Metformin modifies the exercise training effects on risk factors for cardiovascular disease in impaired glucose tolerant adults

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Abstract

Impaired glucose tolerant (IGT) adults are at elevated risk for cardiovascular disease (CVD). Exercise or metformin reduce CVD risk, but the efficacy of combining treatments is unclear. To determine the effects of exercise training plus metformin, compared to each treatment alone, on CVD risk factors in IGT adults. Subjects were assigned to: placebo (P), metformin (M), exercise plus placebo (EP), or exercise plus metformin (EM) (8/group). In a double-blind design, P or 2000mg/d of M were administered for 12 weeks and half performed aerobic and resistance training 3 days/week for approximately 60 minutes/day at 70% pre-training heart rate peak. Outcomes included: adiposity, blood pressure (BP), lipids and high sensitivity C-reactive protein (hs-CRP). Z-scores were calculated to determine metabolic syndrome severity. M and EM, but not EP, decreased body weight compared to P ($p < 0.05$). M and EP lowered systolic BP by 6% ($p < 0.05$), diastolic BP by 6% ($p < 0.05$), and hs-CRP by 20% (M: trend $p = 0.06$; EP: $p < 0.05$) compared to P. Treatments raised HDL-cholesterol ($p < 0.05$; EM: trend $p = 0.06$) compared to P and lowered triacyglcerol ($p < 0.05$) and metabolic syndrome Z-score compared to baseline (EP; trend $p = 0.07$ and EM or M; $p < 0.05$). Although exercise and/or metformin improve some CVD risk factors, only training or metformin alone lowered hs-CRP and BP. Thus, metformin may attenuate the effects of training on some CVD risk factors and metabolic syndrome severity in IGT adults.

Keywords

Prediabetes; Metabolic Syndrome; Type 2 Diabetes; Obesity; Hypertension

Introduction

Individuals with impaired glucose tolerance (IGT) are at elevated risk for cardiovascular disease (CVD) (1, 2) and approximately half of these individuals have metabolic syndrome (i.e. hypertensive, hyperglycemic, and dyslipidemic) (3). CVD risk is largely explained by

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insulin resistance and excess body weight (4, 5). Treatments that raise insulin sensitivity or lower body weight may lower CVD risk in individuals with IGT.

The mechanisms by which exercise lowers CVD risk likely involve increasing insulin sensitivity (6, 7, 8) and lowering circulating lipids (e.g. triacylglycerol, low-density lipoproteins, etc.), blood pressure, and C-reactive protein (9, 10, 11). Metformin treatment can also increase insulin sensitivity (12, 13) and additionally, reduces fasting hyperglycemia and body weight (14, 15). Because the actions of exercise and metformin are potentially additive, it has been suggested that individuals with IGT and at least 1 CVD risk factor (e.g. hypertension, elevated triacylglycerol, low HDL, fasting hyperglycemia, etc.) be considered for metformin treatment while participating in a regular exercise program (16). However, the interactions between exercise and metformin on CVD risk factors have not been systematically evaluated (17, 18). Adding to the uncertainty, we recently showed that metformin blunted the effects of training on insulin sensitivity in men and women with IGT (19). Since insulin resistance is believed to be a key underlying factor causing metabolic syndrome (formerly syndrome X), it is important to understand the effects of metformin on CVD risk after exercise training (20). Therefore, the purpose of this study was to determine the effects of combining metformin with exercise training, compared to either treatment alone, on reducing CVD risk factors in men and women with IGT. Given the opposing effects on insulin sensitivity we observed in this same study group (19), we hypothesized that the combined treatment would oppose the reduction in CVD risk compared to either treatment alone.

Methods

Overview

The effects of exercise training, metformin, or the combined treatment on cardiovascular disease (CVD) risk factors were compared in 32 otherwise healthy men and women with impaired glucose tolerance (IGT). Using a double-blind, placebo-controlled design, individuals were tested before and after 12 weeks of placebo (P), metformin (M), exercise training plus placebo (EP) or exercise training plus metformin (EM). Outcome measures included body weight, waist circumference, blood pressure, and concentrations of blood lipids, and high sensitivity C-reactive protein (hs-CRP) as well as metabolic syndrome severity.

Subjects

These subjects were the same individuals who served as the study population in our prior study on whole-body and hepatic insulin sensitivity (19). Subjects were recruited via newspaper advertisements and flyers posted in the local community. Individuals (see Table 1) were non-smoking, weight stable (<5% weight change over last 3 months) and free of CVD or type 2 diabetes. All subjects had impaired glucose tolerance (IGT). Individuals who were using medications to manage blood pressure (M = 1; EP = 1; EM = 3) or cholesterol (M = 1; EP = 1; EM = 1) were enrolled and continued treatment throughout the study. Subjects were excluded from the study if they had any contraindications to metformin use (e.g. respiratory disease, heart failure, renal/hepatic disease). All subjects were verbally

briefed about the study and signed informed consent documents approved by the Institutional Review Board at the University of Massachusetts Amherst.

