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# Back to basics with active lifestyles: exercise is more effective than metformin to reduce cardiovascular risk in older adults with type 2 diabetes

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**ABSTRACT:** To establish the effect of three types of treatment – multicomponent exercise (MEX); the oral hypoglycaemic drug metformin (MET); combined therapy comprising exercise plus metformin (MEXMET) – on cardiovascular risk in older adults with type 2 diabetes (T2D) and with comorbidities in an early stage of the disease (HbA1c < 7.5%). A sample of 284 participants was evaluated for multifactorial cardiovascular risk at baseline and at 24-month intervention according to anthropometric and hemodynamic components, lipid profile, glycaemia and cardiorespiratory fitness (CRF). Participants underwent one of three conditions: MEX ($n$ = 59), training in three sessions per week; MET ($n$ = 30), using metformin 850 mg twice daily; MEXMET ($n$ = 195), combining exercise and metformin. After the 24-month intervention MEX and MEXMET showed more positive results than MET therapy. MEX decreased body mass (BM; 4%), waist circumference (WC; 4%), body mass index (BMI; 3%), systolic blood pressure (SBP; 11%), diastolic blood pressure (DBP; 11%), triglycerides (21%), and glycaemia (12%), and increased cardiorespiratory fitness (CRF; 18%). Conversely, the MET group showed increased WC (2%), waist-to-hip ratio (WHR) (3%), and SBP (5%). Differences between MEX and MET groups presented large effect sizes for BM, WC, WHR, SBP, DBP and CRF, and moderate effect sizes for BMI and glycaemia. MEX was the most effective therapy in decreasing cardiovascular risk in the early stage of T2D in older adults with multimorbidity and attenuated the adverse effects of pharmacological therapy in MEXMET treatment.

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## INTRODUCTION

The management of diabetes in the elderly is a complex process due to the increased prevalence of comorbidities, heterogeneous functional status, and geriatric syndromes [1,2]. Therefore, an holistic approach to the multiple aetiopathogenic mechanisms of the disease has been recommended to minimize long-term complications [3–5].

International organizations [6,7] recommend a stepwise management approach based on lifestyle modification which includes a behavioural change in nutritional and exercise habits as the first step, but they differ in the introduction of a first-line oral hypoglycaemic drug at the initial diagnosis, usually metformin. Nevertheless, in the elderly population these previous recommendations were based on expert consensus and clinical experience, due to the absence of evidence from clinical trials with older adults, particularly to identify the efficacy of such treatments. Additionally, there is growing evidence demonstrating the adverse side effects of pharmacologic treatment and drug-disease interactions in this specific population [1,2,8]; in fact, metformin was associated with initial gastrointestinal side effects and it was not recommended for frail older people with weight loss [5].

On the other hand, randomized controlled trials have shown that an intensive lifestyle may decrease the rate of diabetes onset in adults at high risk for developing T2D [9–12], and reduce cardiovascular risk [5], but it has also been suggested that pharmacological therapies alone, or in combination with diet and exercise, could be even more effective [13–15]. However, once more, these results should be interpreted with caution, because these previous studies have used wide range age samples, mixing adults of all ages, with different physical cardiovascular profiles, highlighting the need to understand how it acts in an exclusively older adult population. Additionally, it has been reported that greater reductions in morbidity and mortality could result from the control of other cardiovascular risk factors, especially hypertension and lipid profile, rather than from the independent tight glycaemic control [5]. It seems crucial to understand the relative value of exercise training and/or drug treatment in the elderly, faced with the lack of evidence previously demonstrated in this specific population [15]. Therefore, in context of the preceding trends, the aim of the present study is to analyse the effect of three types of treatment – *i)* lifestyle modification with

multicomponent exercise; *ii)* pharmacologic treatment with the oral hypoglycaemic drug metformin; *iii)* and a combined therapy including exercise and metformin – on multifactorial cardiovascular risk factors in older adults with T2D in the early stage of the disease.

## MATERIALS AND METHODS

### *Participants*

This cohort study is part of a larger study involving 1473 community-dwelling adults aged 60 and over to study the effects of long-term multicomponent exercise (MEX) on several variables. Participants were referred to the study by their physician or self-referred from flyers distributed at community centres, media advertisements or word of mouth. The study design has been reported previously [16].

After the initial evaluation, a sub-group of physically independent participants fulfilled the criteria for T2D defined by the International Diabetes Federation [7]. Exclusion criteria included (a) uncontrolled hypertension; (b) severe autonomic neuropathy; (c) severe peripheral neuropathy or history of foot lesions; (d) unstable proliferative retinopathy; (e) participants who were not under regular supervision of the treating physician for the period of the study; (f) known cancer

