BMJ Open Evolution of target organ damage and haemodynamic parameters over 4 years in patients with increased insulin resistance: the LOD-DIABETES prospective observational study

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ABSTRACT

Objectives: We prospectively examined the impact of type 2 diabetes compared with metabolic syndrome (MetS) on the development of vascular disease over 4 years as determined by anatomic and functional markers of vascular disease. By comparing the vascular outcomes of the 2 disorders, we seek to determine the independent effect of elevated glucose levels on vascular disease.

Setting: 2 primary care centres in Salamanca, Spain.

Participants: We performed a prospective observational study involving 112 patients (68 with type 2 diabetes and 44 with MetS) who were followed for 4 years.

Primary and secondary outcome measures: Measurements included blood pressure, blood glucose, lipids, smoking, body mass index, waist circumference, Homeostasis Model Assessment Insulin Resistance (HOMA-IR), hs-c-reactive protein and fibrinogen levels. We also evaluated vascular, carotid intima media thickness (IMT), pulse wave velocity (PWV) and ankle/brachial index, heart and renal target organ damage (TOD). The haemodynamic parameters were central (CAIx) and peripheral (PAIx) augmentation indices.

Results: In year 4, participants with type 2 diabetes had increased IMT thickness. These patients had more plaques and an IMT>0.90 mm. In participants with MetS, we only found an increase in the number of plaques. We found no changes in PWV, CAIx and PAIx. The patients with diabetes had a greater frequency of vascular TOD. There were no differences neither in renal nor cardiac percentage of TOD in the patients with MetS or diabetes mellitus type 2.

Conclusions: This prospective study showed that the evolution of vascular TOD is different in participants with type 2 diabetes compared with those with MetS. While IMT and PWV increased in type 2 diabetes, these were not modified in MetS. The renal

Strengths and limitations of this study

- We analyse the evolution of target organ damage (TOD) and haemodynamic parameters over 4 years in patients with increased insulin resistance.
- The patients with diabetes had an increase in the percentage of vascular TOD as evaluated by intima media thickness and pulse wave velocity.
- The evolution of vascular TOD is different in participants with type 2 diabetes than in those with metabolic syndrome.
- The renal and cardiac TOD evolution did not change in either group.
- The number of participants per group limits the power of analysis and the two groups are not fully balanced in terms of age (4 years of difference), which may influence the course.

and cardiac TOD evolution, as well as the PAIx and CAIx, did not change in either group.

Trial registration number: NCT01065155; Results.

INTRODUCTION

Cardiovascular disease morbidity-mortality is greater in people with type 2 diabetes or metabolic syndrome (MetS).^{1 2} MetS and type 2 diabetes are conditions characterised by insulin resistance; type 2 diabetes is further characterised by increased glucose levels. Both conditions are strongly associated with vascular disease through risk factors that associate with insulin resistance such as hypertension, increased lipid levels and increased inflammation levels.^{3–7} The presence of

target organ damage (TOD) vascular,^{8–11} cardiac¹² and renal^{13 14} increases the risk of cardiovascular complications independently of the existing estimated risk.

The individual role of elevated glucose levels in the development of vascular disease—independent of the other vascular risk factors—is uncertain. Here, we examined a cohort with insulin resistance: one with MetS only and the other with type 2 diabetes.

We prospectively examined the impact of type 2 diabetes versus MetS on the development of vascular disease over 4 years as determined by anatomic and functional markers of vascular disease. By comparing the vascular outcomes of the two disorders, we sought to determine the independent effect of elevated glucose levels on vascular disease.

METHODS

Study design

A prospective observational study was carried out in the primary care setting with a follow-up of 4 years. This study analysed 112 participants who were included in the LOD-DIABETES study (NCT01065155).¹⁵

Study population

Using consecutive sampling, we enrolled 112 patients who visited their family physician between January 2009 and January 2010 with type 2 diabetes (n=68), as defined by the American Diabetes Association criteria,¹⁶ or MetS (n=44), as defined according to the National Cholesterol Education Program, ATP III.¹⁷ The exclusion criteria included patients unable to comply with the protocol requirements such as psychological and/or cognitive disorders, failure to cooperate, educational limitations, problems in understanding the written language and failure to sign the informed consent document. Patients participating or programmed to participate in a clinical trial during the study were also excluded, as were patients with serious comorbidities representing a threat to life over the subsequent 12 months.

