Scientific letters

Obesity and Vascular Events in Type 2 Diabetes Mellitus

Obesidad y episodios vasculares en la diabetes mellitus tipo 2

To the Editor,

Obesity is a vascular risk factor implicated in the pathogenesis of type 2 diabetes mellitus (DM2). There has been some debate about whether obesity in patients with DM2 is associated with greater[1] or less[2] mortality with respect to patients of normal weight with DM2 (the obesity paradox in DM2). In principle, the association between body mass index (BMI) and mortality could be mediated by vascular risk factors, target organ lesions, and vascular events, although we are not aware of studies that have investigated these variables in patients with DM2 and different BMIs. We compared the frequency of vascular events and their associated factors in obese patients with DM2 and those of normal weight with DM2.

This was an observational study conducted in the outpatient clinic of the Metabolic-Vascular Unit of La Paz University Hospital, Madrid, Spain in 2013. We selected all patients with DM2 (according to the American Diabetes Association criteria) attended at least once in the calendar year with a full clinical work-up. Patients had to have a BMI of 30 kg/m^2 or more (obesity) or less than 25 kg/m^2 (normal weight). Weight and height were measured during the first appointment of the year using a height rod and digital scales, calibrated every 6 months (AENOR quality control, UNE-EN ISO 9001 standard). Height was measured to the nearest centimeter and weight was measured in kilograms to 1 decimal place, with the patient wearing no coat, jacket, or shoes. We recorded demographic variables, vascular risk factors, target organ lesions, cardiovascular events, laboratory data, and DM-related treatments, according to the criteria defined in the REACH study,[3] which included patients from Spain. Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

For qualitative variables, the 2 groups, obese and normal-weight patients, were compared with the Pearson chi-square test using a continuity correction or the Fisher exact test when the number of measurements in the sample was small. The Student *t* test for independent samples was used for quantitative variables. The relationship between events in the 2 BMI groups, adjusted for age, sex, smoking, and blood pressure, was studied with binomial logistic regression. $P < .05$ was considered statistically significant.

Overall, 94 patients with DM2 were included: 79 with BMI of 30 kg/m^2 or more and 15 with BMI less than 25 kg/m^2 (Table). The number of patients with at least 1 vascular event was significantly higher among obese patients (n = 29 [37%]) compared with normal-weight patients (n = 1 [7%], $P = .032$). Most of the vascular events affected the heart (ischemic heart disease or heart failure, 18/30 patients [60%]). On multivariate analysis, the association between obesity and vascular events remained significant ($P = .035$). Despite a shorter duration of diabetes ($P < .05$), a greater proportion of obese patients had hypertension ($P = .043$) than normal-weight patients. A greater proportion of obese patients had left ventricular hypertrophy ($P = .004$), metabolic syndrome, and chronic stage III renal failure (glomerular filtration rate of 30-60 mL/min/1.73 m^2; $P = .042$).

Table
Characteristics of Obese and Normal-Weight Patients With Type 2 Diabetes Mellitus

	All	DM2+obesity (BMI ≥ 30.0 kg/m^2)	DM2+normal weight (BMI < 25.0 kg/m^2)	*P*[a]
Patients included	94	79 (84)	15 (16)	
Age, mean (SD), y	65 (10)	65 (10)	64 (10)	.812
Male	64 (68)	56 (71)	8 (53)	.229
Duration of DM2, mean (SD), mo	96 (98)	107 (98)	139 (98)	<.05
Vascular risk factors				
Smoker	13 (14)	10 (13)	3 (20)	.452
Hypertension	87 (93)	75 (95)	12 (80)	.043
Dyslipidemia	71 (76)	59 (75)	12 (80)	.661
Metabolic syndrome	80 (85)	72 (91)	8 (53)	.001
Organ damage				
LVH	27 (30)[b]	27 (37)[c]	0	.004
Microalbuminuria	24 (26)[d]	21 (27)[e]	3 (20)	.752
GFR < 60 mL/min/1.73 m^2	26 (28)[f]	25 (33)[g]	1 (7)	.042
Patients with vascular event	30 (32)[h]	29 (37)	1 (7)	.022
Cerebrovascular event	10	10	0	.001
Cardiac event	18	18	0	.001
Coronary event	14	14	0	.001
Heart failure[i]	10	10	0	.001
Kidney failure	10	10	1	.002
Peripheral artery disease	3	2	1[j]	.850

Table *(Continued)*
Characteristics of Obese and Normal-Weight Patients With Type 2 Diabetes Mellitus