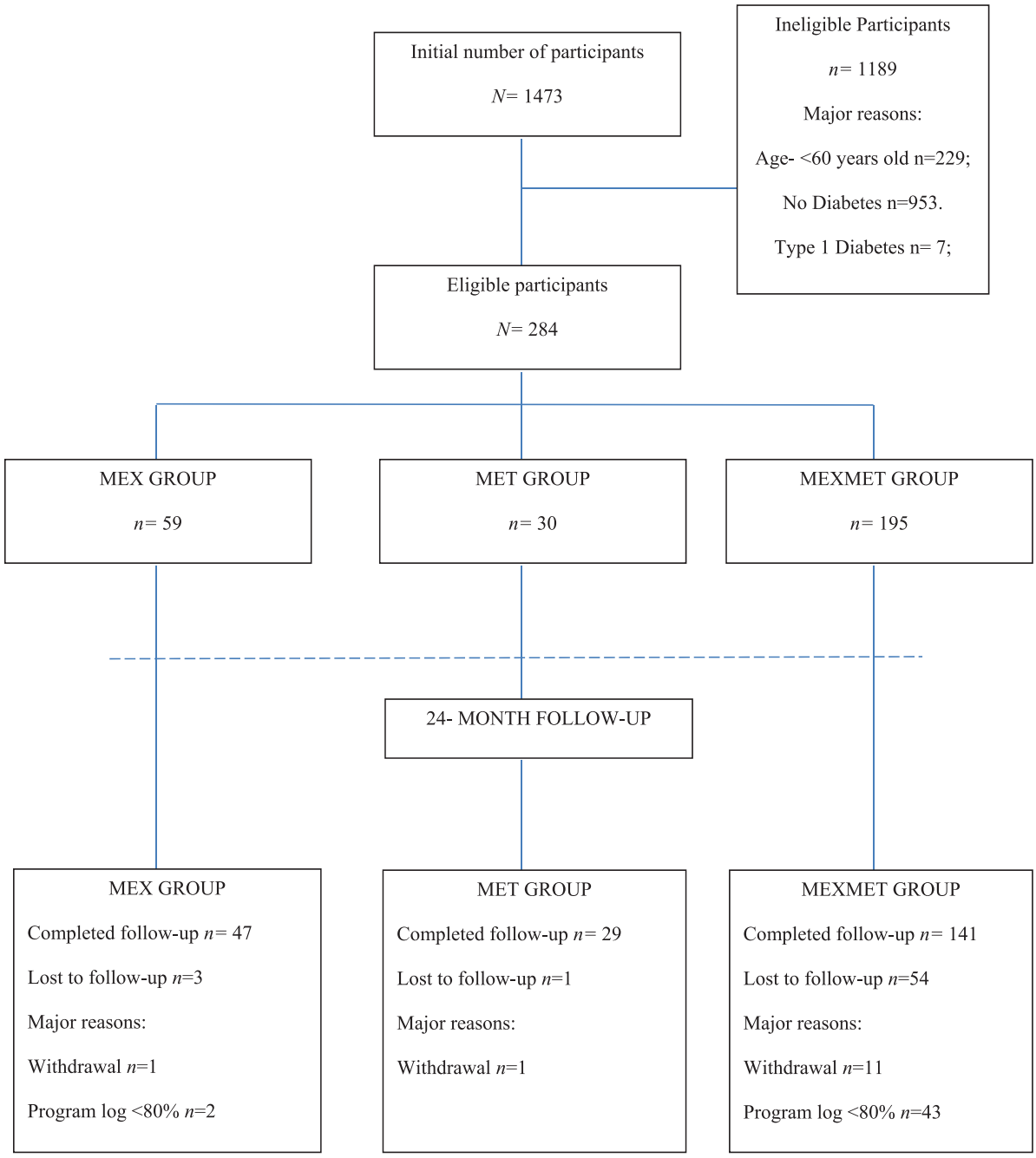


**FIG. 1.** Cohort flux diagram.

or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia; (j) severe visual impairment; and (k) further reasons that made it impossible or highly problematic for the patient to participate and come to the follow-up visits completing baseline and follow-up testing (programme log ≥ 80 %). Thus, a sub-group of 284 were retained as eligible participants. This group was then divided according to 3 therapy conditions as follows: i) lifestyle modification – exercise (MEX; $n$ = 59: 29% male); ii) oral hypoglycaemic therapy – metformin (MET; $n$ = 30: 60% male); and iii) combined therapy – exercise and oral hypoglycaemic therapy with metformin (MEXMET; $n$ = 195: 32% male). After the 24-month intervention, the trial was completed by 217 participants: MEX group ($n$ = 47); MET (n = 29) and MEXMET group ($n$ = 141) (Figure 1).

The criterion for inclusion in the MEX group was exercise engagement according to the guidelines [17], while the MET group used pharmacological therapy with oral hypoglycaemic metformin (i.e., 850 mg twice daily) to manage their disease, and the MEXMET group combined multicomponent exercise training with oral hypoglycaemic metformin treatment.

### *Interventions and procedures*

After the aforementioned recruitment period, in a preliminary meeting, participants were informed about the nature, the benefits and the risks of their participation in this study. Furthermore, in a second meeting, participants completed the health history questionnaire and the anthropometric and hemodynamic components and aerobic fitness were measured. BP, body mass (BM), waist and hip circumferences, and stature were assessed by trained nurses according to standard procedures [18]. Self-reported questionnaires were used to collect data on demographic factors, medical outcomes and lifestyle factors, which were completed only by interviewers trained to carry out data collection with illiterate participants.

Evaluation procedures were performed in the same order at the baseline and at the end of the follow-up, after 24 months. Baseline interviews and clinical examination were performed in September 2013 with the follow-up until September 2015.

Participants of the MEX and MEXMET groups met three times a week for one hour over the 24-month intervention period to perform the multicomponent exercise programme in the local centres of Santa Maria da Feira. The MET and MEXMET groups held trimester consultations with their physician to control their medication treatment. In addition, all participants were instructed to maintain the same nutritional pattern throughout the intervention period and maintain regular supervision of their physician during the follow-up intervention.

All participants agreed to participate in this study and they gave their written informed consent, consistent with the Helsinki Declaration. Methods and procedures were approved by the Institutional Scientific Board of the *University of Coimbra*, the local institution (Santa Maria da Feira County) and the national ethics committees Data Protection Authority (CNPD) and Northern Regional Health Administration Ethics Committee (ARS/Norte).