The sample size was estimated to detect statistically significant differences in carotid intima media thickness (IMT) ≥ 0.03 mm between baseline and 4 years. We used an α risk of 0.05 and a β risk of 0.2 in a two-sided test. We further assumed an SD of 0.11 mm based on previous studies showing that 112 participants are necessary.¹⁸ We anticipated a dropout rate of 5%. An independent ethics committee of health area of Salamanca (Spain) approved the study. All participants gave informed written consent according to the general recommendations of the Declaration of Helsinki.¹⁹

Measurement

A detailed description has been published elsewhere on how the clinical data were collected including anthropometric measurements, blood pressure and TOD assessment.¹⁵

Blood pressure

Three measurements of systolic (SBP) and diastolic blood pressure (DBP) were collected with a validated OMRON model M7 sphygmomanometer (Omron Health Care, Kyoto, Japan). We used the average of the last two according to the recommendations of the European Society of Hypertension.²⁰

Vascular assessment

Carotid femoral pulse wave velocity and peripheral and central augmentation index

These parameters were estimated using the SphygmoCor System (AtCor Medical Pty Ltd, Head Office, West Ryde, Australia). The pulse wave velocity (PWV) was estimated with patients in the supine position. The pulse wave of the carotid and femoral arteries was analysed to estimate the delay with respect to the ECG wave and to calculate PWV. Distance measurements were collected with a measuring tape from the sternal notch to the carotid and femoral arteries at the sensor location. We considered TOD if PWV was higher than 12 m/s.²¹

The central augmentation index (CAIx) is a composite index that integrates the amount of the wave that is reflected back to the aorta depending on the tone of the resistance arteries—these are the main peripheral reflecting sites. We used Px Pulse Wave Analysis with the patient in the sitting position and the arm resting on a rigid surface. The site of study was the radial artery. A mathematical transformation estimated the aortic pulse wave. The reliability of these measurements was evaluated before the study using the CAIx intraclass correlation coefficient, which showed values of 0.97 (95% CI 0.94 to 0.99) for intraobserver agreement on 22 repeat measurements.

According to the Bland-Altman analysis, the mean difference for intraobserver agreement (95% limits of agreement) was 0.45 (−9.88 to 10.79). From the morphology of the aortic wave, the CAIx was estimated using the following formula: increase in central pressure $\times 100$ /pulse pressure. The value was adjusted to a heart rate of 75 by the SphygmoCor System device.

The peripheral augmentation index (PAIx) is a measurement taken directly from the late systolic shoulder of the peripheral arterial waveform. It is the ratio of the difference in amplitude between the second peak and the diastolic pressure over the difference between the first peak and the diastolic pressure.²² The PAIx was calculated as: (second peak SBP (SBP2)−DBP)/(first peak SBP−DBP) $\times 100$. This gave a per cent (%) value.²²

Assessment of vascular structure by carotid IMT

Carotid ultrasound was used to assess carotid IMT by two investigators trained in this protocol prior to starting the study. The reliability of such recordings was evaluated before the study using the intraclass correlation coefficient, which showed values of 0.97 (95% CI 0.94 to 0.99) for intraobserver agreement on repeated measurements in 20 participants and 0.90 (95% CI 0.74 to 0.96) for interobserver agreement. According to the Bland-Altman

analysis, the mean difference for interobserver agreement (95% limits of agreement) was 0.01 (−0.03 to 0.06). A Sonosite Micromax ultrasound (Sonosite Inc, Bothell, Washington, USA) device paired with a 5–10 MHz multi-frequency high-resolution linear transducer with Sonocal software was used for automatic measurements of IMT to optimise reproducibility. Measurements were made on the common carotid after examining a 10 mm longitudinal section 1 cm from the bifurcation. Measurements were also performed at the proximal and distal walls in the lateral, anterior and posterior projections. They followed an axis perpendicular to the artery to discriminate two lines—one for the intima–blood interface and the other for the media–adventitious interface. Six measurements were obtained for the right carotid and six measurements for the left carotid. We used the average values (average IMT) as automatically calculated by the software.²³ The measurements were obtained with the participant lying down with the head extended and slightly turned opposite to the carotid artery under study. We considered the average TOD if the IMT mean was >0.90 mm or if there were atherosclerotic plaques with a

