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Potential Impact of Metabolic Syndrome Control on Cardiovascular Risk in Elderly Patients with Diabetes: A Cross-Sectional Study

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Abstract: Metabolic syndrome (MS), a complex pathology with features like abnormal body fat distribution, insulin resistance, and dyslipidaemia, contributes to higher cardiovascular (CV) risk. A cross-sectional study including 87 individuals assessed CV risk score in elderly patients with type 2 diabetes and MS in Algarve, Portugal. The 10-year CV risk score was estimated using the ADVANCE risk score calculator. The reductions in CV risk score were estimated by adjusting the data inputted on the online tool to achieve systolic blood pressure (SBP) <130 or <120 mmHg, and LDL cholesterol <70 mg/dL Beyond waist circumference, the mean number of clinical features of MS was 3.14 ± 0.84, without significant sex differences. The mean CV risk score was 22.5% (CI: 20.3–24.7). Sex-specific analysis showed higher risk score in males (24.2%, CI: 21.3–27.0) vs. females (19.7%, CI: 16.2–23.3; $p = 0.028$). Hypothetical risk score reductions show that lowering SBP to <130 mmHg could significantly lower the risk score by an average of 9.2% (CI: 7.7–10.7), whereas 34.5% of the participants would be out of the diagnostic criteria for MS. When comparing each potential intervention with current risk score, all interventions significantly reduce the 10-year CV risk score. The study highlights the potential of blood pressure control in reducing CV risk score and the importance of multifaceted risk score reduction strategies.

Keywords: cardiovascular risk; ADVANCE risk score calculator; metabolic syndrome; type 2 diabetes mellitus; elderly

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1. Introduction

Metabolic syndrome (MS) is defined by the International Diabetes Federation (IDF) as a complex pathology characterized by several general features, such as abnormal body fat distribution, insulin resistance, atherogenic dyslipidaemia, proinflammatory state, and prothrombotic state [1]. Persistent insulin resistance often leads to the development of type 2 diabetes mellitus (T2DM), a metabolic disease characterized by chronic hyperglycaemia, due to an impaired capacity of glucose utilization as an energy source, along with impaired gluconeogenesis and glycogenolysis [2,3]. This can lead to both micro- and macrovascular complications in the long term. Microvascular complications include retinopathy (leading to total vision loss), neuropathy (leading to impaired wound healing and amputations in the lower limbs), nephropathy (possible renal failure), and sexual dysfunction (namely erectile dysfunction in males) [4]. Macrovascular complications include peripheral and coronary artery disease, arrhythmias, diabetic cardiomyopathy, and cerebrovascular disease. As previously reported [5,6], the predisposition to T2DM and the prevalence, progression, and pathophysiology of micro- and macrovascular diseases are different between males and females. Also, several putative sex-specific risk factors should be considered regarding these

pathologies. Cardiovascular (CV) diseases are the leading cause of death in patients with T2DM and there is evidence that there are also sex-specific differences regarding CV risk factors [7–9]. In this scenario, it is important to consider these differences and compare the CV risk score across sexes and how males and females react to similar therapeutic strategies.

Ageing of the population is a global phenomenon and Portugal is one of the European countries experiencing a considerable increase in the proportion of elderly people (i.e., individuals aged 65 and over). The ageing index, which measures the ratio of the elderly to the young population, has seen an exponential rise over the years, reaching 185.3% in 2022 [10]. This demographic shift has led to an increase in age-related diseases, including metabolic disorders such as T2DM [11], which is a relevant pathology when considering the occurrence of MS. In this context and considering the life-threatening risk associated with T2DM or, in a broader sense, with MS, it becomes relevant to invest in the prevention of possible complications arising from these health conditions.

Currently, several tools are available to assess CV risk score like the Framingham risk score, the Systematic Coronary Risk Evaluation (SCORE), or QRISK®. The Framingham Risk Score [12] was the first CV risk assessment tool developed with primary prevention in mind, while the SCORE is an algorithm based on 12 European cohort studies and a tool recommended by the European Society of Cardiology [13]. QRISK®, recommended by the National Institute for Health and Care Excellence in the United Kingdom (UK) in its third version [14], now includes, in addition to socio-demographic variables (age, sex) and typical clinical variables (smoking, systolic blood pressure (SBP), or cholesterol), the administration of medications such as glucocorticoids and antipsychotics. These tools consider various factors that can contribute to increased CV risk, including the presence of diabetes, blood pressure (BP) levels, low density lipoprotein cholesterol (LDL cholesterol) levels, age, sex, smoking status, prescribed medications, and the presence of complications. These tools show several advantages, such as a personalized risk assessment and guidance to clinical decision related to the need of lifestyle modifications or the prescription of medication. However, they also have limitations, namely variable accuracy because they are based on average population data. Also, these tools may lead to over-reliance and do not consider all risk factors, such as family history or genetic markers [15–17].