### *Multicomponent exercise programme*

The supervised exercise programme consisted of three 60-minute sessions/week, on Monday, Wednesday and Friday. Aerobic, resistance, balance and flexibility were trained according to the following items: 5-10 minutes of warm-up, 20-30 minutes of aerobic, 15-20 minutes of resistance training, 10 minutes of balance, 10 minutes of stretching, and 5-10 minutes of cool down exercises. Aerobic exercise started with participants in a standing position and involved continuous movement of major muscles of the upper limb, performed alternately with movement of the lower limb. Time and intensity of aerobic exercise were increased from 20 minutes per session at 50%$HR_{max}$ (maximum heart rate) to 30 minutes at 70%$HR_{max}$ per session [18].

Resistance training was conducted every Monday and Friday; on these 2 days, the aerobic session was shortened to approximately 20 minutes. Resistance training involved five to eight exercises from large muscle groups, with one to three sets of 8 to 15 repetitions for each upper and lower body muscle group and came from participants' own body weight or with light free weights. Intensity was set at 50-70% of 1-repetition maximum (1-RM), with 90 to 120 seconds of rest between sets, consistent with recommended guidelines [18]. Balance training was also based on functional tasks required by older adults. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Over the 24-month intervention, progression was guaranteed every 6 weeks through adjustments of duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises). Exercise modifications such as reduced duration, number of repetitions, or use of an exercise auxiliary were recommended by the group instructor when needed.

### *Anthropometrics*

Stature was measured using a standard stadiometer to 0.1 cm in the upright position, with the participants' back square against the wall and eyes looking straight ahead, without shoes. BM was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with precision to the nearest 100 grams, with participants barefoot and in light clothing. Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest at minimal respiration, and hip circumference was taken in a horizontal plane along the pubic symphysis. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated by standard methods.

### *Haemodynamics*

Resting BP was measured using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany) in the seated position, after 5 minutes of rest; the measurements were taken three times with 2-minutes intervals [18] and the mean value

of the 2 nearest measures was used to calculate the systolic (SBP) and diastolic (DBP) BP.

Trained nurses collected venous blood in the morning after 12 hours of fasting. Glycaemia, HbA1c, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) were determined by standard methods in an accredited laboratory.

### *Health history*

The participants' health history was obtained by questionnaire, and data included age, gender, education level, living situation, exercise practice, smoking status and the presence of several conditions including heart disease, hypertension, stroke, diabetes, dyslipidaemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, or other comorbidities. Medication type and dosage were assessed by a detailed questionnaire with visual confirmation of prescription drugs, which was recorded by the staff of the present study.

### *Cardiorespiratory fitness*

Cardiorespiratory fitness (CRF) was evaluated using the six-minute walk test (6MWT) performed on a flat 50-metre rectangular course, marked off in 5-metre segments [19]. The 6MWTs were performed in the morning, between 8 and 10 a.m., to minimize intraday variability, temperature effects, and biological rhythms. Participants were instructed to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue their usual medication. Recommended reasons for immediately stopping the 6MWT include the following: chest pain, intolerable dyspnoea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

### *Statistical analysis*

Descriptive analysis was carried out with measures of central tendency and dispersion; baseline participants' characteristics were compared using means and standard deviations (M ± SD) for the following variables: age, BM, WC, BMI, WHR, SBP, DBP, TC, HDL-C, LDL-C, TG, glycaemia, HbA1c and 6MWT. Kolmogorov-Smirnov and Levene's tests were performed to verify, for all continuous variables, normality of the distribution and the homoscedasticity. One-way ANOVA and analysis of covariance (ANCOVA) were used for comparisons between groups, controlling for the effect of age, sex and number of comorbidities at baseline. A two-way ANOVA for repeated measures was performed in factor groups (MEX, MET and MEXMET) for analysis within groups and differences between groups after 24-month intervention were evaluated with analysis of covariance (ANCOVA), adjusting for baseline score values, age and sex and with pairwise comparisons. Responsiveness was used to detect the magnitude of differences between groups at baseline and after 24-month intervention. It was measured with Hedges' g effect size and the respective 95% confidence intervals, providing a measure of the effect size weighted according to the different relative sample size within our study population [20]. Standardized effect sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80) [21]. The equation $\Delta$% [(Post-pre follow-up/Total Test) x 100] was used to determine the percentage difference across all variables analysed from baseline to the final 24-month evaluation within each group. All analyses were performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 22, at the 95% level of significance.

## RESULTS

### *Baseline characteristics*

The most prevalent comorbidities were hypertension (93%), central obesity (74%), and hypertriglyceridaemia (64%). At baseline (Table 1), the 3 therapy groups did not show significant differences ($P > 0.05$), except for sex ($P = 0.006$), age ($P = 0.044$), BM ($P = 0.005$), WHR ($P = 0.027$), TC ($P = 0.001$), and LDL-C ($P < 0.001$). The MET group had more males, was younger, heavier and had lower TC than the other groups ($P < 0.05$); the MET group had higher WHR than the MEXMET group (0.04 cm; $P = 0.010$). After controlling for the effect of sex, age and number of comorbidities all these differences disappeared. Differences between groups presented small to moderate effect sizes in all variables, except for the large effect size in LDL-C in the MEX group comparatively to the MET group.

### *Evaluation of differences between groups*

At 24-month evaluation (Tables 2 and 3) several significant differences were found ($P < 0.05$). Differences between MEX and MET groups presented large effect sizes in BM, WC, WHR, SBP, DBP and CRF and a moderate effect size in BMI and glycaemia. Additionally, differences between MEXMET and MET revealed a moderate effect size in BMI, SBP and DBP and a large effect size in BM, WC, WHR and CRF.