diameter of 1.5 mm or a focal increase in 0.5 mm or 50% of the adjacent IMT.²¹

Evaluation of peripheral artery involvement

This was assessed using the ankle-brachial index (ABI) and was calculated in the morning for patients who had not drunk coffee or smoked tobacco for at least 8 hours prior to the measurement. The room temperature was 22–24°C. Patients were supine with the feet uncovered. The pressure in the lower limbs was measured after resting for 20 min using a portable Watch BP Office for assessing the ABI (Microlife AG Swiss Corporation Espenstrasse 139; CH-9443 Widnau/Switzerland). The ABI was calculated automatically for each foot by dividing the higher of the two systolic pressures in the ankle by the higher of the two systolic pressures in the arm. An ABI <0.9 was considered peripheral artery TOD.²⁰

Renal assessment

Kidney damage was assessed by measuring the creatinine plasma concentration and glomerular filtration rate (eGFR) as estimated according to the Modification of Diet

Figure 1 Study flow chart. The participants were analysed each year for cardiovascular events in each group. We include the evolution of patients with MetS to type 2 diabetes. CV, cerebrovascular; MetS, metabolic syndrome; DM, type 2 diabetes.

Table 1 Changes in cardiovascular risk factors and medications used in patients with diabetes mellitus and metabolic syndrome