The ADVANCE calculator evaluates the CV risk score in T2DM patients diagnosed with MS [18]. This tool is a specific calculator to assess the 10-year risk of suffering a CV event, for patients with T2DM. Using this calculator, we aimed to estimate how reducing systolic blood pressure (SBP) and/or LDL cholesterol to the recommended levels could decrease the CV risk score and potentially revert the MS diagnosis in elderly patients.

2. Materials and Methods

2.1. Characteristics of the Study

A descriptive cross-sectional study was conducted to assess CV risk score in elderly patients with T2DM and MS. The study analysed a non-random convenience sample of 87 patients, consecutively enrolled, who agreed to participate, residing in the Algarve region (Southern Portugal), aged between 65 and 86 years old, diagnosed with MS according to the IDF criteria [1]. Patients were recruited at the diabetes clinic of the Association for the Study of Diabetes Mellitus and Support for Diabetics in the Algarve (AEDMADA, according to the Portuguese designation), by direct invitation at the time of their consultations for diabetes monitoring. All patients signed an informed consent for their data to be used in this study.

2.2. Data Collection

Clinical data were extracted from the patients' clinical files. These data included sociodemographic characteristics (age, sex, education level), lifestyle factors (exercise frequency, and tobacco and alcohol consumption), clinical profiles (hypertension, dyslipidaemia, duration of diabetes), complications from diabetes (retinopathy, nephropathy, neuropathy), cardiometabolic parameters (weight, body mass index (BMI), waist circum-

ference (WC), SBP, and diastolic blood pressure (DBP)), biochemical parameters (fasting glucose, HbA1c, albumin, creatinine, and cholesterol levels), and the total number of medications used by each patient. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), moderate obesity (30–34.9 kg/m^2), severe obesity (35–39.9 kg/m^2), and very severe obesity (≥40 kg/m^2) [19].

2.3. Cardiovascular Risk Score Calculations and Estimations

The 10-year CV risk score was estimated using the ADVANCE risk score calculator [18], an online tool specifically designed for patients with T2DM. This tool also provides estimates on risk score reduction achievable through specific adjustments in SBP and LDL cholesterol levels. Missing data points for the time of T2DM diagnosis and albumin/creatinine ratio were filled with mean population values, obtained from the ADVANCE calculator used, whenever data were not available.

The reductions in CV risk score were estimated by adjusting the data inputted into the online tool to achieve SBP either below 130 mmHg or 120 mmHg, and lowering LDL cholesterol below 70 mg/dL. These reductions were based on the recommendations from the American Diabetes Association (ADA) [3]. The impact of combined adjustments of SBP (<120 mmHg) and LDL cholesterol (<70 mg/dL) was also analysed. Although ADA proposes that BP target values should be individualized, target values of SBP < 130 mmHg should be considered whenever possible [20]. Nevertheless, reducing SBP below 120 mmHg was also considered as it may benefit CV risk score [21,22].

The possibility of starting antiplatelet therapy was not considered in the potential interventions, as the information for this in-depth analysis of the clinical history was not available.

2.4. Statistical Analysis

Data were presented using absolute and relative frequencies, mean (M), median (Md), standard deviation (SD), and interquartile range (IQR). We used the Kolmogorov–Smirnov test to assess to check for compliance of the data with the normal distribution. Group comparisons were made using Pearson chi-square, Mann–Whitney, and Student's *t*-test, according to the results of the normality test. When the results of the chi-square test were considered non-valid due to low expected frequency count, Fisher's or Fisher–Freeman–Halton's exact tests were computed. Correlations were computed using Spearman's correlation coefficient and paired sample comparisons were made using the Wilcoxon's rank test.

Statistical significance for all procedures was set at 0.05. All analyses were carried out using IBM SPSS Statistics 29.0.