The MEX group showed decreased BM (3.6%), WC (4.2%), BMI (2.7%), SBP (11.1%), DBP (11.3%), TG (21.2%), and glycaemia (12.3%), and increased CRF (17.7%). Conversely, the MET group showed increased WC (2.2%), WHR (3.1%), BMI (1.6%), and SBP (5.4%). The MEXMET group exhibited reductions in BM (1.1%), WC (2.4%), BMI (1.4%), and DBP (8.2%), and increased SBP (0.7%), glycaemia (6.7%), and CRF (18.0%). All differences between groups at 24 months were maintained after controlling for the effects of sex, age and baseline score values, except for TC and LDL-C.

## DISCUSSION

The main finding of this longitudinal study of older adults with T2D and comorbidities in the early stage of the disease (mean HbA1c percentage < 7.5%) is that MEX was the most successful and effective therapy to reduce cardiovascular risk, demonstrating the relative/single value of exercise as a multifactorial intervention. These results are consistent with previous lifestyle interventions [9–11],

**TABLE 1.** Baseline characteristics of participants.

| Variables | Total (N=284) | MEX (n=59) | MET (n=30) | MEXMET (n=195) | Group Effect *P* Values | Between-group differences (95% CI) *P* Value | Group Effect Adjusted *P* Values | Effect Size | Confidence Interval 95% |
|---|---|---|---|---|---|---|---|---|---|
| **Male, n** | 97 | 17 | 18 | 62 | 0.006* | | | | |
| MEX vs. MET | | | | | | 0.3 (0.1 to 0.6); 0.008 * | | | |
| MEXMET vs. MET | | | | | | 0.3 (0.1 to 0.5); 0.003* | | | |
| MEX vs. MEXMET | | | | | | 0.0 (-0.1 to 0.2); 0.959 | | | |
| **Age, years** | 70.6 (6.1) | 71.4 (6.4) | 68.1 (4.3) | 70.7 (6.1) | 0.044* | | | | |
| MEX vs. MET | | | | | | 3.3 (0.1 to 6.5); 0.042* | | -0.570 | -1.018- -0.123 |
| MEXMET vs. MET | | | | | | 2.4 (0.1 to 5.3); 0.042* | | -0.441 | -0.827- -0.054 |
| MEX vs. MEXMET | | | | | | 0.6 (-1.5 to 2.7); 0.854 | | -0.113 | -0.405-0.178 |
| **Comorbid disease** | 1.79 (1.3) | 1.9 (1.3) | 2.2 (1.5) | 1.7 (1.3) | 0.070 | | | | |
| MEX vs. MET | | | | | | -0.3 (-1.0 to 0.4); 0.669 | | 0.219 | -0.222-0.660 |
| MEXMET vs. MET | | | | | | -0.6 (-1.1 to 0.0); 0.062 | | 0.377 | -0.009-0.763 |
| MEX vs. MEXMET | | | | | | 0.3 (-0.2 to 0.7); 0.451 | | -0.154 | -0.445-0.138 |
| **Body mass, kg** | 77.5(13.5) | 77.4(13.0) | 84.9(12.8) | 76.4(13.5) | 0.005* | | 0.743 | | |
| MEX vs. MET | | | | | | -7.5 (-14.6 to -0.4); 0.033* | | 0.580 | 0.132-1.028 |
| MEXMET vs. MET | | | | | | -8.6 (-14.3 to -2.8); 0.001* | | 0.634 | 0.245-1.023 |
| MEX vs. MEXMET | | | | | | 1.1 (-3.5 to 5.6); 0.925 | | -0.075 | -0.366-0.217 |
| **Waist circumference, cm** | 94.9(10.1) | 94.5 (8.7) | 98.7(10.2) | 94.4(10.4) | 0.091 | | 0.392 | | |
| MEX vs. MET | | | | | | -4.2 (-9.5 to 1.1); 0.166 | | 0.455 | 0.011-0.900 |
| MEXMET vs. MET | | | | | | -4.3 (-8.6 to 0.1); 0.054 | | 0.414 | 0.028-0.801 |
| MEX vs. MEXMET | | | | | | 0.1 (-3.4 to 3.5); 1.000 | | -0.010 | -0.301-0.281 |
| **BMI, kg/m$^2$** | 30.0 (4.6) | 30.1 (4.3) | 30.4 (4.2) | 30.0 (4.7) | 0.805 | | 0.309 | | |
| MEX vs. MET | | | | | | -0.4 (-2.8 to 2.0); 0.976 | | 0.070 | -0.369-0.510 |
| MEXMET vs. MET | | | | | | -0.6 (-2.6 to 1.4); 0.866 | | 0.086 | -0.298-0.471 |
| MEX vs. MEXMET | | | | | | 0.2 (-1.4 to 1.8); 0.987 | | -0.022 | -0.313-0.270 |
| **Waist-to-hip ratio** | 0.91(0.07) | 0.91(0.07) | 0.95(0.08) | 0.91(0.07) | 0.027* | | 0.684 | | |
| MEX vs. MET | | | | | | -0.03 (-0.07 to 0.04); 0.099 | | 0.544 | 0.098-0.991 |
| MEXMET vs. MET | | | | | | -0.04 (0.01 to 0.06); 0.010* | | 0.560 | 0.173-0.948 |
| MEX vs. MEXMET | | | | | | 0.04 (-0.02 to 0.03); 0.966 | | 0.000 | -0.291-0.291 |
| **Systolic BP, mmHg** | 140 (18) | 140 (20) | 139 (15) | 141 (19) | 0.911 | | 0.339 | | |
| MEX vs. MET | | | | | | 1.3 (-8.3 to 10.9); 0.982 | | -0.054 | -0.494-0.385 |
| MEXMET vs. MET | | | | | | 1.5 (-6.3 to 9.3); 0.952 | | -0.108 | -0.492-0.277 |
| MEX vs. MEXMET | | | | | | -0.2 (-6.4 to 6.0); 1.000 | | 0.052 | -0.239-0.343 |
| **Diastolic BP, mmHg** | 79 (11) | 79 (13) | 77 (10) | 79 (11) | 0.673 | | 0.505 | | |
| MEX vs. MET | | | | | | 1.9 (-3.9 to 7.8); 0.811 | | -0.166 | -0.606-0.275 |
| MEXMET vs. MET | | | | | | 1.9 (-2.9 to 6.6); 0.718 | | -0.184 | -0.569-0.201 |
| MEX vs. MEXMET | | | | | | 0.1 (-3.7 to 3.9); 1.000 | | 0.000 | -0.291-0.291 |
| **Total cholesterol, mg/dL** | 182 (35) | 199 (37) | 169 (26) | 180 (34) | 0.001** | | 0.084 | | |
| MEX vs. MET | | | | | | 30.6 (9.6 to 51.6); 0.002* | | 0.889 | 0.431-1.348 |
| MEXMET vs. MET | | | | | | 11.4 (-4.5 to 27.3); 0.237 | | -0.333 | -0.718-0.053 |
| MEX vs. MEXMET | | | | | | 19.2 (5.2 to 33.2); 0.003* | | -0.547 | -0.842- -0.252 |
| **HDL-cholesterol, mg/dL** | 49 (17) | 48 (9) | 45 (10) | 50 (19) | 0.334 | | 0.663 | | |
| MEX vs. MET | | | | | | 2.9 (-7.8 to 13.7); 0.883 | | 0.321 | 0.121-0.763 |
| MEXMET vs. MET | | | | | | 5.1 (-2.9 to 13.1); 0.330 | | -0.276 | -0.662-0.109 |
| MEX vs. MEXMET | | | | | | -2.2 (-9.5 to 5.1); 0.856 | | 0.116 | -0.175-0.408 |

