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ORIGINAL RESEARCH

Metformin enhances left ventricular function in patients with metabolic syndrome

La metformina mejora la función ventricular izquierda en pacientes con síndrome metabólico

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Key words: Metabolic syndrome, metformin, left ventricular diastolic dysfunction, tissue Doppler imaging, speckle tracking.

Palabras clave: *Síndrome metabólico, metformina, disfunción diastólica del ventrículo izquierdo, Doppler tisular, rastreo de manchas.*

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ABSTRACT

Background: Metabolic syndrome foretells several cardiovascular complications, including heart failure (HF). Left ventricular (LV) dysfunction accompanies the MS. Although metformin improves LV function in diabetics with HF, there is no evidence of its effect on LV dysfunction in MS patients. We studied the effect of metformin on LV dysfunction in MS patients using tissue Doppler myocardial imaging and two-dimensional speckle tracking. **Aims:** To evaluate the effects of metformin on metabolic syndrome (MS) induced left ventricular dysfunction. **Material and methods:** Patients with MS were randomly allocated into two groups (n = 20 each) receiving, an antagonist of angiotensin 2 receptors and; statins, fibrates or both. One group received 850 mg of metformin daily. LV mass, relative wall thickness (RWT), ejection fraction, E/A and E/E' relationship, systolic tissue Doppler velocity (Sm), mean peak systolic strain (SS), and peak early diastolic strain rate (SR-LVe) echocardiographic measurements, at baseline and six months were obtained. **Results:** All patients had LH concentric hypertrophy or remodeling. Metformin reduced LV mass and RWT. There were LV systolic and diastolic alterations in both groups that metformin improved significantly. SR-LVe increased nearly 2-fold with metformin. Diastolic function improvement was not related to regression of hypertrophy. **Conclusions:** Patients with MS experienced subtle alterations of systolic and diastolic functions, which improved significantly with a small dosage of metformin over a treatment period of six months.

RESUMEN

Antecedentes: *El síndrome metabólico (SM) predice varias complicaciones cardiovasculares, como la insuficiencia cardiaca (IC). La disfunción ventricular izquierda (DVI) acompaña al síndrome metabólico. Aunque la metformina mejora la función del ventrículo izquierdo en pacientes diabéticos con insuficiencia cardiaca, no hay evidencia de su efecto sobre la disfunción ventricular izquierda en pacientes con síndrome metabólico. Se estudió el efecto de la metformina sobre la disfunción ventricular izquierda en pacientes con síndrome metabólico utilizando imágenes Doppler de tejido miocárdico y rastreo de manchas bidimensional.* ***Objetivos:*** *Evaluar los efectos de la metformina sobre la disfunción ventricular izquierda inducida por el SM.* ***Material y métodos:*** *Los pacientes con SM fueron asignados al azar en dos grupos (n = 20 cada uno) que recibieron, un antagonista de la angiotensina 2 y receptores; estatinas, fibratos o ambos. Un grupo recibió 850 mg de metformina diaria. La masa del VI, el espesor relativo de la pared (ERP), fracción de eyección, E/A y relación E/E', la velocidad Doppler tisular sistólica (Sm), el promedio de pico de tensión sistólica (SS), y la velocidad de deformación diastólica precoz pico (VDDPP) se obtuvieron por mediciones ecocardiográficas al inicio del estudio y a los seis meses.* ***Resultados:*** *Todos los pacientes presentaban hipertrofia concéntrica o remodelado. La metformina reduce la masa del VI y el ERP. Había alteraciones del ventrículo izquierdo sistólica y diastólica, alteraciones en ambos grupos que la metformina mejoró significativamente. VDDPP aumentó casi al doble con metformina. La mejoría de la función diastólica no se relacionó con regresión de la hipertrofia.* ***Conclusiones:*** *Los pacientes con SM experimentaron alteraciones sutiles de las funciones sistólica y diastólica, lo que mejoró significativamente con una pequeña dosis de metformina en un periodo de tratamiento de seis meses.*

BACKGROUND

Obesity and metabolic syndrome (MS)[1,2] constitute two main public health challenges affecting the urban population in contemporary Mexico.[3-5] The clinical and epidemiological relevance of MS resides first in its capacity to predict the development of type 2 diabetes mellitus (T2DM) in genetically predisposed individuals.[6] In addition, through multiple pathogenic mechanisms, MS results in the pathogenic triad of endothelial dysfunction,[7] nitroxidation[8] and low-grade inflammation,[9] the starting points of arterial and myocardial structural and functional damage. Therefore, MS itself is closely related to an increased risk of cardiovascular, cerebrovascular, and coronary morbidity and mortality.[10] Furthermore, MS has a cluster of pathogenic mechanisms that deleteriously impact cardiac performance, resulting in the development of heart failure (HF),[11] increased likelihood of a poor prognosis, physical disablement and large expenses.[12] Halting or slowing the progression of cardiac impairment from asymptomatic cardiac dysfunction to clinical HF is attainable through several therapeutic interventions, e.g., the pharmacological modulation of the renin-angiotensin system.[13] To obtain better results, however, the sooner the diagnosis of cardiac dysfunction is made, the greater the opportunity is for a patient to improve with therapeutic interventions that could delay the development of HF, which is the last and lethal stage on the cardiovascular continuum.