Patients with type 2 diabetes mellitus	1st year (n=68)	2nd year (n=67)	3rd year (n=67)	4th year (n=67)	p Value
Smokers, n (%)	16 (23.5)	16 (25.0)	15 (22.4)	15(22.4)	0.733
Ischaemic heart disease, n (%)	8 (11.8)	8 (12.5)	9 (13.4)	9 (13.4)	0.392
Cerebrovascular disease, n (%)	2 (2.9)	2 (2.5)	2 (3.0)	2 (3.0)	1.000
BMI (kg/m ²)	30.1±5.0	29.7±5.3	29.8±5.4	29.8±5.4	0.243
Waist circumference (cm)	102.9±12.7	101.6±13.7	102.1±13.6	102.5±13.1	0.453
Total cholesterol (mg/dL)	187.5±34.0	185.8±37.1	182.4±26.5	176.94±31.1	0.065
Triglycerides (mg/dL)	143.9±68.3	141.6±76.0	142.9±75.4	139.1±70.8	0.913
LDL cholesterol (mg/dL)	108.6±28.5	108.0±28.9	102.3±25.6	100.7±28.0	0.089
HDL cholesterol (mg/dL)§	48.6±11.7	48.5±12.1	51.6±13.8	50.5±12.4	0.035
Serum glucose (mg/dL)	126.7±35.3	132.5±45.8	129.1±44.6	127.4±35.7	0.538
HbA1c (%)	6.96±1.17	7.0±1.32	7.0±1.06	6.9±1.08	0.433
HbA1c (mmol/mol)	51±12.78	53±14.52	53±11.56	52±11.83	0.448
HOMA-IR	3.29±2.73	3.30±3.80	2.61±4.42	3.12±2.51	0.062
hs-c-reactive protein (mg/dL)	0.34±0.51	0.31±0.42	0.31±0.52	0.33±0.69	0.465
Fibrinogen (mg/dL)	337.2±61.2	365.8±93.2	350.9±73.5	339.9±74.7	0.064
Office SBP (mm Hg)	136.1±19.1	132.49±18.8	134.8±18.1	133.4±18.2	0.536
Office DBP (mm Hg)*,†,‡,§	82.6±11.6	78.9±9.8	79.2±9.1	75.3±10.3	<0.01
Mean antihypertensive drugs†	1.51±1.16	1.60±1.21	1.84±1.27	1.75±1.31	0.012
Antihypertensive drugs, n (%)	51 (76.1)	51 (76.1)	55 (82.1)	52 (77.6)	0.187
Mean lipid-lowering drugs	0.70±0.55	0.70±0.55	0.79±0.57	0.81±0.56	0.037
Lipid-lowering drugs, n (%)	44 (65.7)	44 (65.7)	48 (71.6)	49 (73.1)	0.274
Mean antidiabetic drugs†,§	1.36±0.73	1.34±0.75	1.55±0.8	1.42±0.76	0.018
Antidiabetic drugs, n (%)	62 (92.5)	61 (91.0)	64 (95.5)	63 (94.0)	0.463
Patients with metabolic syndrome	1st year (n=44)	2nd year (n=43)	3rd year (n=43)	4th year (n=43)	p Value
Smokers, n (%)	9 (20.5)	9 (20.9)	4 (9.3)	4 (9.3)	0.007
Ischaemic heart disease, n (%)	2 (4.5)	2 (4.7)	2 (4.7)	2 (4.7)	1.000
Cerebrovascular disease, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0.392
BMI (kg/m ²)	31.1±3.5	30.8±4.1	31.1±4.1	30.6±3.6	0.183
Waist circumference (cm)	104.8±9.8	104.8±9.0	105.7±9.6	103.6±9.7	0.059
Total cholesterol (mg/dL)‡	219.0±44.2	208.5±41.3	206.0±38.0	198.4±28.8	0.012
Triglycerides(mg/dL)	167.7±53.1	151.0±83.7	155.5±106.1	149.9±147.8	0.761
LDL cholesterol (mg/dL)‡	140.3±39.7	130.6±35.9	126.0±34.8	123.1±27.3	0.017
HDL cholesterol (mg/dL)†,‡,§	45.2±11.0	47.4±11.4	50.1±11.7	49.7±10.8	<0.01
Serum glucose (mg/dL)	92.67±11.8	88.9±12.5	90.7±14.3	89.6±12.9	0.190
HbA1c (%)	5.6±0.67	5.8±0.32	5.8±0.32	5.7±0.42	0.169
HbA1c (mmol/mol)	37±7.30	38±3.46	39±3.52	39±4.63	0.130
HOMA-IR*	2.98±1.82	2.22±1.30	2.21±1.37	2.51±1.64	0.007
hs-c-reactive protein (mg/dL)	0.26±0.21	0.27±0.25	0.39±0.42	0.22±0.19	0.107
Fibrinogen (mg/dL)†	327.1±59.1	345.2±66.6	368.1±74.4	347.7±51.9	0.001
Office SBP (mm Hg)*,†,‡,§	142.4±12.5	135.0±15.5	136.5±13.2	129.6±12.3	<0.01
Office DBP (mm Hg)†,‡,§	88.6±9.6	84.9±10.3	84.9±10.9	79.2±8.2	<0.01
Mean antihypertensive drugs*,†,‡	0.77±0.10	1.37±1.20	1.42±1.22	1.49±0.94	<0.01
Antihypertensive drugs, n (%)*,†,‡	20 (46.5)	31 (72.1)	30 (69.8)	36 (83.7)	<0.01
Mean lipid-lowering drugs†,‡	0.30±0.46	0.44±0.55	0.51±0.59	0.51±0.55	0.001
Lipid-lowering drugs, n (%)‡	13 (30.2)	19 (44.2)	20 (46.5)	21 (48.8)	0.003

Data for qualitative variables are expressed as n: number (%) and for quantitative variables as mean±SD.

*p<0.05 between first and second year.

†p<0.05 between first and third year.

‡p<0.05 between first and fourth year.

§p<0.05 between second and third year.

||p<0.05 between second and fourth year.

¶p<0.05 between third and fourth year.

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment Insulin Resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure.

in Renal Disease-Isotopic Dilution Mass Spectrometry (MDRD-IDMS).²⁴ Proteinuria was assessed by the albumin/creatinine ratio following the 2013 European Society of Hypertension/European Society of Cardiology Guidelines

criteria. The TOD renal was defined as 1.3 mg plasma creatinine per 100 mL or higher in men and 1.2 mg per 100 mL or higher in women, as well as an eGFR below 60 mL/min or albumin/creatinine ratio ≥30 mg/g.²⁰

Table 2 Changes in target organ damage and arterial stiffness in patients with type 2 diabetes mellitus and metabolic syndrome