**TABLE 1.** Baseline characteristics of participants (continued).

| Variables | Total (N=284) | MEX (n=59) | MET (n=30) | MEXMET (n=195) | Group Effect *P* Values | Between-group differences (95% CI) *P* Value | Group Effect Adjusted *P* Values | Effect Size | Confidence Interval 95% |
|---|---|---|---|---|---|---|---|---|---|
| **LDL-cholesterol, mg/dL** | | | 97 (26) | 106 (31) | <0.001** | | 0.055 | | |
| MEX vs. MET | | | | | | 29.9 (9.9 to 49.9); 0.001* | | 0.973 | 0.510- 1.435 |
| MEXMET vs. MET | | | | | | 8.9 (-6.1 to 23.9); 0.395 | | -0.296 | -0.681-0.089 |
| MEX vs. MEXMET | | | | | | 21.1 (7.7 to 34.4); 0.001* | | -0.667 | -0.964-0.370 |
| **Triglycerides, mg/dL** | | | 131 (70) | 130 (58) | 0.941 | | 0.443 | | |
| MEX vs. MET | | | | | | -4.9 (-42.7 to 32.9); 0.985 | | 0.082 | -0.358-0.522 |
| MEXMET vs. MET | | | | | | -1.5 (-29.9 to 27.0); 0.999 | | 0.017 | -0.368-0.401 |
| MEX vs. MEXMET | | | | | | -3.4 (-28.6 to 21.8); 0.983 | | 0.070 | -0.222-0.361 |
| **Glycaemia, mg/dL** | | | 136 (47) | 128 (33) | 0.547 | | 0.079 | | |
| MEX vs. MET | | | | | | -8.3 (-29.1 to 12.5); 0.711 | | 0.229 | -0.212-0.670 |
| MEXMET vs. MET | | | | | | -7.6 (-23.6 to 8.3); 0.578 | | 0.228 | -0.157-0.613 |
| MEX vs. MEXMET | | | | | | -0.7 (-14.8 to 13.5); 0.999 | | 0.000 | -0.291-0.291 |
| **HbA1c, %**<br>**HbA1c, mmol/mol** | | | 6.81 (1.4)<br>51 (15.3) | 6.67 (1.0)<br>49 (10.9) | 0.800 | | 0.913 | | |
| MEX vs. MET | | | | | | -0.3 (-1.3 to 0.7); 0.878 | | 0.273 | -0.169-0.714 |
| MEXMET vs. MET | | | | | | -0.1 (-0.7 to 0.5); 0.943 | | 0.132 | -0.253-0.517 |
| MEX vs. MEXMET | | | | | | -0.2 (-0.9 to 0.6); 0.941 | | 0.138 | -0.153-0.430 |
| **6-min walk distance, m** | | | 427 (76) | 447 (113) | 0.430 | | 0.248 | | |
| MEX vs. MET | | | | | | 2.4 (-57.7 to 62.4); 1.000 | | -0.018 | -9.457-0.422 |
| MEXMET vs. MET | | | | | | 20.4 (-28.6 to 69.5); 0.682 | | -0.184 | -0.568-0.201 |
| MEX vs. MEXMET | | | | | | -18.1 (-57.1 to 20.9); 0.604 | | 0.155 | -0.137-0.446 |

Data are expressed as mean (SD)* Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$). [a] Differences between groups adjusting for age, sex and comorbidity number.

which produced long-term benefits for BM, CRF, CVD risk factors, diabetes management, and ultimately, morbidity and mortality. However, the independent effect of exercise has been difficult to determine because the lifestyle interventions usually combine exercise with caloric restrictions [15], with pharmacological treatment [13], or with another form of intervention [22]. Nevertheless, our results reinforce the importance of the independent effect of exercise training in the enhancement of glucose control, presenting similar effects as with intensive metformin treatment [23].