Although metformin constitutes a fundamental aspect in the treatment of T2DM and is also widely employed in the treatment of MS, until recently, its use in diabetic patients with HF was a matter of controversy due to the fear of provoking lactic acidosis.[14] However, current evidence indicates that metformin is not only harmless but in fact beneficial in these patients, reducing the 2-year mortality by 24%.[15] Although the pleiotropic effects of metformin,[16] such as anti-atherosclerotic actions, decrease of lipid accumulation in macrophages, reduction of oxidative stress, platelet activation, antitumoral and neuroprotective effects, among others, have attracted great interest, the study of its possible effects on the ventricular function in non-diabetic patients with MS has not been fully explored.

In this work, we studied the effect of six months of treatment with metformin, a classical antidiabetic drug, on the primeval and subtle left ventricular systolic and diastolic functional abnormalities in patients with MS, as assessed by tissue Doppler myocardial imaging and two-dimensional speckle tracking.[17,18]

MATERIAL AND METHODS

The patients comprising this subanalysis belong to a larger cohort, the Lindavista II study, a long-term, interventional investigation encompassing patients of both genders with abdominal obesity and with MS diagnosed according to the ATP III criteria.[1] Assuming the differences in the LV mass index among patients without either hypertrophy nor the MS, and people with both conditions,[19] utilizing the equation for sample size calculation comparing two proportions and, assigning a value for α of 0.01, with a power of 90%, a sample size of six patients per group (controls and those medicated with metformin). Anticipating some losses in the follow-up, we randomly selected 20 subjects per group, of any gender, aged 35 to 60 years. All patients received the same dietary and exercise counseling as well as an antagonist of angiotensin two receptors and; statins, fibrates or both, if needed. The protocol was approved by the Ethics and Research Institutional Committees, and the study was conducted according to standards derived from the Declaration of Helsinki,[20] and Federal Mexican regulations.[21]

All patients had at least three of the five diagnostic criteria of MS, including compulsorily abdominal obesity. For that purpose, it was taken into account the cut-off points that have been established for Mexicans: ≥ 80 cm in women and ≥ 90 cm in men.[22] Subjects with diabetes mellitus, with a history of coronary, cerebral or peripheral vascular disease, with another type of structural heart disease or antecedents of heart failure, with severe systemic disorders such as chronic liver disease, renal failure, AIDS, malignant diseases or alcohol or drug abuse were excluded.

All participants underwent a medical history and complete physical examination. The

body weight in kilograms was obtained with a clinical scale, and height in centimeters was obtained by a stadiometer. The body mass index (BMI) was calculated by dividing the weight by height squared. The waist circumference was measured with a measuring tape, midway between the last rib and the iliac crest. The blood pressure (BP) was measured with a calibrated mercury sphygmomanometer.

The serum fasting glucose and lipid profile total cholesterol, TC; triglycerides, TG; and high density lipoprotein cholesterol (HDL-c), were measured using the enzymatic method at baseline and six months afterward. Low-density lipoprotein cholesterol (LDL-c) was calculated using Friedwald's formula. the homeostasis model assessment (HOMA-IR) technique was used to estimate insulin sensitivity.[23]

Echocardiographic observations. At the start of the study and six months afterward, all patients underwent an echocardiographic transthoracic study with a Phillips model IE33 echocardiographic apparatus, a mechanical sector transducer with a frequency of 2 to 5 MHz and Q-Lab software. The echocardiographic study was conducted and analyzed by a registered expert echocardiographist (HV) who was blinded to the type of treatment. With the patient in the supine or left lateral recumbent position and the transducer placed in the third or fourth intercostal space, images of the short and long axes of the heart were acquired. From the two-dimensionally parasternal short-axis view, oriented M-mode echo images perpendicular to the septum and ventricular posterior wall were obtained, just above the level of the papillary muscles, and the chamber dimensions and wall thicknesses were acquired in diastole and systole, following the American Society of Echocardiography and the European Association of Echocardiography criteria.[24] The diastolic and systolic left ventricular volumes (EDV, ESV) were then estimated using the method based on the modified Simpson's rule. The ejection fraction (EF) was calculated by the usual method (EF = [EDV-ESV] α EDV). Using the Devereux-Penn[25] formula, ventricular mass was calculated:

$$LVM\ (g) = 1.04\ ([LVIDD + PWTD + IVSTD]^3 - [LVIDD]^3) - 13.6\ g$$

Where LVM is the left ventricular mass, LVIDd is the left ventricular internal diameter in diastole, PWTD is the posterior wall thickness in diastole and IVSTD is the interventricular septum thickness in diastole.

