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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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 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), systolic function improvement was not related to regression of hypertrophy.

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 eyeción, 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 hiperтроfia 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 mejora de la función diastólica no se relacionó con regresión de la hiperтроfia.

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 período 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 \(\alpha\) 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: \(\geq 80\) cm in women and \(\geq 90\) 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 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 echocardiographer (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] / EDV). Using the Devereux-Penn25 formula, ventricular mass was calculated:

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LVM \text{ (g)} = 1.04 \left(\frac{LVIDD + PWTD + IVSTD}{3} - [LVIDD]^3\right) - 13.6 \text{ 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.

LVM is the LVM indexed to BM, expressed in g/m². 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 ≥ 0.42 but LV mass has not yet increased. LVM 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/m²)                    | 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 versus 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-
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. 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. 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. 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. The clinical importance of asymptomatic diastolic dysfunction has only been recognized recently. Diastolic failure appears to affect 35% of patients with MS, and its prevalence increases in diabetics and in symptomatic coronary patients. Even modest abnormalities of myocardial relaxation are associated with a twofold increase in cardiac mortality. 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), e.g., free carbonyls, anti-inflammatory effects, increases in HDL paraoxonase activity, a direct reduc-
tion of the atherogenic process, and antitumoral activity. Experimental evidence suggests that the myocardial effects of metformin are also a consequence of the activity of AMPK, 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 beginning (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).
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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 non-parametric Wilcoxon matched-paired test, statistical values are expressed in figure.

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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