The majority of patients with T2D are overweight or obese (6), but weight loss has been shown to improve glycaemic control, diminishing the risk of progression of T2D in overweight and obese older adults [24,25]. In fact, even decreases as small as 1 kg or 1% of the BM can benefit glycaemic control, morbidity, and mortalit [26], which means that the reductions in BM, WC, and BMI observed particularly in our MEX group, and to a lesser extent in the MEXMET group, are surely important to decrease the risk of aggravated morbidity and mortality. On the other hand, pharmacological treatments, including some oral antidiabetic agents, are usually associated with BM gains, which is considered a negative side effect [5]. In this context, metformin therapy is generally considered the first oral medication choice because of the favourable effects on BM, low risk of hypoglycaemia, and low cost [7]. However, findings from the present study showed that MET therapy increased BM, WC and BMI after the 24-month intervention, indicating that long-term effects of metformin may involve pro-inflammatory anthropometric evolution that still requires elucidation. Moreover, the effects of metformin on all-cause mortality, cardiovascular mortality or incidences of myocardial infarction, stroke and heart failure have been studied in patients aged less than 30 years, which limits the generalization of the conclusions to older adults with multimorbidity [27].

**TABLE 2.** Comparisons between group therapy after 24-month intervention

| Variables | MEX (n= 47) | MET (n= 29) | MEXMET (n=141) | Group Effect *P* Value | Group Effect Adjusted *P* Value | Between group differences (95% CI) *P* Value | Effect Size | Confidence Intervals 95% |
|---|---|---|---|---|---|---|---|---|
| **Body mass, kg** | 75.1 (13.6) | 86.0 (12.7) | 75.6 (12.3) | 0.001** | 0.020* | | | |
| MEX vs. MET | | | | | | -1.9 (-3.2 to -0.6); 0.006* | 0.819 | 0.363-1.275 |
| MEXMET vs. MET | | | | | | -1.3 (-2.4 to -0.2); 0.027* | 0.842 | 0.450-1.234 |
| MEX vs. MEXMET | | | | | | -0.7 (-1.6 to 0.3); 0.189 | 0.040 | -0.252-0.331 |
| **Waist circumference, cm** | 90.7 (9.7) | 100.9 (9.4) | 92.2 (9.7) | 0.002** | <0.001** | | | |
| MEX vs. MET | | | | | | -4.8 (-7.0 to -2.5); <0.001** | 1.062 | 0.596-1.529 |
| MEXMET vs. MET | | | | | | -4.2 (-6.1 to -2.4); <0.001** | 0.900 | 0.507-1.294 |
| MEX vs. MEXMET | | | | | | -0.5 (-2.1 to 1.1); 0.527 | 0.155 | -0.137-0.446 |
| **BMI, kg/m2** | 29.3 (4.7) | 30.9 (4.3) | 29.6 (4.3) | 0.503 | 0.014* | | | |
| MEX vs. MET | | | | | | -0.8 (-1.3 to 0.3); 0.004* | 0.350 | -0.092-0.793 |
| MEXMET vs. MET | | | | | | -0.5 (-0.9 to -0.1); 0.026* | 0.302 | -0.083-0.688 |
| MEX vs. MEXMET | | | | | | -0. 3(-0.7 to 0.1); 0.134 | 0.068 | -0.223-0.360 |
| **Waist-to-hip ratio** | 0.90 (0.07) | 0.98 (0.08) | 0.91 (0.07) | 0.002** | 0.001* | | | |
| MEX vs. MET | | | | | | -0.04 (-0.06 to -0.01); 0.001* | 1.098 | 0.621-1.556 |
| MEXMET vs. MET | | | | | | -0.03 (-0.05 to -0.01); <0.001** | 0.981 | 0.586-1.376 |
| MEX vs. MEXMET | | | | | | -0.00 (-0.02 to 0.01); 0.651 | 0.143 | -0.149-0.434 |
| **Systolic BP, mmHg** | 126 (15) | 147 (14) | 129 (14) | 0.011* | <0.001** | | | |
| MEX vs. MET | | | | | | -22.2 (-28.6 to -15.9); <0.001** | 1.431 | 0.944-1.918 |
| MEXMET vs. MET | | | | | | -18.4 (-24.0 to – 13.6); <0.001** | 0.300 | -0.085-0.686 |
| MEX vs. MEXMET | | | | | | -3.4 (-8.0 to 1.2); 0.147 | 0.211 | -0.081-0.503 |
| **Diastolic BP, mmHg** | 71 (7) | 79 (11) | 73 (10) | 0.439 | 0.007* | | | |
| MEX vs. MET | | | | | | -7.0 (-11.4 to -2.7); 0.002* | 0.936 | 0.476-1.397 |
| MEXMET vs. MET | | | | | | -4.7 (-8.3 to -1.1); 0.011* | 0.592 | 0.204-0.980 |
| MEX vs. MEXMET | | | | | | -2.4 (-5.5 to 0.8); 0.144 | 0.213 | -0.079-0.505 |