LVMI is the LVM indexed to BM, expressed in g/m^2. The relative wall thickness (RWT) = ([2 x PWTD]/LVIDD) is a useful index allowing both the categorization of an increase in the LV mass as either concentric (RWT ≥ 0.42) or eccentric (RWT ≤ 0.42), as well as the characterization of concentric remodeling when RWT is ≥ 0.42 but LV mass has not yet increased. LVMI was classified into four categories according to the mass and RWT values: normal, concentric remodeling, concentric hypertrophy and eccentric hypertrophy.[26] By placing the transducer at the cardiac apex, a four-chamber view was obtained. The ultrasound beam and sample volume were then placed between the two mitral veils and a pulsed Doppler wave was registered, measuring the magnitudes of the E (peak velocity of early left ventricular rapid filling) and A (peak velocity of late atrial ventricular filling) waves. Afterward, the sample volume was placed at the junction of the myocardial basal septal wall segment with mitral annulus (tissue Doppler imaging, TDI), measuring the velocity of the waves reflecting mitral displacement, both the systolic (Sm) and two diastolic waves, reflecting rapid filling and atrial transport (Em and Am), respectively. Then, analysis of the myocardial deformation and displacement phenomena, independent of organ translation and the sound beam angle, was conducted with the newer technique known as speckle tracking echocardiography (STE).[27] In a two-dimensional four-chamber apical view, a complete heartbeat was registered, processed and analyzed off-line. An ultrasound beam interferes with myocardial tissue, causing scattering and reflection, thereby resulting in acoustic «speckles», «markers» or «spots» that can be traced along the entire cardiac cycle to provide information about tissue deformation and motion. Based on these images, both the peak systolic strain (a measure of deformation or percentage change of the original dimension) and the early diastolic strain rate (the velocity of that change) can be estimated.

Statistical analysis. The data were analyzed using Prizm 5 for Windows. For all numerical

variables, the mean ± SE was calculated. A paired Student's t test was used to compare the mean values before and after the treatment, or nonparametric analysis was used when appropriate. Statistical significance was determined by a p value of ≤ 0.05. Linear regression analysis was performed to explore any possible correlation between variables and to analyze the changes in the slopes after treatment.

RESULTS

Forty recruited patients (18 women and 22 men) completed the study. The experimental group had a mean age of 44.5 ± 5.6 years and the control had a mean age of 44 ± 7 years.

Blood pressure, somatometric, and metabolic results. The effects of metformin on blood pressure, BMI, serum glucose, HOMA-IR, lipid profile and CRP are shown in *table I*.

All patients were hypertensive and well controlled with ARBs. Neither BMI nor abdominal circumference comparison exhibited significant changes from the basal values, despite the dietary and exercise counseling. Patients treated with metformin had a significant glycemic reduction of 6.5% (from 101 to 94 mg/dL), whereas the control subjects did not show any change. Patients treated with metformin had a 27% reduction (from 4.4 to 3.2) for the HOMA-IR value, exhibiting significantly greater insulin sensitivity at the end of the study compared with the controls that did not show any change in this variable. In the same manner, patients treated with metformin had significant reductions for TC and TG (10.7 and 25.9%, respectively) and a 6.7% increase in HDL-c, in contrast with the insignificant changes observed in the control subjects.

Echocardiographic data *(Figures 1 and 2)*. At baseline, all patients in both groups had preserved systolic LV function, according to the normal values of EF (~0.71) and Sm wave (systolic tissue Doppler velocity [DTI], 8.1 cm/s). Nevertheless, the mean value of the SS was less than normal (-18.6 ± 0.1%), indicat-

Table I. Effects of metformin on arterial pressure BMI, abdominal circumference, glucose, insulin sensitivity, lipids and inflammation.

	Control group			Metformin group		
	Basal Mean ± SD	6 months Mean ± SD	p value	Basal Mean ± SD	6 months Mean ± SD	p value
SAP (mmHg)	123.2 ± 12.7	120.4 ± 11.8	0.201	123.9 ± 13.4	120.4 ± 11.8	0.185
DAP (mmHg)	78 ± 9.7	74 ± 9.4	0.1926	76.6 ± 8	73.5 ± 9.3	0.065
BMI (kg/m^2)	31.98 ± 4.7	31.76 ± 4.4	0.719	30.26 ± 5.2	30.48 ± 4.4	0.780
Abdominal circumference	103.56 ± 10.5	98.34 ± 13.6	0.201	100.91 ± 10.1	101.03 ± 10.4	0.901
Glycemia (mg/dL)	99.18 ± 11	99.63 ± 12	NS	101.1 ± 9.7	94.44 ± 11.2	**0.0184**
HOMA-IR (mg/dL*mU/L)	4.0	4.3	NS	4.4	3.2	0.06
TC (mg/dL)	184.2 ± 51.5	189.8 ± 45	NS	198.7 ± 49.8	177.4 ± 37.6	**0.0186**
HDL-c (mg/dL)	36.71 ± 12.4	39.59 ± 8.2	NS	38.49 ± 6.8	45.27 ± 11.1	**0.0012**
TG (mg/dL)	199.2 ± 105.6	251.9 ± 165.9	NS	236.2 ± 131.9	174.9 ± 66.94	**0.0232**
hsCRP (mg/dL)	0.79 ± 0.2	0.8718 ± 0.3	NS	0.8048 ± 0.2	0.8076 ± 0.3	NS