3. Results

3.1. Sociodemographic Characteristics of the Population and Metabolic Syndrome Diagnosis

To assess the CV risk score in elderly patients with T2DM, 87 patients (62% males; n = 54) aged 65 years or more were included in this study. The mean age was 75 ± 5 years, without significant differences between the sexes (p = 0.133) (Table 1). Regarding academic level, most participants had completed elementary school (67.8%), followed by middle school (14.9%), and high school (6.9%). Only 4.6% of the participants completed a higher degree course. The mean time since the T2DM diagnosis was 13 ± 8 years. On average, patients were taking 6 ± 3 medicines. Table 1 presents the sociodemographic, clinical and lifestyle characteristics of the participants.

The anthropometric variables were significantly different between the sexes (Table 1). Males had a higher body weight (83.8 ± 10 kg) compared to females (75.4 ± 12.9 kg; p < 0.001), and a larger WC (100 ± 5 cm for males vs. 92 ± 10 cm for females; p < 0.001). Overall mean BMI was 29.8 ± 3.9 kg/m^2. Even if the differences in average BMI were not statistically significant between sexes (p = 0.07), the BMI classification indicates a higher prevalence of males with a BMI above the normal range (p = 0.008).

Table 1. Sociodemographic, clinical, and lifestyle characteristics for all participants and by sex.

Characteristics		Total Sample (n = 87)	Males (n = 54)	Females (n = 33)	*p*-Value
Age (years) M ± SD		71.6 ± 5.2	70.8 ± 4.8	72.8 ± 5.6	0.113 [a]
Academic level:	Cannot read or write; n (%)	5 (5.7)	3 (5.6)	2 (6.1)	0.697 [b]
	Primary school (4 years); n (%)	59 (67.8)	33 (61.1)	26 (78.8)	
	Middle school (5–9 years); n (%)	13 (14.9)	10 (18.5)	3 (9.1)	
	High school (10–12 years); n (%)	6 (6.9)	5 (9.3)	1 (3.0)	
	College level degree; n (%)	4 (4.6)	3 (5.6)	1 (3.0)	
Years after T2DM diagnosis	M ± SD	12.9 ± 8.0	12.5 ± 8.2	13.5 ± 7.7	0.371 [a]
Number of medications	M ± SD	6.0 ± 2.9	5.7 ± 2.8	6.5 ± 3.0	0.240 [a]
Weight (kg)	M ± SD	80.6 ± 11.8	83.8 ± 10.0	75.4 ± 12.9	**0.001** [c]
Waist circumference (cm)	M ± SD	96.8 ± 8.3	99.7 ± 5.1	92.0 ± 10.2	**<0.001** [a]
BMI (kg/m^2)	M ± SD	29.8 ± 3.9	29.1 ± 2.7	31.0 ± 5.2	0.07 [c]
BMI (category):	Normal weight; n (%)	5 (5.7)	1 (1.9)	4 (12.1)	**0.008** [b]
	Overweight; n (%)	45 (51.7)	33 (61.1)	12 (36.4)	
	Moderate obesity; n (%)	28 (32.2)	18 (33.3)	10 (30.3)	
	Severe obesity; n (%)	7 (8.0)	2 (3.7)	5 (15.2)	
	Very severe obesity; n (%)	2 (2.3)	0	2 (6.1)	
Systolic BP (mmHg)	M ± SD	153.6 ± 22.4	153 ± 22.6	154.5 ± 22.7	0.776 [c]
Diastolic BP (mmHg)	M ± SD	80.4 ± 11.0	79.5 ± 10.3	81.8 ± 12.0	0.349 [c]
Total cholesterol (mg/dL)	M ± SD	184.3 ± 37.8	180.2 ± 36.8	191 ± 39.1	0.195 [a]
HDL cholesterol (mg/dL)	M ± SD	46.5 ± 12.0	45.4 ± 12.5	48.4 ± 11.2	0.261 [a]
LDL cholesterol (mg/dL)	M ± SD	106.9 ± 27.6	105.1 ± 26.6	109.9 ± 29.5	0.441 [a]
Triglycerides (mg/dL)	M ± SD	143.5 ± 57.2	146.1 ± 56.7	139.4 ± 58.6	0.47 [a]
HbA1c (%)	M ± SD	8.3 ± 1.1	8.1 ± 1.0	8.6 ± 1.2	0.072 [a]
Fasting glycaemia (mg/dL)	M ± SD	164.7 ± 45.4	165.6 ± 51.4	163.2 ± 33.9	0.726 [a]
Smokes tobacco	n (%)	2 (2.3)	2 (3.7)	0	**<0.001** [d]
Drinks alcohol	n (%)	59 (67.8)	47 (87.0)	12 (36.4)	**<0.001** [d]
Exercises regularly	n (%)	53 (60.9)	34 (63.0)	19 (57.6)	0.656 [b]
Hypertension	n (%)	79 (90.8)	50 (92.6)	29 (87.9)	0.471 [f]
Dyslipidaemia	n (%)	49 (56.3)	31 (57.4)	18 (54.5)	0.827 [b]
Retinopathy	n (%)	27 (31.0)	16 (29.6)	11 (33.3)	0.812 [b]
Neuropathy	n (%)	2 (2.3)	2 (3.7)	0	0.524 [f]
Nephropathy	n (%)	3 (3.4)	2 (3.7)	1 (3.0)	0.680 [d]

