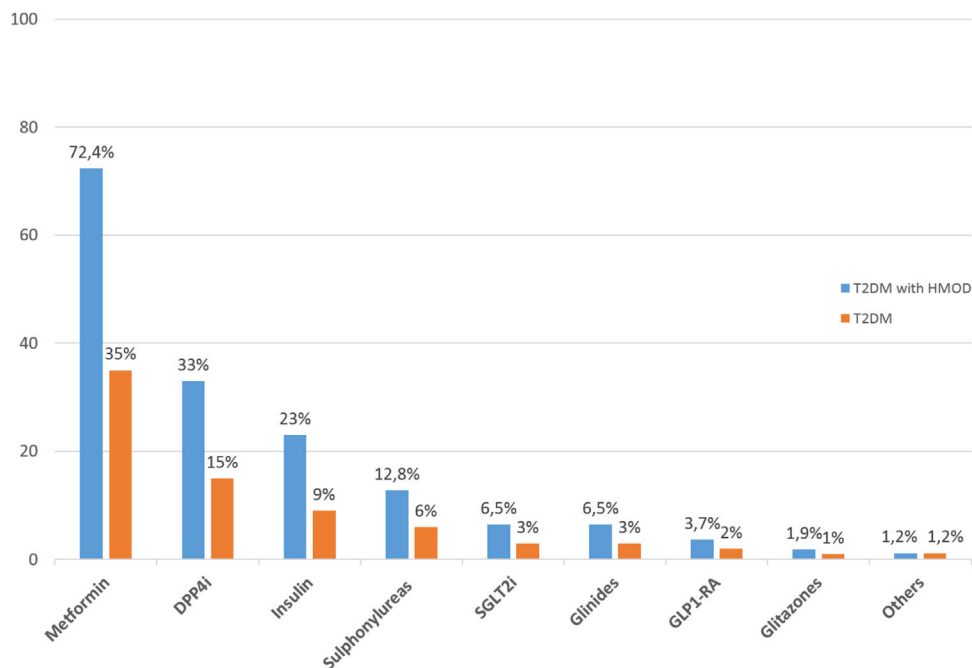


Figure 2 Glucose-lowering agents in patients with T2DM and HMOD (vs total T2DM population). DPP4i: dipeptidyl peptidase IV inhibitors; GLP1-RA: glucagon-like peptide-1 receptor agonists; SGLT2i: sodium-glucose cotransporter-2 inhibitors; T2DM: type 2 diabetes mellitus; HMOD: hypertension-mediated organ damage.

and HMOD was more common in this population, compared to patients without T2DM. This is in line with previous studies that have shown that the management of patients with T2DM is challenging, as these patients have many comorbidities, particularly CV risk factors and HMOD.^{23,24}

The presence of T2DM significantly increased the risk of having CV risk factors, particularly hypertension (OR 4.4) and dyslipidemia (OR 3.6). Of note,

these diabetes-associated conditions share bidirectional pathogenic relationships.²⁵ Thus, the incidence of hypertension increases markedly in patients with T2DM through different mechanisms, including the hyperactivation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, oxidative stress, inflammation, endothelial dysfunction or abnormal sodium processing in the kidneys.²⁶ Hypertension in patients with T2DM markedly increases the

risk of CV events and appropriate control with combined therapy, on the top of renin angiotensin system inhibition is mandatory.^{26,27} On the other hand, patients with T2DM exhibit high plasma triglycerides and small dense LDL cholesterol levels, as well as a low HDL cholesterol concentration, leading to a more proatherogenic lipid profile.²⁵ Therefore, attaining LDL cholesterol recommended targets through intensive lipid lowering therapy seems essential to reduce CV burden in diabetic population.⁴