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HOMA-IR = homeostasis model of assessment - insulin resistance index. TC = total cholesterol; HDL-c = high-density lipoproteins cholesterol; TG = triglycerides; hsCRP = high sensitivity C-reactive protein.

ing a slight systolic dysfunction in both groups at baseline. SS in the patients treated with metformin improved significantly from 16.9 to 20.1%, whereas the controls did not show any change *(Table II)*.

SR-LVe was less than normal (1.55 ± 0.01 1/s) in both groups at baseline but rose significantly by 21.5% (from 1.02 to 1.27 1/s) in metformin-treated subjects. At baseline, 80% of the patients had LV hypertrophy or concentric remodeling. In the control patients, the septal and posterior wall thicknesses and LVMI did not show any significant changes from measurements obtained at baseline verses those obtained at the end of the study; however, in the patients treated with metformin, SWT, PWT and LV mass decreased significantly (-8.4, -8.8 and -10.7%, respectively). Diastolic dysfunction was observed in all patients in both groups at baseline (relationship of E/A in the mitral flow Doppler of less than 1). The control patients showed an appreciable reduction of the E wave, but the metformin-treated subjects showed an increase in the size of this wave, a significant reduction of the A wave, and an improvement (but not significant) of the E/A ratio (+ 12%). The E/Em ratio, expressing the magnitude of the LV filling pressures, did not change in either group. SR-LVe showed no discernible modification in the controls but increased twofold in the metformin patients; however, the wide standard deviation prevented a significant result.

In *table III*, the data of the left ventricular geometry is shown. Twenty percent of the patients in both groups had a normal left ventricular geometry at baseline. In the control subjects, the proportion of remodeling diminished from 50 to 35%, whereas concentric hypertrophy increased slightly (6 to 8 cases, 30 to 40%). In contrast, in the metformin group, the proportion of normal geometry increased (4 to 6 cases, 20 to 30%). Similarly, remodeling increased (8 to 9 cases, 40 to 45%), but concentric hypertrophy was reduced (8 to 5 cases, 40 to 25%). Although the variation in sample size prevented a significant result by these changes, never-

Table II. Echocardiographic data.

	Control group			Metformin group		
Variable	Basal	Six months	p value	Basal	Six months	p value
SWT	11.7 ± 1.7	11.6 ± 1.5	NS	11.5 ± 1.8	10.6 ± 1.6	**< 0.002**
PWT	10.9 ±1.8	11 ± 1.8	NS	10.8 ± 1.5	9.9 ± 1.6	**< 0.0001**
LVIDd	43.3 ± 3.5	44.3 ± 2.8	**0.02**	44.3 ± 3.4	44.5 ± 3	NS
LVIDs	22.9 ± 2.1	22.8 ± 2.7	NS	23.1 ± 2.9	23.6 ± 2.1	NS
EF	0.71 ± 0.40	0.68 ± 0.29	**0.0007**	0.71 ± 0.55	0.73 ± 0.58	**< 0.003**
LVMI	96 ± 26	98 ± 23	NS	99.7 ± 20	89 ± 18	**< 0.0001**
RWT	0.50 ± 0.07	0.49 ± 0.07	NS	0.51 ± 0.08	0.46 ± 0.07	**< 0.0001**
E wave	76.8 ± 19.6	73.3 ± 17.2	**0.01**	80.8 ± 17	87 ± 15.8	**< 0.046**
A wave	81.8 ± 13.7	77.6 ± 23	NS	75.3 ± 10.2	75.2 ± 9	NS
E/A ratio	0.97 ± 0.32	0.94 ± 0.35	NS	1.1 ± 0.29	1.19 ± 0.25	0.06
Sm (DTI)	8.1 ± 1.4	7.8 ± 1.3	< 0.01	8.1 ± 1.1	8.5 ± 0.8	**0.009**
Em (DTI)	7.3 ± 1.7	7.1 ± 1.8	NS	8.7 ± 1.9	9.2 ± 1.3	NS
Am (DTI)	9.5 ± 2.2	9.2 ± 2.0	NS	9.7 ± 2.4	9.1 ± 2.2	**0.05**
E/Em ratio	10.6 ± 2.3	10.4 ± 1.5	NS	9.5 ± 2.5	9.59 ± 2.1	NS
SSP	17.1 ± 1.2	17 ± 1.5	NS	16.9 ± 1.3	20.1 ± 1.6	**0.0001**
SR-LVe 1/s	1.03 ± 0.25	0.9 ± 0.28	**0.006**	1.02 ± 0.2	1.27 ± 0.2	**0.0001**

LVIDs = left ventricular internal diameter in systole; other abbreviations as in text.