M—mean; SD—standard deviation; BMI—body mass index; BP—blood pressure. Sex differences computed with: [a]—Mann–Whitney's test; [b]—chi-square test; [c]—Student's *t*-test; [d]—Fisher–Freeman–Halton exact test; [f]—Fisher's exact test. Statistical significance ($p < 0.05$) is boldfaced.

Significant differences between sexes were also observed in tobacco and alcohol consumption (Table 1). Only males reported smoking (3.7%), and a higher percentage of males reported alcohol consumption (87.0%) compared to females (36.4%) ($p < 0.001$). Regular exercise was reported by 60.9% of the total sample, without significant sex differences ($p = 0.656$).

Clinical parameters such as SBP and DBP, cholesterol levels, triglycerides, HbA1c, and fasting glycaemia showed no significant differences between the sexes. The prevalence of clinical conditions such as hypertension, dyslipidaemia, retinopathy, neuropathy, and nephropathy also did not differ significantly according to sex.

To determine whether the patients gathered the required components of MS, specific clinical and biochemical characteristics were considered (Table 2). According to the IDF criteria, MS diagnosis includes central obesity (waist circumference ≥94 cm for males, and ≥80 cm for females) plus any two of the following four factors: elevated triglycerides, reduced high density lipoprotein cholesterol (HDL cholesterol), elevated BP, and elevated fasting glycemia [1]. In addition to the increased waist circumference (Table 1), the mean number of clinical features identified in the participants was 3.14 ± 0.84 (Table 2). There were no significant differences between sexes in the number of characteristics or in the prevalence of any of the MS characteristics.

Table 2. Prevalence of MS characteristics for all participants and by sex.

Metabolic Syndrome Characteristics	Total Sample (n = 87)	Males (n = 54)	Females (n = 33)	*p*-Value
BMI showing obesity; n (%)	37 (42.5)	20 (37.0)	17 (51.5)	0.264 [a]
Triglycerides ≥ 150 mg/dL; n (%)	35 (40.2)	23 (42.6)	12 (36.4)	0.655 [a]
HDL cholesterol < 40 mg/dL in males or <50 mg/dL in females; n (%)	38 (43.7)	19 (35.2)	19 (57.6)	**0.040** [a]
Blood pressure ≥ 130/85 mmHg	78 (89.7)	48 (88.9)	30 (90.9)	1 [a]
Fasting glucose ≥ 100 mg/dL	85 (97.7)	52 (96.3)	33 (100)	0.524 [b]
No. of clinical features for MS diagnosis in addition to increased waist circumference:				
M ± SD	3.1 ± 0.8	3.0 ± 0.7	3.4 ± 1.0	
Md (IQR)	3.0 (1.0)	3.0 (0.0)	3.0 (1.0)	0.109 [c]

M—mean; SD—standard deviation; Md—Median; IQR—interquartile range. Sex differences computed with: [a]—chi-square test; [b]—Fisher's exact test; [c]—Mann–Whitney's test. Statistical significance ($p < 0.05$) is boldfaced.

3.2. Calculation of the ADVANCE Risk Score

The ADVANCE risk score, a CV disease risk prediction tool specifically developed for patients with T2DM, takes into consideration diabetes-specific variables [23]. The estimated risk percentages for myocardial infarction, stroke, or vascular death over a 10-year period were calculated using the ADVANCE risk score online tool (Table 3). The mean risk score for all participants was 22.5% (CI: 20.3–24.7). Sex-specific analysis reveals a significantly higher current risk score in males (24.2%, CI: 21.3–27.0) than in females (19.7%, CI: 16.2–23.3) ($p = 0.028$).

Table 3. Risk score for myocardial infarction, stroke, or vascular death in the next 10 years, and potential interventions.