	All	DM2+obesity (BMI ≥ 30.0 kg/m^2)	DM2+normal weight (BMI < 25.0 kg/m^2)	*P*[a]
Number of events per patient (all), mean (SD)	0.6 (1.0)	0.7 (1.1)	0.1 (0.5)	.006
Physical examination				
BMI, mean (SD)	32 (5)	33.5 (3.5)	23.5 (1.3)	<.001
SBP, mean (SD), mmHg	136 (14)	137 (13)	134 (16)	.513
DBP, mean (SD), mmHg	79 (9)	80 (9)	75 (9)	.030
Laboratory analysis				
Glucose, mean (SD), mg/dL	149 (48)	146 (46)	160 (57)	.292
HbA_{1c}, mean (SD), %	6.9 (1.1)	6.9 (1.1)	7.1 (1.1)	.446
Cholesterol, mean (SD), mg/dL	170 (44)	170 (45)	173 (42)	.809
Triglycerides, mean (SD), mg/dL	176 (115)	185 (122)	126 (47)	.070
HDL-C, mean (SD), mg/dL	46 (12)	45 (12)	51 (11)	.094
LDL-C, mean (SD), mg/dL	98 (35)	97 (34)	100 (41)	.795
Non-HDL cholesterol, mean (SD), mg/dL	124 (44)	125 (44)	122 (42)	.843
Treatments				
Insulin	20 (21)	16 (20)	4 (27)	.731
Oral antidiabetic agents	80 (85)	70 (89)	10 (67)	.029
Antihypertensives	81/87 (93)	70/75 (93)	11/12 (92)	.990
Two or more drugs	63/87 (72)	58/75 (77)	5/12 (42)	.038
Lipid-lowering agents	87 (93)	72 (91)	15 (100)	.231

BMI, body mass index; DBP, diastolic blood pressure; DM2, type 2 diabetes mellitus; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
[a] Comparison between obese patients with DM2 and normal-weight patients with DM2.
[b] Of the 87 patients with hypertension.
[c] Measured in 70 out of 75 patients with hypertension.
[d] Measured in 93 out of 94 patients.
[e] Measured in 78 out of 79 patients.
[f] Measured in 92 out of 94 patients.
[g] Measured in 77 out of 79 patients.
[h] Sum of vascular events is > 30 because some patients had more than 1 event.
[i] Of the 10 patients with heart failure, the cause was ischemic in 6 and nonischemic in 4.
[j] Only 1 patient with normal weight had chronic renal failure and peripheral artery disease.
Unless otherwise indicated, the data are expressed as No. (%).

In the study, obese patients with DM2 had a higher frequency of vascular events than normal-weight patients with DM2, as well as a higher frequency of hypertension and target organ lesions. In more than half the patients with a vascular event, the heart was affected (60%) and all these patients were obese. The association between obesity and vascular events was maintained in the multivariate analysis. This finding does not support the concept of the obesity paradox in DM2[1,2] (apparent benefit of obesity). The study was designed to verify whether the worse prognosis of obese patients with DM2 compared with patients with normal weight[1] was associated with a greater frequency of risk factors, organ damage, and vascular events. As such, the results cannot be extrapolated to all patients with DM2, given that this was not a population-based sample.

Among the study strengths, we highlight that the diagnosis of DM2 and target organ involvement, as well as assessment of the vascular events, were assessed by the same team, based on written medical records according to accepted criteria.[3] Moreover, the characteristics of our series are very similar to those of other populations from different autonomous regions of Spain (mean age, 67 years; frequency of vascular events, 32%).[4–6] Among the study limitations, we should highlight that we analyzed a case series, with all patients available in the clinic during 1 year. Despite the small sample size, the results help to stress that obesity in patients with diabetes is associated with vascular events and that these may be associated with hypertension and its complications, especially in the case of cardiac events.

FUNDING

Health Research Grant from the *Instituto de Salud Carlos III* (FIS, 08/0009 and 11/0598), and the Spanish Primary Care Network (2009/70) and RECAVA (RD/12/0042/0024).

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Available online 29 November 2014

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http://dx.doi.org/10.1016/j.rec.2014.09.006

Mitochondrial Cardiomyopathies Associated With the m.3243A>G Mutation in the *MT-TL1* Gene: Two Sides of the Same Coin

Miocardiopatías mitocondriales asociadas a la mutación m.3243A>G en el gen MT-TL1: dos caras de la misma moneda

To the Editor,

We report 2 patients diagnosed with cardiomyopathy caused by a single genetic defect in the mitochondrial DNA. Both patients illustrate the importance of integrating clinical information when establishing a diagnosis, and allow us to discuss the unique characteristics of reproductive counselling for this type of genetic disease.