T2DM also increased the risk of having HMOD. In fact, the prevalence of HMOD raised from 23.5% in patients without T2DM (28.6% in the general population) to 49.3% among patients with T2DM (OR 2.42). The most common HMOD found in T2DM population were high pulse pressure (29.6%), followed by albuminuria (16.2%) and moderate renal dysfunction (13.6%). High pulse pressure, defined as the difference between systolic and diastolic blood pressure, is the clinical manifestation of arterial stiffness and is more frequent in patients with T2DM. In fact, high pulse pressure has been associated with a higher risk of mortality in patients with T2DM.^{28,29} Albuminuria and renal impairment are two common early complications in the evolution of T2DM. According to the last European guidelines, the concomitance of both conditions in patients with T2DM are considered as very high CV risk, regardless of SCORE2-Diabetes.^{4,30} As guidelines recommend, patients with T2DM should be routinely screened for kidney disease by assessing eGFR and UACR.^{4,31} Although less than 10% of patients with T2DM exhibited left ventricular hypertrophy and low ankle brachial index, both conditions markedly increase the risk of MACE, and should be routinely ruled out in all patients with T2DM, particularly in those patients with other CV risk factors, such as hypertension.³²⁻³⁴ A recent study has shown in a Mediterranean region of Spain, that the majority of patients with T2DM have other CV risk factors, and that half of them have a very high CV risk and 40% a high CV risk (less than 10% have moderate CV risk).³⁵ Therefore, as guidelines recommend, the presence of severe HMOD should be screened in every patient with T2DM.⁴ Moreover, our study showed that among patients with T2DM, those patients with HMOD exhibited more CV risk factors (except smoking), and any CV disease, regardless of the vascular bed (i.e., ischemic heart disease, stroke or peripheral artery disease). As a result, it is obligatory the clinical assessment of atherosclerotic vascular disease in patients with T2DM on a regular basis, particularly when HMOD are present. Of note, stricter goals and intensification of treatment are required in these patients.⁴ On the other hand, although some studies have suggested a different CV risk in patients with T2DM according to sex, mainly due to hormonal factors or different artery diameter, the fact is that more than a half of patients with T2DM have a very high CV risk, regardless of sex.^{35,36} Moreover, our study showed that although albuminuria was more common in men and moderate renal impairment in women, the prevalence of any HMOD was similar regardless of gender and a similar approach should be performed in men and women.

Guidelines recommend an optimal and holistic management of patients with T2DM with the control of all comorbidities, including CV risk factors with specific goals, and CV disease.⁴⁻⁶ With regard to the antihyperglycemic treatment, in the light of evidence, the therapeutic management has been moved from a glucocentric approach, to a

CV and renal protection approach in addition to metabolic control.^{4,37} Thus, different meta-analyses have shown that both SGLT2 inhibitors and GLP-1 receptor agonists provide CV benefits in patients with T2DM, particularly in those with a high or very high CV risk, regardless of glycemic control or metformin use.³⁸⁻⁴⁰ In this context, international guidelines recommend tight glycemic control (HbA1c < 7%) to reduce microvascular complications and also the use of glucose-lowering agents with proven CV benefits (i.e., SGLT2 inhibitors and GLP-1 receptor agonists), mainly in patients at high/very high CV risk, such as those with HMOD.^{4,37} Unfortunately, our study showed that despite control of DM was numerically higher in patients with HMOD (74.4% vs 66.2%; $P=0.81$), the use of SGLT2 inhibitors and GLP-1 receptor agonists was marginal in patients with T2DM and HMOD (6.5% and 3.7%, respectively). A higher use of these drugs with proven CV benefit should be promoted.

This study has some limitations. First, the lack of randomization of investigators, with the participation of the most motivated physicians in CV care, could have overestimated the control of CV risk factors. Moreover, although the definition of HMOD was carried out in accordance with the 2013 European Society of Hypertension/European Society of Cardiology guidelines, as it was an observational study of clinical practice, there may have been an underestimation in the detection of some of them, particularly albuminuria and ankle-brachial index. However, the high number of patients included could reduce this potential limitation. In addition, this was an observational study, without a control group and this may difficult to ascertain the impact of changes in the management of patients on the incidence of CV complications. Finally, patients were selected from primary care setting in Spain and this could limit the generalizability of the results to the overall Spanish population.

In conclusion, the presence of HMOD is common in patients with T2DM and is associated with a higher risk of having CV risk factors and CV disease. Despite these patients have a very high CV risk, the use of glucose-lowering agents with proven CV benefits was markedly low. Therefore, the search for HMOD in patients with T2DM should be strengthened in clinical practice. It is necessary to increase the awareness and knowledge of primary care physicians about the importance of the early identification of HMOD in this high risk population and the implementation of the more appropriate therapeutic approach in this population.

Authors' contributions

Conceptualization, methodology, writing-review and editing: AARS, JDE, MAPD, VPC, ABG, RMMP, JPG, SMVZ, VMS, ASF, LGM, VMAV, SCS; writing-original draft preparation: AARS, JDE, MAPD, VMAV, SCS and VPC; supervision: SMVZ, ABG, JPG, MAPD, ASF, RMMP, SCS and VPC; project administration: SCS; funding acquisition: VPC, SCS, MAPD, JPG, RMMP, VMS, SMVZ, ABG and LGM. All authors have read and agreed to the published version of the manuscript.