Screening

A 75 gram oral glucose tolerance test (OGTT) was used to screen individuals for IGT after a minimum 5 hour fast. Individuals with glucose concentrations between 7.8–11.1mM (140–199mg/dl) 120 minutes after consuming glucose met the criterion for IGT. Approximately half of the subjects with IGT also had impaired fasting glucose (IFG), i.e. fasting glucose concentrations between 5.5–6.9mM (100–125mg/dl). Most of the individuals in each treatment group (M = 6; EP = 7 and EM = 6) also met ATP III criteria for metabolic syndrome (21). Only 2 participants in the P group had metabolic syndrome. To minimize the potential for Type-1 and Type-2 errors, we restricted the presentation of results to the 3 treatment groups

Exercise testing

VO_2peak was used to characterize cardiorespiratory fitness, and 1-repetition max (1-RM) tests were performed to determine strength as previously described (19).

Metformin or placebo protocol

A member of the research group, blinded to the protocol, administered pills to the subjects. All subjects were instructed to take their pills with food to minimize potential side effects. Subjects started treatment with 500 mg/d of metformin. The dose was increased 500 mg/d each week until a standard clinical dose of 2000 mg/d was reached by week 4. This dose was maintained for the ensuing 8 weeks of the protocol.

Exercise training

Subjects underwent supervised exercise sessions 3 days/week for 60–75 minutes per session (approximately 190minutes/week total). Subjects cycled for 45 minutes at 70% of their pre-training heart rate peak 3days/week, and performed whole-body resistance exercise at 70% of the subject's 1-RM 2days/week. Subjects performed 2 sets of 12 repetitions for: chest press, latissimus pull down, leg press, bicep curl, triceps pushdown, and upright rows. Pedometers (Omron HJ112, Lake Forest, IL) were provided to all subjects and worn around the waistband for 7 consecutive days at week 0, 6 and 12. These data were averaged to characterize habitual ambulation. Habitual ambulation did not change in any group after the intervention, nor were there differences across groups (data not shown).

Body weight, composition & waist circumference

Body weight was recorded without shoes, to the nearest 0.1kg on a calibrated scale, every 2 weeks at consistent times of day. Subjects were weighed in the fasted state for the first and last measurements. As previously described (19) body fat and central fat (defined as fat mass in the region bounded by the last floating rib to the top of the iliac crest/total fat mass) were assessed by Dual-energy x-ray absorptiometry (DEXA; Lunar Prodigy, Madison, WI). Waist circumference (WC) was measured to the nearest 0.25 cm with a plastic tape measure in the standing position approximately 2 cm above the umbilicus.

Food intake

Food intake was assessed using 3-day food records at week 0, 6, and 12. Subjects selected 3 days of the week at the start of the study and the same 3 days of the week were used each time food intake was assessed. Results were averaged across the 3 days to generate a single value for energy intake at each time point. Participants were given verbal and written instructions to accurately record the types and quantities of all food and beverages consumed, including brand names and methods of food preparation. Food records were analyzed (by the same investigator S.C.) using a commercial software program (Fitday, El Segundo, California).

Blood pressure, lipids and high sensitivity-CRP

Subjects were provided isocaloric meals (~55% carbohydrate, 30% fat, and 15% protein multiplied by 1.3 activity factor) 24 hours before baseline and week 12 measurements. Energy intake was based on resting metabolic rate measurements for 30 minutes in the supine position by indirect calorimetry (SensorMedics 800, Yorba Linda, CA). On the day of testing, subjects reported to the laboratory after an overnight fast. Systolic (SBP) and diastolic (DBP) blood pressure was determined once in the left arm using an automated system (Mark of Fitness, Inc., Shrewsbury, NJ) after at least 5–10 minutes of quiet sitting. Next, indwelling catheters were placed in a superficial vein of the forearm and fasting blood samples were collected in 3 mL syringes. All vacutainers were kept on ice prior to blood collection. Blood samples for the analysis of glucose were transferred to vacutainers containing sodium fluoride to inhibit glycolysis. Blood samples for the analysis of total cholesterol (TC), high-density lipoproteins (HDL), and triacylglycerol (TAG) were collected in vacutainers containing the anticoagulant EDTA. Serum samples for the analysis of hs-CRP were collected in vacutainers containing a serum separator and allowed to clot for 15 minutes. Blood samples were centrifuged at room temperature for 10 minutes at 3000 RPM. Samples were immediately aliquoted and transferred to a –80°C freezer until analysis.