| **Total cholesterol, mg/dL** | 189 (41) | 156 (50) | 177 (39) | 0.001*** | 0.602 | | | |
| MEX vs. MET | | | | | | 10.7 (-12.3 to 33.7); 0.360 | 0.747 | 0.294-1.200 |
| MEXMET vs. MET | | | | | | 9.5 (-9.8 to 28.8); 0.333 | 0.517 | 0.130-0.905 |
| MEX vs. MEXMET | | | | | | 1.2 (-13.7 to 16.1); 0.874 | 0.304 | 0.012-0.596 |
| **HDL-cholesterol, mg/dL** | 49 (10) | 43 (7) | 50 (11) | 0.110 | 0.882 | | | |
| MEX vs. MET | | | | | | 1.3 (-3.8 to 6.4); 0.621 | 0.659 | 0.209-1.109 |
| MEXMET vs. MET | | | | | | 0.8 (-3.7 to 5.2); 0.735 | 0.663 | 0.273-1.052 |
| MEX vs. MEXMET | | | | | | 0.5 (-2.8 to 3.8); 0.754 | 0.093 | -0.199-0.384 |
| **LDL-cholesterol, mg/dL** | 121 (36) | 102 (23) | 102 (32) | 0.005* | 0.418 | | | |
| MEX vs. MET | | | | | | -4.8 (-22.4 to 12.8); 0.592 | 0.589 | 0.141-1.037 |
| MEXMET vs. MET | | | | | | -8.9 (-23.6 to 5.8); 0.231 | 0.000 | -0.384-0.384 |
| MEX vs. MEXMET | | | | | | 4.1 (-7.5to 15.8); 0.485 | -0.576 | -0.872—0.281 |
| **Triglycerides, mg/dL** | 104 (44) | 130 (99) | 133 (74) | 0.441 | 0.100 | | | |
| MEX vs. MET | | | | | | -26.6 (-60.1 to 6.9); 0.118 | 0.385 | -0.058-0.828 |
| MEXMET vs. MET | | | | | | -3.6 (-32.5 to 25.3); 0.805 | 0.039 | -0.423-0.346 |
| MEX vs. MEXMET | | | | | | -23.0 (-44.7 to -1.3); 0.038* | 0.425 | 0.131-0.718 |
| **Glycaemia, mg/dL** | 114 (27) | 142 (54) | 137 (39) | 0.090 | 0.008* | | | |
| MEX vs. MET | | | | | | -19.6 (-37.6 to -1.6); 0.033* | 0.733 | 0.281-1.186 |
| MEXMET vs. MET | | | | | | 0.0 (-15.0 to 15.0); 0.995 | 0.121 | -0.263-0.506 |
| MEX vs. MEXMET | | | | | | -19.7 (-32.2 to -7.2); 0.002* | 0.629 | 0.332-0.925 |
| **HbA1c, %**<br>**HbA1c, mmol/mol** | 6.21 (0.4)<br>44 (4.4) | 6.76 (1.1)<br>50 (12.0) | 6.75 (0.9)<br>50 (9.8) | 0.521 | 0.179 | | | |
| MEX vs. MET | | | | | | -0.5 (-1.0 to 0.1); 0.114 | 0.770 | 0.316-1.224 |
| MEXMET vs. MET | | | | | | -0.0 (-0.4 to 0.4); 0.877 | 0.011 | -0.374-0.395 |
| MEX vs. MEXMET | | | | | | -0.4 (-0.9 to 0.0); 0.068 | 0.664 | 0.368-0.961 |
| **6-min walk distance, m** | 521 (83) | 426 (62) | 545 (110) | 0.004** | <0.001** | | | |
| MEX vs. MET | | | | | | 131.9 (87.8 to 175.9); <0.001** | 1.240 | 0.764-1.715 |
| MEXMET vs. MET | | | | | | 144.4 (107.9to 180.6); <0.001** | 1.133 | 0.735-1.532 |
| MEX vs. MEXMET | | | | | | -12.5 (-44.5to 19.5); 0.440 | 0.230 | -0.062-0.522 |

Data are expressed as mean (SD) * Differences between evaluations (P ≤ 0.05). ** Differences between evaluations (P ≤ 0.001). [a] Differences between groups adjusting for age, sex and baseline score values.

**TABLE 3.** Percentage difference within groups from baseline to final 24 month intervention.

| Variables | Δ MEX % | Within Group Effect *P* Value | Δ MET % | Within Group Effect *P* Value | Δ MEXMET % | Within Group Effect *P* Value |
|---|---|---|---|---|---|---|
| Body mass, kg | -3.6 | 0.008* | 1.3 | 0.247 | -1.1 | 0.005* |
| Waist circumference, cm | -4.2 | 0.004* | 2.2 | 0.021* | -2.4 | <0.001** |
| BMI, kg/m2 | -2.7 | 0.007* | 1.6 | 0.048* | -1.4 | 0.016* |
| Waist-to-hip ratio | -1.1 | 0.343 | 3.1 | 0.005* | 0 | 0.246 |
| Systolic BP, mmHg | -11.1 | <0.001** | 5.4 | 0.001* | 0.7 | <0.001** |
| Diastolic BP, mmHg | -11.3 | <0.001** | 2.5 | 0.416 | -8.2 | <0.001** |
| Total cholesterol, mg/dL | 3.7 | 0.196 | -8.3 | 0.489 | -1.7 | 0.537 |
| HDL-cholesterol, mg/dL | 0 | 0.212 | -11.6 | 0.492 | 0 | 0.214 |
| LDL-cholesterol, mg/dL | -5.0 | 0.338 | 4.9 | 0.579 | -3.9 | 0.328 |
| Triglycerides, mg/dL | -21.2 | 0.019* | -0.8 | 0.763 | 2.3 | 0.547 |
| Glycaemia, mg/dL | -12.3 | 0.003* | 4.2 | 0.769 | 6.7 | 0.017* |
| HbA1c, % | -5.3 | 0.194 | -0.7 | 0.908 | 0.01 | 0.579 |
| 6-min walk distance, m | 17.7 | <0.001** | -0.2 | 0.716 | 18.0 | <0.001** |

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).