	1st year (n=68)	2nd year (n=67)	3rd year (n=67)	4th year (n=67)	p Value
<i>Patients with type 2 diabetes mellitus</i>					
Vascular					
Carotid IMT average (mm)‡,ll,¶	0.76±0.12	0.76±0.10	0.76±0.13	0.80±0.12	<0.01
Carotid IMT average >0.90 mm, n (%)	5 (7.6)	4 (6.0)	6 (9.0)	10 (14.9)	0.021
Carotid IMT maxima average (mm)‡,ll,¶	0.94±0.14	0.94±0.13	0.92±0.15	0.99±0.15	<0.01
Carotid IMT maxima average >0.90 mm, n (%)	40 (61.5)	36 (53.7)	34 (50.7)	43 (64.2)	0.067
Plaques carotid, n (%)	16 (23.9)	15 (22.4)	20 (29.9)	24 (35.8)	0.016
ABI*,‡,ll	1.11±0.13	1.20±0.12	1.18±0.13	1.15±0.12	<0.01
PWV (m/s)	9.59±2.32	9.78±2.50	9.84±2.47	10.22±2.81	0.219
CAIx	30.44±9.33	28.24±11.56	24.16±13.74	27.27±12.38	0.151
PAIx	96.05±21.00	82.59±19.44	94.94±23.94	93.58±28.98	0.744
Renal					
Serum creatinine (mg/dL)	0.86±0.17	0.86±0.21	0.83±0.20	0.87±0.23	0.092
eGFR (mL/min/1.73 m ²)	90.50±18.15	92.01±20.70	94.69±20.48	89.64±21.20	0.081
Albumin/creatinine ratio (mg/g)	35.26±83.19	33.51±74.36	37.62±115.57	50.95±159.81	0.246
Heart					
Cornell VDP (mm/ms)	1648.15±659.62	1584.79±522.69	1658.15±665.41	1657.46±722.40	0.822
Sokolow (mm/ms)§	19.28±6.08	18.56±6.09	20.39±6.24	19.150±6.39	0.008
<i>Patients with metabolic syndrome</i>					
Vascular					
Carotid IMT average (mm)	0.75±0.12	0.76±0.12	0.73±0.10	0.74±0.11	0.177
Carotid IMT average >0.90 mm, n (%)‡,§	4 (9.5)	4 (9.3)	2 (4.7)	3 (7.0)	0.300
Carotid IMT maxima average (mm)	0.93±0.15	0.93±0.15	0.89±0.12	0.92±0.15	0.109
Carotid IMT maxima average >0.90 mm, n (%)	23 (53.5)	23 (53.5)	15 (34.9)	19 (44.2)	0.019
Plaques carotid, n (%)	3 (7.0)	3 (7.0)	5 (11.6)	8 (18.6)	0.014
ABI†	1.12±0.12	1.17±0.09	1.20±0.11	1.17±0.08	0.006
PWV (m/s)	9.29±2.70	8.57±2.22	8.90±2.08	8.61±2.02	0.068
CAIx	28.65±11.00	25.98±10.54	26.12±11.36	26.81±14.51	0.290
PAIx	94.55±29.51	90.56±20.60	91.08±25.95	89.90±22.51	0.453
Renal					
Serum creatinine (mg/dL)	0.89±0.16	0.90±0.19	0.87±0.18	0.87±0.16	0.164
eGFR (mL/min/1.73 m ²)§,ll	87.64±14.05	87.33±18.75	91.24±18.17	90.29±17.75	0.252
Albumin/creatinine ratio (mg/g)	15.81±38.23	28.33±133.22	4.68±10.15	4.08±7.23	0.297
Heart					
Cornell VDP (mm/ms)*	1477.67±459.16	1661.89±536.98	1616.19±539.66	1521.41±500.32	0.004
Sokolow (mm/ms)§,ll	20.82±5.83	19.54±5.54	21.94±6.19	21.37±6.13	<0.01

Data for qualitative variables are expressed as n: number and (%) and quantitative variables as mean±SD.

*p<0.05 between first and second year.

†p<0.05 between first and third year.

‡p<0.05 between first and fourth year.

§p<0.05 between second and third year.

llp<0.05 between second and fourth year.

¶lp<0.05 between third and fourth year.

ABI, ankle brachial index; CAIx, central augmentation index; Cornell VDP, Cornell voltage duration product; eGFR, estimated glomerular filtration rate; IMT, intima media thickness carotid; PAIx, peripheral augmentation index; PWV, pulse wave velocity.