Table III. Analysis of left ventricle morphology.

	Control group			Metformin group		
	Basal	6 months	p value	Basal	6 months	p value
Normal	4 (20%)	5 (25%)		4 (20%)	6 (30%)	
Concentric remodeling	10 (50%)	7 (35%)	NS versus normal	8 (40%)	9 (45%)	NS versus normal
Concentric hypertrophy	6 (30%)	8 (40%)	0.054 versus remodeling	8 (40%)	5 (25%)	0.09 versus remodeling

theless, the greater proportion of concentric hypertrophy in the controls nearly reached significance (p = 0.054).

Because the patients treated with metformin exhibited a significant reduction of hypertrophy, we tried to link the diastolic dysfunction improvement observed in these subjects with the diminution of LV mass. There was a relatively high negative correlation coefficient (-0.6) between the LVMI and E/A ratio. No differences between the slopes were observed after six months of the metformin treatment. Similar results were found with the comparison between the LV mass and the SR-LVe and Em values.

DISCUSSION

The occurrence of multiple organ damage in MS has been extensively described, as well as the numerous probable mechanisms responsible for LV damage.[28,29] Patients with MS have the deleterious combined effects of arterial hypertension, dysglycemia, dyslipidemia, and hyperinsulinism, all of which are cardiovascular risk factors or direct causal mechanisms for atherosclerosis, hypertensive arteriosclerosis, LV hypertrophy, endothelial dysfunction, low grade inflammation and nitroxidation.[8] These functional and structural abnormalities can explain, at least in part, the increased cardiovascular morbidity and mortality in MS patients. Hypertension is most likely the main cause of LV chronic damage, which can lead to heart failure. However, more recently, it has been established that patients with the MS have LV diastolic dysfunction independent of LV mass. The LV functional abnormalities affect inclusive patients with only two of the MS criteria diagnosis, and the functional derangement is proportional to the severity of obesity and the clustering of co-morbidities.[29] The exact nature of the pathogenic mechanisms of LV diastolic dysfunction has not yet been fully revealed, but they appear to be the same as those affecting diabetic LV derangement, including several intertwined factors: typical cardiovascular risk factors (hypertension, hyperglycemia and dyslipidemia); a pro-inflammatory state related to visceral obesity; the over expression of TNFα; a diminished expression of adiponectin; endothelial dysfunction; nitroxidation-induced damage; persistent sympathetic reaction; altered myocardial perfusion or altered metabolic substrate utilization; hyperleptinemia; lipid infiltration and fibrosis in the heart interstice (adipositas cordis); and the response of RAGE receptors to advanced glycation end-products, among others.[30] The clinical importance of asymptomatic diastolic dysfunction has only been recognized recently.[31] Diastolic failure appears to affect 35% of patients with MS, and its prevalence increases in diabetics and in symptomatic coronary patients.[32] Even modest abnormalities of myocardial relaxation are associated with a twofold increase in cardiac mortality.[33] Unfortunately, there are few well-documented therapies for diastolic heart failure.

Recently, several pleiotropic effects of metformin have been described: antioxidant activity mainly against the precursors of advanced glycation end-products (AGEs), (8) e.g., free carbonyls, anti-inflammatory effects, increases in HDL paraoxonase activity,[34] a direct reduc-

tion of the atherogenic process, and antitumoral activity.[16] Experimental evidence suggests that the myocardial effects of metformin are also a consequence of the activity of AMPK,[35] inducing the inhibition of cardiac remodeling, a greater endothelial production of nitric oxide, and attenuation of ischemia/reperfusion injury in experimental animals. Additionally, antifibrotic action has been observed, explained as the expression of the activation of AMPK, which inhibits protein