Risk for Myocardial Infarction, Stroke, or Vascular Death in the Next 10 Years (%)	ADVANCE Risk Score Mean (95% Confidence Interval)			Sex Differences *p*-Value
	Total Sample (n = 87)	Males (n = 54)	Females (n = 33)	
Current risk score	22.5 (20.3–24.7)	24.2 (21.3–27)	19.7 (16.2–23.3)	**0.028**
Risk score if SBP < 130 mm Hg *	13.4 (11.8–15.1)	14.6 (12.4–16.8)	11.7 (9.1–14.4)	0.061
Risk score if SBP < 120 mm Hg *,**	11.8 (10.3–13.3)	13.0 (11.1–14.9)	9.8 (7.6–11.9)	**0.024**
Risk score if LDL cholesterol < 70 mg/dL *	18.8 (16.6–20.9)	20.3 (17.6–23.1)	16.3 (12.9–19.8)	**0.026**
Risk score if SBP < 120 mmHg and LDLC < 7 0 mg/dL *	9.7 (8.4–11.0)	10.8 (9.1–12.6)	7.9 (6.1–9.7)	**0.013**

SBP—systolic blood pressure; LDLC—LDL cholesterol. Sex differences computed with Mann–Whitney's test. *—Paired comparison with current risk score is statistically significant ($p < 0.001$) for all participants, males, and females; **—Paired comparison with BP < 130 mm Hg is statistically significant ($p < 0.001$) for all participants, males, and females. Risk score comparisons between interventions computed with Wilcoxon's rank test. Statistical significance ($p < 0.05$) is boldfaced.

Potential risk score reductions indicate that reducing SBP levels below 130 mmHg could decrease the risk score by an average of 9.2% (CI: 7.7–10.7), resulting in a risk score of 13.4% (CI: 11.8–15.1) for the total sample. This potential risk score after the intervention is statistically significant ($p < 0.001$) when compared to current risk score (22.5%), albeit it does not show significant differences between the sexes ($p = 0.061$). In contrast, sex differences are observed in potential interventions that successfully lower SBP below 120 mmHg ($p = 0.024$), lower LDL cholesterol below 70 mg/dL ($p = 0.026$), or lower both SBP below 120 mmHg and LDL cholesterol below 70 mg/dL ($p = 0.013$) (Table 3). Thus, males seem to maintain a higher risk score than females, except when the intervention is more conservative (SBP < 130 mm Hg).

When comparing each potential intervention with the current risk score, all interventions significantly reduce the risk score for myocardial infarction, stroke, or vascular death over the next 10 years ($p < 0.001$). Nevertheless, mean risk score reduction is not significantly different between sexes when considering all potential interventions.

As expected, the most substantial risk score reduction is observed when combining both BP and LDL cholesterol interventions, which places overall risk score at 9.7% (CI: 8.4–11.0) for the total sample, at 10.8% (CI: 9.1–12.6) for males, and at 7.9% (CI: 6.1–9.7) for females. This intervention yields statistically significant decreases from the current baseline ($p < 0.001$, with an overall decrease of 12.7%, CI: 9.4–14.3), placing males at a higher risk than females ($p = 0.013$). Nevertheless, the decrease in the risk score is not statistically different between males and females ($p = 0.512$): 13.3% (CI: 9.2–15.2) for males and 11.8% (CI: 6.7–15.1) for females.

The calculated current risk score for myocardial infarction, stroke, or vascular death over the next 10 years shows a positive correlation with both age (r = 0.728, $p < 0.001$) and time since T2DM diagnosis (r = 0.681, $p < 0.001$), when sex is controlled for. This association was to be expected, as time elapsed since T2DM diagnosis and sex are variables used in the calculation of the ADVANCE score. The associations are maintained when controlling for sex, suggesting that older patients and those who have the disease longer have a higher risk for CV events. Also, when sex is controlled for, risk score reduction still shows important significant correlations: risk score reduction observed when SBP is less than 130 mmHg is positively correlated with age (r = 0.411, $p = 0.003$) and time since T2DM diagnosis (r = 0.425, $p = 0.002$); risk score reduction observed when SBP is less than 120 mmHg is also positively correlated with age (r = 0.510, $p < 0.001$) and time since the diagnosis (r = 0.503, $p < 0.001$); risk score reduction observed when LDL cholesterol is less than 70 mg/dL is positively correlated with time since the T2DM diagnosis (r = 0.319, $p = 0.024$), but not with age (r = 0.197, $p = 0.171$). Our results suggest that older patients can benefit more from SBP control, but not necessarily from reducing LDL cholesterol levels. Patients who have had T2DM for a longer duration benefit from interventions that favour lower SBP and LDL cholesterol. According to our data, an effective intervention that lowers SBP to less than 130 mmHg in our sample would result in 34.5% of participants (n = 30) no longer meeting the diagnostic criteria for MS.