The first patient was a black Angolan man aged 47 years, who had moved to Spain to study ophthalmology. His clinical history included long-standing diabetes mellitus, recurrent tuberculosis, and bilateral sensorineural hearing loss. He was admitted for fever and acute respiratory failure. The echocardiogram (Figure) showed concentric left ventricular hypertrophy and severe systolic dysfunction. The cardiologic study was complemented with magnetic resonance imaging (absence of late-enhancement) and coronary angiography (normal). Other findings included marked cachexia, with steppage gait and renal failure with microalbuminuria. His mother had died of heart problems, his children were healthy, and a sister had an unspecified heart disease. Mitochondrial disease was suspected, specifically MIDD syndrome (maternally inherited diabetes and deafness) (Table). Sequencing of mitochondrial DNA from a blood sample revealed an m.3243A>G mutation in the *MT-TL1* gene encoding mitochondrial tRNALeu, with 50% heteroplasmy. The patient was discharged with treatment for heart failure and returned to his home country.

The second patient was a 36-year-old woman with multiple brain microbleeds identified during a study for hearing loss, and in whom cardiac evaluation revealed a possible noncompaction cardiomyopathy (Figure). The patient had had type 1 diabetes since the age of 24 years, and had short stature and low body mass index. There was no family history of heart disease, myopathy, or sensorineural problems. The patient reported frequent migraines. She was in New York Heart Association functional class II-III for exercise intolerance, had normal levels of creatine kinase and the amino terminal fraction of brain natriuretic peptide, and oscillating lactate levels (>2.5 mmol/L in several readings).

No further treatment was indicated, as ventricular function was normal. In this patient, the suspected clinical phenotype was MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) (Table). Muscle biopsy showed 8% ragged red fibers, mostly cyclooxygenase-positive (Figure), and the genetic study again revealed the m.3243A>G mutation in MT-TL1, with 87% to 91% heteroplasmy in the muscle biopsy.

Mitochondrial diseases are characterized by dysfunction of the respiratory chain, leading to cellular energy deficit. The most commonly affected organs are those with the highest metabolic demand, such as the nervous system and muscle. Common manifestations include encephalopathy, myopathy, diabetes, and hearing loss. The simultaneous involvement of several of these organs without an apparent common cause or manifestations early in life, such as diabetes or stroke before age 40 years, should serve as a guide to this diagnosis. These syndromes may present with widely different percentages of cardiac abnormalities (from 3%-81%, depending on the series) and in the form of both cardiomyopathies (usually hypertrophic or dilated) and conduction disorders (Table). The m.3243A>G mutation in mitochondrial tRNALeu is one of the most common, and can result in different syndromes such as MIDD (case 1) and MELAS (case 2), with considerable variation in cardiac manifestations.[1] It is common to observe onset or worsening of symptoms after stressful situations (in the first patient, the hearing loss attributed to tuberculosis drugs had actually started years earlier, following an episode of malaria). In the presence of a classical clinical syndrome, the diagnosis can be confirmed by genetic analysis. Treatment is symptomatic, and should avoid drugs such as metformin (risk of lactic acidosis) or statins (worsening myopathy). Antioxidants or alternative therapies with coenzyme Q10 and L-carnitine are used, although there is controversy about their beneficial effects. Anesthesia should be used with special caution due to the risk of respiratory failure, with avoidance of nondepolarizing muscle relaxants and barbiturates.

Following diagnosis, the patient in case 2 expressed a desire to have children without this disease. Providing genetic counseling is one of the tasks facing cardiologists managing patients with familial heart disease.[2]

Mitochondrial genetics has a number of peculiarities to be taken into account when giving reproductive advice. Since zygote mitochondria come from the oocyte, inheritance is matrilineal, with women transmitting to all their descendants. The coexistence of more than one type of mitochondrial DNA molecule is called heteroplasmy. A minimum percentage of mutated DNA is necessary for symptoms to become evident (threshold effect). In cell division, the distribution of mitochondria is random, and daughter cells do not necessarily receive the same amount of mutated DNA. Mitochondrial DNA continues to replicate independently of cell division, such that initially healthy tissues may develop signs of disease over time. These features explain the phenotypic variation and clinical expression of these disorders, as well as the difficulty in preventing them by using assisted reproduction techniques. The reproductive options that guarantee the absence of disease transmission to offspring are adoption, gestation of an embryo from another couple, or fertilization of a donated egg. All have the disadvantage that the genetic link to the mother is lost.[3]

Preimplantation diagnosis for mitochondrial genetic disorders can only reduce the chances of disease by transferring embryos with low levels of heteroplasmy. Under current Spanish law, it is unlikely that this treatment would be authorized, since it does not ensure the use of embryos without genetic defects.[4]

Although still in the experimental stage, the future of prevention for these diseases lies in mitochondrial replacement techniques. These techniques consist of creating embryos with