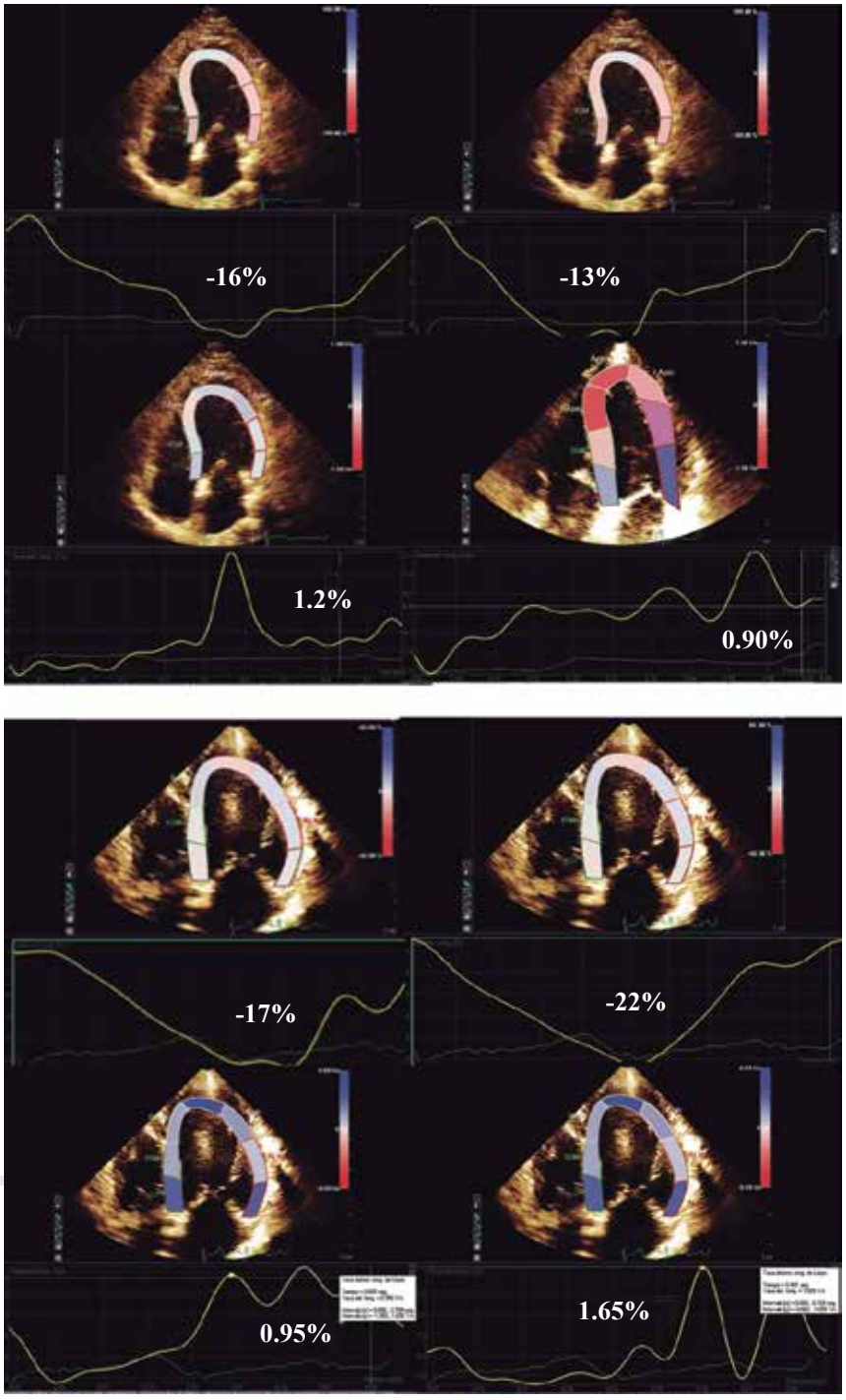

Figure 1.

Representative echocardiographic images of SR-LVe and strain rate. Compose image on top, control subject. SR-LVe was -16% at the begining (upper left), SR-LVe decrease to -13% (upper right) after six months. The basal strain rate was 1.2% (lower left) and 0.9 % after six months (lower right). Lower compose image, metformin treated subject. SR-LVe was -17% at the beginning (upper left), SR-LVe increase to -22% (upper right) after six months of treatment with metformin. The basal strain rate was 0.95% (lower left) and 1.65% after six months of treatment (lower right).