4. Discussion

Given the increased susceptibility of elderly adults to CV diseases and their associated complications, it becomes crucial to identify and address modifiable risk factors to mitigate these health concerns. This study examines a cohort of Portuguese elderly individuals diagnosed with both T2DM and MS. The aim is to estimate their CV risk score and identify suitable clinical targets, i.e., key modifiable factors such hypertension and dyslipidaemia, to reduce this calculated risk score.

As individuals age, which is a non-modifiable factor, the prevalence of T2DM tends to increase. In Portugal, diabetes affects more than a quarter of the population aged between 60 and 79 years, with a higher prevalence observed in males [11]. According to data from the Portuguese population survey, approximately one-fifth of the general population and more than half of the elderly (those aged 65 and over) have only four years of schooling [24]. This low level of education is consistent with the studied sample, suggesting that this sample may be considered as representative of the elderly Portuguese population.

Our study demonstrates that aggressive BP control, particularly lowering SBP below 120 mmHg, can significantly reduce the estimated 10-year CV risk score for all participants. Lowering BP to less than 130 mmHg also appears to have a significant impact on reducing 10-year CV risk score. Considering the risks associated with more aggressive control (to less than 120 mmHg) in patients with T2DM, this study shows that the values recommended by the ADA [20] and the European Society of Cardiology [25] for BP control (less than 130 mmHg) may have beneficial effects in reducing CV risk. More importantly, the combined effect of SBP and LDL cholesterol interventions results in the most significant risk score reduction. Our findings emphasize the potential benefits of multifaceted intervention strategies that target both BP and lipid levels to mitigate CV risk in patients with T2DM and MS, as already reported in other studies [25].

The ADA recommends using the American College of Cardiology/American Heart Association ASCVD risk calculator for calculating the 10-year CV risk. However, it states that although this calculator includes T2DM as a risk factor, it does not consider the duration of the disease or the presence of long-term complications [20]. The tool used in this study (ADVANCE) includes both factors in the calculation of CV risk score [18], making it a potentially effective guide for therapeutic strategies and goal setting in individuals with T2DM. In the present study, a positive correlation was observed between the time since the T2DM diagnosis ($r = 0.681$, $p < 0.001$) and these events, after controlling for sex. This suggests that patients with a longer duration of the disease have a higher risk. The positive correlations between age, time since T2DM diagnosis, and estimated CV risk score underscore the progressive nature of CV risk accumulation over time in individuals with T2DM. Older individuals and those with a longer duration of T2DM exhibit a higher baseline risk for CV events, highlighting the importance of early and sustained intervention strategies to prevent or delay adverse outcomes in this vulnerable population [26]. De Jong et al. [27], in a prospective cohort study of UK Biobank participants, described that a 5-year increase in the duration of T2DM was associated with a CV risk increase of around 20%. Yao et al. [28] also reported that the duration of diabetes increases the 10-year CV risk. Thus, it seems crucial to consider the time of diagnosis when calculating the 10-year CV risk in these patients.

The current study revealed significant differences in body weight, BMI, and abdominal circumference between males and females. The results obtained in relation to overweight or obesity are in line with the data reported in the WHO European Regional Obesity Report 2022 [29], since the prevalence is higher in males than in females, but when we analyse the data relating to obesity, there is a reversal, since females have higher levels of obesity. These results are also consistent with studies carried out in Portugal [30,31]. These findings underscore the importance of considering sex-specific factors in the assessment and management of MS among elderly individuals with T2DM. CV risk management must consider several factors, including the patient's sex, since this will be a factor to consider in risk stratification, the therapy implemented, and the expected outcomes in terms of metabolic health [25]. Although the differences in BMI between the sexes were not statistically significant, the higher prevalence of males above the normal BMI range highlights the need for targeted interventions to address overweight and obesity and its associated CV risks in the elderly population with diabetes [32,33]. This finding could prompt a discussion on the role of BMI as a predictor of CV risk score and the importance of comprehensive risk assessment beyond traditional measures. In a study that included 23,961 Chinese patients with diabetes, Hu et al. found that every 5 years of early diagnosis increased the risk of heart disease by 14%. This association was even higher in patients with obesity [34], showing that BMI should be a factor to consider when calculating CV risk score.