Hypertensive adults with T2D obtain benefits by reducing BP [28,29]. In fact, there is a strong linear association between BP and incidence of adverse outcomes for stroke, and a J-shaped curve for mortality and cardiac events [7]. Consequently, pharmacological therapy has been recommended in individuals with diabetes for BP above 140/90 mmHg, along with non-pharmacological therapy. Nevertheless, exercise seems to have a significant beneficial effect for lowering BP in adults, including those with hypertension, on average by 2–5 mmHg in SBP and 1–4 mmHg in DBP [5]. In the present study, after 24 months of intervention, the MEX group showed surprising decreases of 14 mmHg in SBP and 8 mmHg in DBP, while the MET group showed an increase of 8 mmHg in SBP, and the MEXMET group showed an increase of 1 mmHg in SBP and decrease of 6 mmHg in DBP. These results illustrate the importance of exercising and also seem to indicate that in the MEXMET group the pharmacological treatment mitigated the positive effects of exercise on BP. This finding may be explained by the molecular effect of metformin on the T2D cardiovascular mechanism [30], since the relevance of copper metabolism in T2D has been demonstrated [31]. Furthermore, copper sequestration has been shown to improve diabetes-related cardiovascular disease [32], which might not occur with the metal-binding properties of metformin in copper-ion transport or exchange [30]. Contrarily, exercise has shown an anti-inflammatory effect, by acting through several mechanisms involving inhibition of the pro-inflammatory and stimulation of the anti-inflammatory pathway [33].

The MEXMET group surprisingly showed an increase in glycaemia by 6.7%, which may be explained by lifestyle choices; that is, since the participants are taking metformin to control the diabetes they expect full benefits from the medicine, without limiting other risk behaviours. Contrarily, MEX therapy diminished glycaemia by 12.3%, highlighting the clinical benefits of exercise as the best strategy for glycaemic control, minimizing the effects on an aggregate composite of macro-microvascular and nonvascular end points, similar to what is produced with an intensive pharmaceutical intervention [25].

The lipid profile is within recommended values not only at baseline but also at 24-month evaluation in all groups. Nevertheless, differences between groups disappeared after controlling for the covariates of age, sex and baseline score values, revealing that baseline score differences influenced the 24-month evaluation in all groups, except for TG in the MEX and MEXMET groups. These differences occurred because the MEX group suffered an interesting reduction of 21% in TG, from 126 mg/dL to 104 mg/dL, in contrast to the 2% increase in the MEXMET group. TG has emerged as a significant risk factor [34] which could be of high importance. In fact, assuming that 1-mmol/L (18.02 mg/dL) increases in TG imply an increase of 13% in CVDs and 12% in all-cause mortality [35], our decrease of 1.22 mmol/L (22 mg/dL) in the MEX group would represent a decrease of respectively 16% and 15%, which highlights the clinical significance of exercise therapy [36].

Finally, the results of the present study revealed very promising gains of 18% in CRF in both MEX and MEXMET groups. An interesting study [37] showed that MET decreased the peak $VO_2$ and the ability to work, unlike exercise, which not only improved the CRF when used alone, but also cancelled the negative effects of MET in the MEXMET group. In fact, these conclusions are in line with our results, and the physiological mechanisms underlying aerobic exercise, including cardiac output and the arteriovenous oxygen difference,

may explain the unchanged CRF in the MET and the improvements achieved by the MEXMET group in our intervention. Importantly, several studies have reported an inverse relationship between CRF and mortality risk in the context of T2D with and without additional risk factors [38–41].

This longitudinal interventional study has several strengths including a strong methodological design, a large community sample exclusively of older adults with T2D, long-term supervised exercise training, pharmacologic treatment, and inclusion of several confounders relevant to older age and diabetes, such as sex and number of comorbidities. The major limitations of this study are the different sample sizes within each group and the lack of control of nutritional intake as a potential confounder. Additionally, the retrospective selection of the participants may also introduce a bias in the obtained results as the treatment decision might have been related to differences in the enrolled population.

Future studies should address different types, intensities and volumes of exercise that may lead to different results [42,43]. Additionally, a randomized controlled trial could explore whether these 3 treatment therapies may lead to greater and sustained multifactorial cardiovascular risk benefits, particularly in the lipid profile in the high-risk group, such as those with unstable diabetes.

Despite the limitations, regular exercise emerged as important therapy to manage T2D in older adults, reducing overall CVD risk comparatively to a major reduction in one risk factor as occurs with pharmacological treatment, because CVD risk factors tend to cluster, leading to a deleterious additive/synergistic cumulative effect [7]. This cluster of risk factors has relevant clinical significance, explaining 59% of the CVD [43].

These results have important clinical implications, demonstrating that long-term MEX should be widely adopted into standard care and communities for older adults with T2D, particularly the elderly with multimorbidity, as highly effective therapy to improve the multifactorial cardiovascular profile and attenuate the negative effects of pharmacological therapy.

## CONCLUSIONS

MEX was the most effective therapy decreasing multi-cardiovascular risk factors in the early stage of T2D in older adults with multimorbidity and attenuated the adverse effects of pharmacological therapy in MEXMET treatment.

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