Funding

Investigators, members of the Scientific Committee/Steering Committee, the General Coordinator, and

the Principal Investigator have not received any honoraria for participating in the IBERICAN study. The IBERICAN study is financed by the SEMERGEN Foundation with its own funds. It has received grants to defray occasional expenses for statistical analysis and dissemination of results (Astra Zeneca, Menarini).

Conflict of interest

All the authors declare that they have no type of conflict of interest that may affect the contents of this article.

Acknowledgments

To the redGDPS Foundation for the financial support for this manuscript. To the SEMERGEN Foundation for financing the global IBERICAN study. To the researchers who have actively participated in the recruitment of patients. We also want to thank all patients for their participation in the study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.semerg.2024.102220](https://doi.org/10.1016/j.semerg.2024.102220).

References

1. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es study. *Diabetologia*. 2012;55:88–93.
2. International Diabetes Federation. IDF diabetes atlas—10th edition. Brussels: International Diabetes Federation; 2021. Available from: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf.
3. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215–22.
4. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023;44:4043–140.
5. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 10. Cardiovascular disease and risk management: standards of care in diabetes-2023. *Diabetes Care*. 2023;46 Suppl. 1:S158–90.
6. Martín-Rioboó E, Brotons-Cuixart C, Ruiz García A, Villafañe Sanz F, Frías Vargas M, Moyá Amengual A, et al. Lights and shadows of the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Rev Esp Salud Publica*. 2023;97:e202308064.
7. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJL, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380:1662–73.
8. Brownrigg JR, Hughes CO, Burleigh D, Karthikesalingam A, Paterson BO, Holt PJ, et al. Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study. *Lancet Diabetes Endocrinol*. 2016;4:588–97.
9. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2022; 102(Suppl. 5S):S1–S127.
10. Cinza Sanjurjo S, Llisterri Caro JL, Barquilla García A, Polo García J, Velilla Zancada S, Rodríguez Roca GC, et al. Description of the sample, design and methods of the study for the identification of the Spanish population at cardiovascular and renal risk (IBERICAN). *Semerger*. 2020;46:4–15.
11. Cinza-Sanjurjo S, Micó-Pérez RM, Velilla-Zancada S, Prieto-Díaz MA, Rodríguez-Roca GC, Barquilla García A, et al. Factors associated with cardiovascular risk and cardiovascular and renal disease in the IBERICAN study: final results. *Semerger*. 2020;46:368–78.
12. Llisterri JL, Micó-Pérez RM, Velilla-Zancada S, Rodríguez-Roca GC, Prieto-Díaz MÁ, Martín-Sánchez V, et al. Prevalence of chronic kidney disease and associated factors in the Spanish population attended in primary care: results of the IBERICAN study. *Med Clin (Barc)*. 2021;156:157–65.
13. Peral Martínez IM, Martínez Pastor A, Gomariz García JJ, Barquilla García A, Martín Sánchez V, Micó Pérez R, et al. Regional differences in the degree of glycaemic diabetes control in Spain and associated factors. IBERICAN study. *Endocrinol Diabetes Nutr (Engl Ed)*. 2023;70:448–58.
14. Moyá-Amengual A, Ruiz-García A, Pallarés-Carratalá V, Serrano-Cumplido A, Prieto-Díaz MÁ, Segura-Fragoso A, et al. Elevated pulse pressure and cardiovascular risk associated in Spanish population attended in primary care: IBERICAN study. *Front Cardiovasc Med*. 2023;10:1090458.
15. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–357.
16. Cosentino F, Grant P, Aboyans V, Bailey C, Ceriello A, Delgado V, et al. 2019 Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41:255–323.
17. Gil-Guillen V, Orozco-Beltran D, Redon J, Pita-Fernandez S, Navarro-Pérez J, Pallares V, et al. Rationale and methods of the cardiometabolic Valencian study (Escarval-Risk) for validation of risk scales in Mediterranean patients with hypertension, diabetes or dyslipidemia. *BMC Public Health*. 2010;10:717.
18. Grau M, Elosua R, Cabrera de León A, Guembe MJ, Baena-Díez JM, Vega Alonso T, et al. Cardiovascular risk factors in Spain in the first decade of the 21st Century, a pooled analysis with individual data from 11 population-based studies: the DARIOS study. *Rev Esp Cardiol*. 2011;64:295–304.
19. Graciani A, León-Muñoz LM, Guallar-Castillón P, Rodríguez Artalejo F, Banegas JR. Cardiovascular health in a southern Mediterranean European country: a nationwide population based study. *Circ Cardiovasc Qual Outcomes*. 2013;6:90–8.
20. Marrugat J, Subirana I, Ramos R, Vila J, Marín-Ibañez A, Guembe MJ, et al. Derivation and validation of a set of 10-year cardiovascular risk predictive functions in Spain: the FRESCO study. *Prev Med*. 2014;61:66–74.
21. Cosín-Sales J, Campuzano Ruiz R, Díaz Díaz JL, Escobar Cervantes C, Fernández Olmo MR, Gómez-Doblas JJ, et al. Impact of physician's perception about LDL cholesterol control in clinical practice when treating patients in Spain. *Atherosclerosis*. 2023;375:38–44.
22. Banegas JR. El Proyecto IBERICAN. The IBERICAN Project. Progressing in the knowledge of cardiovascular risk in primary care in Spain. *Semerger*. 2020;46:1–3.
23. Eder S, Leierer J, Kerschbaum J, Rosivall L, Wiecek A, de Zeeuw D, et al. A prospective cohort study in patients with type 2 diabetes mellitus for validation of biomarkers (PROVALID) – study