The observed disparities in smoking and alcohol consumption between sexes underscore the influence of lifestyle behaviours on CV health outcomes. According to 2019 data from the National Statistics Institute, tobacco was considered the primary risk factor for premature death and lost years of healthy life in Portuguese males [35]. In this national report, although the number of smokers decreased, an increase in the consumption of alcoholic beverages, compared to previous years, was observed. Smoking and alcohol consumption significantly impact the components of MS and CV risk, leading to the definition of intervention strategies targeting modifiable risk factors in elderly patients with T2DM [25]. The fact that habits of tobacco and alcohol consumption were higher in males than females may be an important contributor to the increased risk score observed in males.

Despite the absence of significant differences between the sexes in clinical parameters such as BP, cholesterol levels, and glycaemic control, it is essential to consider the cumulative impact of these factors on CV risk in elderly individuals with diabetes [25]. The finding of no significant sex differences in the prevalence of MS characteristics highlights the uniform burden of metabolic features among the individuals regardless of their sex.

Relimpio et al. [36] carried out a study of diabetic patients attending a T2DM clinic in Spain with the aim of assessing the influence of age and other factors on the presence of MS. The average HbA1c in elderly patients (>70 years) was slightly lower (7.0 ± 2.1% for males and 7.2 ± 1.5% for females) than that found in the present study. Abdominal perimeter, on the other hand, showed higher average values (100.0 ± 7.8 cm for males and 106.5 ± 11.6 cm for females), although the average BMI was like the one found. Most of the cardiometabolic parameters did not show differences between the sexes either. Another study carried out in Spain with 501 diabetic patients followed in an endocrinology clinic showed similar results. Around 75% of the patients had a diagnosis of hypertension, the average SBP was 143 ± 17 mmHg, and the average DBP was 80 ± 10 mmHg [37], very similar to what we found. A study in Jordan also showed results of uncontrolled cardiometabolic parameters in patients with T2DM. Around 62% of the patients were obese and 87% had a high abdominal circumference. The prevalence of hypertension was 74.6% and the rate of uncontrolled hypertension was higher in the elderly (>60 years) [38]. Naseri et al. involved 321 patients with T2DM and analysed various cardiometabolic parameters of these patients. Although their mean age was much lower than that our study (53.86 ± 11.54), their HbA1c values were higher than those found in the present study (HbA1c = 9.27 ± 2.4%). On the other hand, the BP values were like those obtained, where 70.5% of the patients had high BP values, with an average SBP of 146.94 ± 23.19 mmHg [39].

There were also no significant differences between sexes in the prevalence of microvascular complications of T2DM. In fact, the diagnosis of neuropathy and nephropathy was relatively lower than that described in the literature [4,40]. However, as mentioned in the literature, the prevalence of these complications was higher in males than in females [41]. A study conducted in Portugal with the aim of assessing the prevalence of CV disease and CV risk factors in patients with T2DM followed up in hospital included 715 patients with an average age of 66.6 years and an average duration of the disease of 17.4 years and described neuropathy as the second most common complication in these patients (26.4%) [42]. The results obtained, especially in the case of neuropathy, may be because these patients are followed up in a specialised clinic and therefore have tighter control of the pathology and its complications, or on the other hand, because neuropathy often has few symptoms that patients may not notice (asymptomatic or mildly symptomatic) [40] or consider normal for their age, since all the patients in this study were elderly. The presence of retinopathy, on the other hand, showed results more in line with the literature (31%) [4]. This could be because in the region there are public screening programmes available, which could result in early diagnosis of this microvascular complication.

Dyslipidaemia is a crucial factor in the diagnosis of MS, as defined by the IDF [1], and is a major factor for the development of CV disease [43]. This study suggests that while elderly patients may derive greater benefit from SBP control, the effects of the intervention on LDL cholesterol may not be as pronounced in this population. However, the impact of lowering lipid parameters in the elderly appears to mirror the results observed in the prevention of CV events in younger individuals. No additional safety concerns were identified, supporting the use of lipid-lowering agents in older individuals [44]. In fact, 56.3% of the patients evaluated in this study were treated for dyslipidaemia. It is worth noting that the most recent tools developed to estimate CV risk score in the general and older European population, namely SCORE-2 and SCORE-2-OP, use total cholesterol levels as an indicator of dyslipidaemia. This allows the estimation of absolute 10-year risk reduction for CVD events from risk factor treatment [43,45]. However, while T2DM was considered a predictive factor in the development of these tools, it is not an indicator used in their operationalization. Hence, the ADVANCE tool was chosen to calculate the 10-year risk of fatal CV events in the elderly population with T2DM analysed in this study, based on previous studies [18,46,47]. Also, the European Association of Preventive Cardiology (EAPC) recommends the use of a U-Prevent tool, namely the use of the ADVANCE risk score in patients with T2DM, pointing out that all U-Prevent risk algorithms have been extensively validated in the European population and that geographical updates are applied