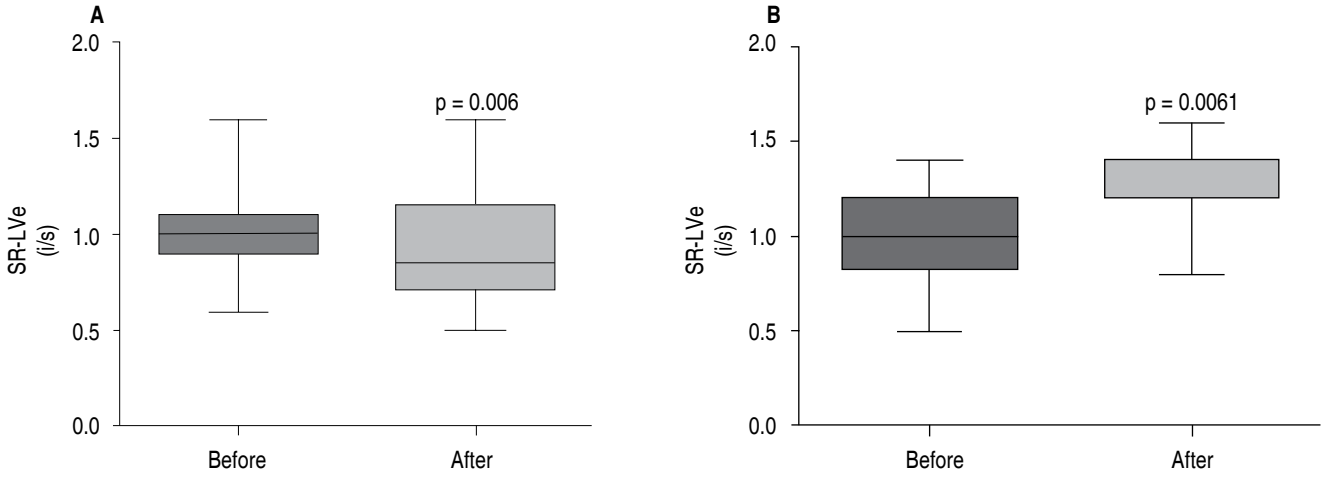

Figure 2. Graphic representation of changes in SR-LVe. **A)** Plot of SR-LVe values at the beginning of study and after six months in the control group, **B)** plot of SR-LVe values at the beginning of study and after six months of treatment with metformin. Data were analyzed using a nonparametric Wilcoxon matched-paired test, statistical values are expressed in figure.

synthesis. Furthermore, at least in post-infarcted rats, metformin inhibits remodeling and LV dilatation and preserves systolic function.[36] Other evidence indicates that alone or in combination with atorvastatin, metformin reduces hypertrophy and cardiomyocyte size in experimental animals.[36] Both combined actions (improving the diastolic properties and reducing the LV hypertrophy) can explain the beneficial role on cardiac performance of metformin in experimental animals. However, in contrast with the large body of experimental evidence on the effect of metformin in LV performance, there is little documentation regarding its effects on cardiac function in patients with MS or full-blown T2DM.

The results of this rather small study highlight the advantages of metformin on several variables reflecting the diastolic and systolic derangements in MS. As in other studies, our research did not find a noticeable effect of metformin on blood pressure, BMI, or lipid concentration. There was indeed a salutary effect, although marginal, on dysglycemia. However, the clear and convincing impact of metformin on the LV diastolic function over a rather short period of observation was a noteworthy finding of this study.

The methodology used in this study, indices derived from tissue Doppler imaging and LV strain and strain rate (speckle tracking echocardiography), are very precise instruments that measure the complexity of diastolic function, with some of its diverse components: isovolumic relaxation, intraventricular pressures and early and late filling. This methodology also allowed us to be confident in the results found.

CONCLUSIONS

Patients with MS but without T2DM exhibit subtle signs of LV systolic and diastolic dysfunction and concentric hypertrophy or concentric remodeling of the LV. Metformin enhanced the systolic and diastolic LV function and induced the regression of hypertrophic growth. The improvement of diastolic function did not correlate with the reduction of LV mass; therefore, this effect is most likely secondary to the AMPK activation. In accordance with other evidence, the use of metformin should be mandatory in the management of abdominal obesity associated with MS, not only for preventing the development of T2DM but also to reduce several metabolic and structural derangements, mainly due to early LV damage, a hallmark of diastolic HF. The effects of metformin on the functionality of diastole in both humans and laboratory animals support the possibility of using this drug to treat the diastolic failure of the senescent heart.

LIMITATIONS OF THE STUDY

The size of the sample could be a limitation to the generalization of our results. In addition, because this study was not blind, our results must be confirmed by a second, much larger double-blind study. However, the echocardiographic studies and the measurement and analysis of the tracings were conducted by a completely blinded investigator, fact that increase the confidence in the obtained results.