Cardiac assessment

The ECG examination was performed using a General Electric MAC V.3.500 ECG System (General Electric, Niskayuna, New York, USA) that automatically measures the voltage and duration of waves and estimates the criteria of the Cornell voltage–duration product (Cornell

VDP) and the Sokolow Lyon product.²⁵ The TOD heart was defined according to the 2013 European Society of Hypertension/European Society of Cardiology Guidelines criteria (Sokolow-Lyon index (SV1+RV5>3.5 mV), the modified Sokolow-Lyon index (largest S-wave+largest R-wave>3.5 mV) or the Cornell

voltage QRS duration product (>2440 mV ms).²¹ The individuals performing the different tests were blinded to the clinical data. All assessments were made within 10 days.

Statistics

Continuous variables were expressed as a mean $\pm$ SD and qualitative variables used a frequency distribution. We analysed changes in quantitative variables at follow-up with repeated analysis with the General Linear Model (GLM) procedure corrected by the Bonferroni method. We considered the presence or absence of sphericity and performed the Greenhouse and Geisser correction. The IMT and PWV were analysed with repeated measurements unadjusted and adjusted for age, gender, office mean blood pressure and atherogenic index. We used the Cochran tests to contrast the hypothesis of two or more related proportions. The data were analysed using the SPSS V.20.0

statistical package (SPSS Inc, Chicago, Illinois, USA). A value of $p<0.05$ was considered statistically significant.

RESULTS

Throughout the first year of follow-up, two males died as a result of acute myocardial infarction—one with type 2 diabetes and the other with MetS (aged 76 and 65 years, respectively). Subsequently, two non-fatal cardiovascular events occurred in the type 2 diabetes group. In the MetS group, there was a cerebrovascular event, and four participants developed type 2 diabetes. The flow chart is shown in figure 1.

The mean age was 57 ± 12 years (60 ± 12 years in diabetic people and 55 ± 12 years in MetS). The frequency of males was 63.4% (63.2% in people with diabetes, 63.6% in those with MetS).

Table 1 shows the cardiovascular risk factors, biochemical data and drugs analysed in each of the four evaluations in participants with type 2 diabetes and MetS. The evolution time of diabetes type 2 from the moment of

Figure 2 Changes between the 4 years of follow-up in TOD. (A) TOD in type 2 diabetes. (B) TOD in metabolic syndrome. In type 2 diabetes: $p<0.01$ in TOD overall, TOD vascular, carotid and cf-PWV. IMT, intima media thickness; cf-PWV, carotid femoral pulse wave velocity; ABI, ankle brachial index; GFR, glomerular filtration rate; ACR, albumin creatinine ratio; TOD, target organ damage.

the diagnosis was over two years. Table 2 shows the annual assessments of vascular, renal and cardiac TOD in patients with type 2 diabetes and MetS.

Type 2 diabetes had increased IMT, with more participants presenting with plaques, and a higher percentage of participants with IMT>0.9 mm in the follow-up. There were also changes in the ABI ($p<0.01$) and the Sokolow criteria.

Likewise, in participants with MetS, there were changes in the number of participants with a mean maximum IMT>0.9 mm and the percentage of participants with plaques ($p=0.014$). There were also changes in the ABI ($p=0.006$) in the Sokolow and Cornell PDV criteria.

The average IMT mean increased by 0.010 mm in patients with diabetes and by 0.001 mm in participants with MetS per year ($p=0.011$). PWV increased by 0.162 m/s in patients with diabetes and decreased by 0.182 m/s in participants with MetS per year ($p=0.002$). Figure 2A, B shows the trend and the percentage of patients with type 2 diabetes or MetS with vascular, renal

and cardiac TOD in each of the four measurements. The most prevalent TOD in both groups is carotid artery injury (43% in type 2 diabetes and 21% in MetS) in the last assessment.

In participants with type 2 diabetes, the percentage of patients with overall and vascular TOD increased ($p<0.01$). We found no changes in TOD in patients with MetS.