where appropriate [45,48]. As mentioned, this calculator considers the time since diagnosis and the presence of long-term complications, which are important factors in calculating the 10-year CV risk score. Interestingly, while waist circumference is a mandatory factor for diagnosing MS according to the IDF [1], it is not considered in any CV risk calculation tool. This could be significant, especially in patients with MS. Conversely, scoring systems for non-alcoholic fatty liver disease (NAFLD) such as the Fatty Liver Index (FLI), which are strongly associated with high CV risk score [49], do include waist circumference in their calculation [50]. BMI is a required parameter when calculating 10-year CV risk using the DIAbetes Lifetime perspective (DIAL) model. However, the online calculator model indicates that this tool may underestimate the 10-year and lifetime risk score without a history of CV disease, and that the algorithm is currently being calibrated [51]. Although the recalibration has been published, the new algorithm is not yet available for online calculations [52].

HbA1c levels, indicative of the glycaemic control, have been linked to a decrease in non-fatal CV events, such as stroke, and microvascular and macrovascular complications [53–55]. Consequently, attaining optimal glycaemic control is a current recommendation in the individualized treatment to all persons with T2DM [56]. Nonetheless, the IDF criteria for diagnosing MS consider fasting blood glucose rather than this parameter [1]. Given that HbA1c represents the average blood glucose values over the past three months, it could be a relevant parameter to assessing uncontrolled diabetes [57], and thus a criterion for MS.

The results of this study suggest that effective SBP control alone (<130 mmHg) could result in a significant proportion of participants (34.5%) no longer fulfilling the diagnostic criteria for MS. Furthermore, this possible intervention alone could significantly reduce the CV risk score in the studied population, compared to the current risk score. This highlights the potential role of aggressive risk factor modification in ameliorating metabolic abnormalities and reducing the overall burden of CV risk in diabetic groups. The fact that the calculator used (ADVANCE) does not allow the control of all the parameters considered in the CV risk score calculation and/or MS, such as HbA1c, HDL cholesterol, or total cholesterol, hinders the feasibility of quantitatively calculating the impact of changes in CV risk score for each individual. This would be probably a complex task, since the therapeutic objectives for some of these parameters need to be defined, considering the individual characteristics of the patient. It might be beneficial to include additional parameters not covered here, such as health literacy, as previously suggested [58], to further reduce CV risk.

The clustering of MS may play a significant role in the identifying priority interventions associated with CV risk. This contributes to the emphasis on early detection and intervention to mitigate adverse outcomes in this population. The burden of CV diseases attributable to metabolic risk factors has been growing over the last few decades. This trend is expected to continue, considering global aging and the increase in life expectancy [59].

It is important to acknowledge the limitations of the study, such as the cross-sectional design and the use of population mean for albumin creatinine ratio parameter in the risk score calculation on ADVANCE calculator due to the lack of information regarding this parameter. Another limitation of the present study is related to the size of our sample, which limited the conclusions drawn from the statistical treatment of the data, especially when considering the comparison between males and females.

Future research is essential. This includes longitudinal studies to assess the prospective trajectory of MS and its relationship with CV outcomes in elderly individuals with T2DM. It would also be beneficial to develop or upgrade tools that allow the adjustment of other important modifiable parameters in the CV risk score of patients with T2DM and MS, such as HDL cholesterol, triglycerides, fasting glucose, and/or HbA1c levels.

5. Conclusions

The current study examines the intricate relationship between MS, T2DM, and CV risk in the elderly population. Our findings highlight the heightened CV risk score faced by individuals with T2DM and MS, particularly as they age and the duration of their

disease increases. Sex disparities found in the CV risk score highlight the need for tailored interventions that address specific risk factors in both male and female populations.

This study shows the considerable potential of aggressive BP control in reducing the CV risk score, with notable reductions observed across the entire study cohort. The synergistic effect of simultaneously addressing SBP and LDL cholesterol levels further emphasizes the importance of multifaceted risk reduction strategies in optimizing patient outcomes.

Further research is needed to explore additional therapeutic approaches and modifiable factors that aim to enhance CV health in elderly patients with T2DM and MS.

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