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REFERENCES

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001; 285 (19): 2486-2497.
2. Zimmet PZ, Alberti KG, Shaw JE. Mainstreaming the metabolic syndrome: a definitive definition. This new definition should assist both researchers and clinicians. Med J Aust. 2005; 183: 175-176.
3. Sánchez-Castillo CP, Velázquez-Monroy O, Lara-Esqueda A, Fanghänel G, Violante R, Tapia-Conyer R et al. Diabetes and hypertension increases in a society with abdominal obesity: results of the Mexican National Health Survey 2000. Pub Health Nutr. 2004; 8: 53-60.
4. Aguilar-Salinas CA, Rojas R, Gómez-Pérez FJ, Valles V, Ríos-Torres JM, Franco A et al. High prevalence of metabolic syndrome in Mexico. Arch Med Res. 2004; 35: 76-81.
5. Meaney E, Lara-Esqueda A, Ceballos-Reyes GM, Asbun J, Vela A, Martínez-Marroquín Y et al. Cardiovascular risk factors in the urban Mexican population: the FRIMEX study. Public Health. 2007; 121: 378-384.
6. Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. N Engl J Med. 2008; 359: 2220-2223.
7. Duncan E, Ezzat V, Kearney M. Insulin and endothelial function: physiological environment defines effect on atherosclerotic risk. Curr Diabetes Rev. 2006; 2: 51-60.
8. Meaney E, Vela A, Samaniego V, Meaney A, Asbún J, Zempoalteca JC et al. Metformin, arterial function, intima-media, thickness and nitroxidation in metabolic syndrome: the MEFISTO study. Clin Exp Pharmacol Physiol. 2008; 35: 895-903.
9. Després JP. Inflammation and cardiovascular disease: is abdominal obesity the missing link? Int J Obes Relat Metab Disord. 2003; 27 Suppl 3: S22-S24.
10. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 2001; 24: 683-689.
11. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG et al. Obesity and the risk of heart failure. N Engl J Med. 2002; 347: 305-313.
12. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009; 119: 480-486.
13. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991; 325: 293-302.
14. Inzucchi SE. Metformin and heart failure. Innocent until proven guilty. Diabetes Care. 2005; 28: 2585-2587.
15. Aguilar D, Chan W, Bozkurt B, Ramasubbu K, Deswal A. Metformin use and mortality in ambulatory patients with diabetes and heart failure. Circ Heart Fail. 2011; 4: 53-58.
16. Kittappa P, Mitra S. Merformin beyond hypoglycemic effect. IJCCI. 2012; 4: 5-12.
17. Nagueh SF. Tissue Doppler imaging for the assessment of left ventricular diastolic function. J Cardiovasc Ultrasound. 2008; 16: 76-79.
18. Sitia S, Tomasoni L, Turiel M. Speckle tracking echocardiography: a new approach to myocardial function. World J Cardiol. 2010; 26: 1-5.
19. De Simone G, Devereaux RB, Chinali M, Roman MJ, Lee ET, Resnick HE et al. Metabolic syndrome and left ventricular hypertrophy in the prediction of cardiovascular events. Nutr Metab Cardiovasc Dis. 2009; 19: 98-104.
20. World Medical Association, Declaration of Helsinki. Adoptada por la 18 Asamblea Médica Mundial. Helsinki, Finlandia, 1964 y corregida por la 29 Asamblea (Tokio, Japón, 1975), la 35 (Venecia, Italia, 1983) y la 41 (Hong Kong, 1989). Disponible en: http://ohsr.od.nih.gov/Helsinki.php3
21. Ley General de Salud, Reglamento de Investigación Clínica. Título 5o. Capítulo único. Diario Oficial de la Federación, 24 de diciembre de 1986. Disponible en: http://www.salud.gob.mx/unidades/cdi/nom/compi/rlgsmis.html
22. Sánchez-Castillo CP, Velázquez-Monroy O, Berber A, Lara-Esqueda A, Tapia-Conyer R, James WP. Anthropometric cutoff points predicting chronic diseases in the National Health Survey 2000. Obes Res. 2003; 11: 442-451.
23. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 2008; 294: E15-E16.
24. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Com-

mittee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18: 1440-1463.
25. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation. 1977; 55: 613-618.
26. Gerdts E. Left ventricular structure in different types of chronic pressure overload. Eur Heart J. 2008; 10 (Supplement E): E23-E30.
27. Goffinet C, Vanoverschelde JL. Speckle tracking echocardiography. Eur Cardiol. 2007; 3: 1-3.
28. Aijaz B, Ammar KA, Lopez-Jimenez F, Redfield MM, Jacobsen SJ, Rodeheffer RJ. Abnormal cardiac structure and function in the metabolic syndrome: a population-based study. Mayo Clin Proc. 2008; 83: 1350-1357.
29. de las Fuentes L, Brown LA, Mathews SJ, Waggoner AD, Soto PF, Gropler RJ et al. Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass. Eur Heart J. 2007; 28: 553-559.
30. Roberts AW, Clark AL, Witte KK. Left ventricular dysfunction and heart failure in metabolic syndrome and diabetes without overt coronary artery disease – do we need to screen our patients? Diab Vasc Dis Res. 2009; 6: 153-163.
31. von Bibra H, St John-Sutton M. Diastolic dysfunction in diabetes and the metabolic syndrome: promising potential for diagnosis and prognosis. Diabetologia. 2010; 53: 1033-1045.
32. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S et al. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J. 2003; 24: 320-328.
33. Owan TE, Hodge DO, Herges RM, Jacobson SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006; 355: 251-259.
34. Meaney E, Sierra-Vargas P, Meaney A, Guzmán-Grenfell M, Ramírez-Sánchez I, Hicks JJ et al. Does metformin increase paraoxonase activity in patients with the metabolic syndrome? Additional data from the MEFISTO study. Clin Transl Sci. 2012; 5: 265-268.
35. Sasaki H, Asanuma H, Fujita M, Takahama H, Wakeno M, Ito S et al. Metformin prevents progression of heart failure in dogs. Circulation. 2009; 119: 2568-2577.
36. Yin M, van der Horst IC, van Melle JP, Qian C, van Gilst WH, Silljé HH et al. Metformin improves cardiac function in a nondiabetic rat model of post-MI heart failure. Am J Physiol Heart Circ Physiol. 2011; 301: H459-H468.

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