In the unadjusted repeated measurement analyses, we found differences in IMT ($p=0.002$), but not in PWV ($p=0.709$; figure 3A–D). After adjusting for age, gender, mean blood pressure and atherogenic index, the differences in the 4 years of follow-up of IMT disappeared ($p=0.909$), but did not modify PWV ($p=0.223$). Adjusted for age, this is only seen in online supplementary figures S1A and S1B. An interaction effect is observed between the IMT $\times$ group ($p=0.004$) and the PWV $\times$ group ($p=0.033$). Thus, from the third year, both IMT and PWV are higher in participants with type 2 diabetes than in those with MetS (figure 3). However, in the post hoc

Figure 3 Estimated unadjusted means (A and C), and adjusted by age, gender, atherogenic index and office blood pressure (B and D) of IMT and PWV in patients with type 2 diabetes and metabolic syndrome. IMT, intima media thickness; PWV, pulse wave velocity.

contrasts, statistical significance ($p \leq 0.01$) is only reached in the first case.

DISCUSSION

Unlike previous studies that examined the prevalence of cardiovascular diseases in relation to glucose disorders, we analysed the difference between patients with type 2 diabetes or MetS in terms of vascular, renal and cardiac TOD. This study included a 4-year follow-up period of patients with type 2 diabetes or MetS. It showed an increase in carotid IMT and PWV TOD that is higher in type 2 diabetes than in MetS. There were no significant differences in the frequency of renal and cardiac TOD in type 2 diabetes. Participants with MetS have no significant increases in TOD.

In people with diabetes, the evolution of subclinical cardiovascular diseases is worse than in those with only an increased resistance to insulin without changes in blood sugar levels as in patients with MetS.³ The evolution of vascular parameters (IMT and PWV over time) is a controversial matter probably due to the control of cardiovascular risk factors and the influence of the drugs used to control it.

A meta-analysis of Lorenz *et al.*²⁶ (based on 1339 strokes from 16 studies) concluded that the association between IMT progression (evaluated with ultrasound and cardiovascular risk) and the risk of subsequent cardiovascular events in the general population has yet to be confirmed. An intensive intervention on people with diabetes with different cardiovascular risk factors over 2 years reduced the IMT, but no markers (including endothelial function parameters) were useful in predicting such changes.²⁷

The Tromsø study had higher levels of IMT at follow-up in participants with MetS than in those without MetS.²⁸ MetS predicted IMT progression in people 50 years of age and younger, but not in other age groups. This indicated that MetS may be involved in the initiation of the atherosclerotic process. In the European Lacidipine Study on Atherosclerosis (ELSA),²⁹ IMT progression was slightly greater in patients with MetS. However, this was not significant after adjusting for other cardiovascular risk factors. Only patients with type 2 diabetes had an increase in $PWV \geq 12$ m/s during the monitoring period.

Our findings suggest that patients with increased insulin resistance did not have differences in CAIx and PAIx. These results are consistent with previously published³⁰ data in a Chinese cohort.^{30–31} The behaviour of ABI was similar in both patient groups both in terms of absolute ABI values and the percentage of patients with $ABI < 0.9$. Similar data have been published in other studies with patients with type 2 diabetes.^{32–34} However, it must be remembered that in patients with diabetes, the standard threshold sensitivity (0.9) is lower, and thus the efficiency of ABI is limited.

This study has some limitations that must be considered. First, the number of participants per group limits the power of the analysis. Furthermore, these patients were not randomised, but involved consecutive sampling. The two groups are not fully balanced in terms of age (4 years of difference), which may influence the course. One remarkable point is that this study shows the differences in the progression of many parameters including IMT and PWV between 2 groups prospectively for 4 years.

This prospective study showed that the evolution of vascular TOD is different in participants with type 2 diabetes than in those with MetS. While IMT and PWV increased in type 2 diabetes, especially in diabetic women, these were not modified in MetS. The renal and cardiac TOD evolution, as well as the PAIx and CAIx, did not change in either group.

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Contributors MÁG-M designed the study, wrote the protocol, participated in fundraising, interpreted the results, prepared the manuscript draft, performed all analytical testing, interpreted the results and reviewed the manuscript and corrected the final version of the manuscript. JIR-R and CA-C participated in the study design, data collection and manuscript review. LG-S, MG-S, ER-S and JAM-F participated in the study design, interpretation of results and manuscript review. MCP-A participated in the analysis of results and final review of the manuscript. LG-O participated in the protocol design, fundraising, analysis of results and final review of the manuscript. All authors reviewed and approved the final version of the manuscript.

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