- design and baseline characteristics. *Kidney Blood Press Res.* 2018;43:181–90.
24. Zatońska K, Basiak-Rasała A, Różańska D, Karczewski M, Wołyniec M, Szuba A, et al. Changes in diabetes prevalence and corresponding risk factors – findings from 3- and 6-year follow-up of PURE Poland cohort study. *BMC Public Health.* 2020;20:843.
 25. Teck J. Diabetes-associated comorbidities. *Prim Care.* 2022;49:275–86.
 26. Tsimihodimos V, Gonzalez-Villalpando C, Meigs JB, Ferrannini E. Hypertension and diabetes mellitus: coprediction and time trajectories. *Hypertension.* 2018;71:422–8.
 27. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens.* 2023, <http://dx.doi.org/10.1097/HJH.0000000000003480>. Epub ahead of print.
 28. Alemi H, Khaloo P, Mansournia MA, Rabizadeh S, Salehi SS, Mir-miranpour H, et al. Pulse pressure and diabetes treatments: Blood pressure and pulse pressure difference among glucose lowering modality groups in type 2 diabetes. *Medicine (Baltimore).* 2018;97:e9791.
 29. Cockcroft JR, Wilkinson IB, Evans M, McEwan P, Peters JR, Davies S, et al. Pulse pressure predicts cardiovascular risk in patients with type 2 diabetes mellitus. *Am J Hypertens.* 2005;18:1463–7.
 30. SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk Collaboration. SCORE2-Diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe. *Eur Heart J.* 2023;44:2544–56.
 31. George C, Echouffo-Tcheugui JB, Jaar BG, Okpechi IG, Kengne AP. The need for screening, early diagnosis, and prediction of chronic kidney disease in people with diabetes in low- and middle-income countries-a review of the current literature. *BMC Med.* 2022;20:247.
 32. Lv J, Liu Y, Yan Y, Sun D, Fan L, Guo Y, et al. Relationship between left ventricular hypertrophy and diabetes is likely bidirectional: a temporality analysis. *J Am Heart Assoc.* 2023;12:e028219.
 33. Moroney M, Verma R, Hibino M, Mazer CD, Connelly KA, Yan AT, et al. Impact of diabetes duration on left ventricular mass regression with empagliflozin. *ESC Heart Fail.* 2023;10:2134–40.
 34. Nie F, He J, Cao H, Hu X. Predictive value of abnormal ankle-brachial index in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract.* 2021;174:108723.
 35. Cebrián-Cuenca AM, Mata-Cases M, Franch-Nadal J, Mauricio D, Orozco-Beltrán D, Consuegra-Sánchez L. Half of patients with type 2 diabetes mellitus are at very high CV risk according to the ESC/EASD: data from a large Mediterranean population. *Eur J Prev Cardiol.* 2022;28:e32–4.
 36. Spence JD, Pilote L. Importance of sex and gender in atherosclerosis and CV disease. *Atherosclerosis.* 2015;241:208–10.
 37. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. *Diabetes Care.* 2023;46 Suppl. 1:S140–57.
 38. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZ, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with CV and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol.* 2021;6:148–58.
 39. Sattar N, Lee MM, Kristensen SL, Branch KR, Del Prato S, Khurmi NS, et al. CV, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021;9:653–62.
 40. Escobar C, Barrios V, Cosin J, Gámez Martínez JM, Huelmos Rodrigo AI, Ortiz Cortés C, et al. SGLT2 inhibitors and GLP1 agonists administered without metformin compared to other glucose-lowering drugs in patients with type 2 diabetes mellitus to prevent cardiovascular events: a systematic review. *Diabetes Med.* 2021;38:e14502.