Biochemical analyses

Fasting Plasma glucose (FPG), TC and HDL concentrations were determined enzymatically (GL5 Analyzer, Analox Instruments, Lunenberg, MA). TAG concentrations were measured by colorimetric assay (Sigma Aldrich, St. Louis, MO). Serum hs-CRP concentrations were measured using high-sensitivity ELISA kit (Diagnostic Systems Laboratory, Webster, TX). Calculations: Mean arterial pressure (MAP) was calculated as: MAP = (2/3DBP) + (1/3SBP). The cardiac risk ratio (CRR) was calculated as TC divided by HDL (19). Low density lipoprotein (LDL) was calculated using the Friedwald equation (LDL = TC – HDL – (TAG* 0.2) (20). Metabolic syndrome Z-scores and ATP III criteria were calculated to describe the efficacy of each treatment on metabolic syndrome severity and total number of risk factors (18). Sex specific Z-scores were calculated as: male Z-score = [(40-HDL)/10.7] + [(TAG-150/88.5)] + [(FPG-100)/11.9] + [(WC-102/14.3] + [(MAP-100)/8.8], and female Z-score = [(50-HDL)/11.0] + [(TAG-150/88.5)] + [(FPG-100)/11.9] + [(WC-88)/13.6] + [(MAP-100)/8.8].

Statistical Analysis

Data were analyzed using the R statistical software package (version 2.4.0, The R foundation, Vienna, Austria, 2006). Baseline subject characteristics were measured across conditions by one-way analysis of variance (ANOVA). There was no statistical difference in any baseline value except DBP. Using baseline DBP as a co-variate did not affect the response to the treatments. All other condition means were analyzed before and after the intervention using 2-way (condition by test) repeated measures ANOVA. Because baseline hs-CRP concentrations were not normally distributed, the data were log transformed for statistical analysis. When there was a significant condition × test interaction, Tukey's Post hoc analysis was used to detect differences across conditions. Paired t-tests were used to assess pre- to post differences within a condition, including caloric intake, metabolic syndrome Z-score and ATP III score. McNemar's test was used to assess metabolic syndrome prevalence (i.e. yes/no) after each treatment (22). Pearson's correlation was used to examine relationships between weight loss, cardiorespiratory fitness, CVD risk factors and insulin sensitivity (19). Significant differences were accepted as α 0.05 and trends were reported as $0.05 < \alpha < 0.10$.

Results

The raw data for fitness, body composition, fasting glucose and insulin have been published previously (19). However, given the obvious relevance of those data to risk for CVD they are summarized here for clarity.

Cardiorespiratory fitness and strength

Exercise training plus metformin (EM) and exercise training plus placebo (EP) increased VO_2peak by 10–20% compared to baseline and strength by approximately 15% compared to baseline (19).

Weight change, body composition & food intake

Metformin (M) and EM, but not EP, decreased body weight more than P (p < 0.05; Figure 1a). EM and EP also lowered percent body fat (P = −0.8 ± 0.6%; M = 0.1 ± 0.5%; EP = −2.2 ± 0.8%; EM = −1.5 ± 0.7%) and central body fat (P = −0.6 ± 0.1%; M = −0.1 ± 0.6%; EP = −1.4 ± 0.5%; EM = −1.9 ± 0.6%) by similar amounts. Waist circumference was 2–3% lower after all 3 treatments compared to baseline (time effect: p < 0.01; Figure 1b), but was not different across groups. Caloric intake was decreased by approximately 15% from baseline for M (2107.3 ± 103.2 vs. 1819.8kcal; p < 0.05) and EM (2251.0 ± 135.7 vs. 1777.3 ± 130.2kcal; p < 0.05). Both EP (2292.0 ± 177.8 vs. 2149.2 ± 138.1kcal; p = 0.57) and P (1923.22 ± 135.6 vs. 1861.3 ±144.5; p = 0.69) had no effect on intake.

Fasting plasma glucose and insulin

Exercise training and/or metformin had no effect on fasting glucose concentrations (P = −0.1 ± 0.2mM; M = −0.2 ± 0.3mM; EP = 0.0 ± 0.3mM; EM = −0.4 ± 0.2mM). All 3 treatments lowered fasting insulin concentrations (P = 1.5 ± 2.3uU/ml; M = −5.2 ± 1.9 uU/ml; EP = −1.7 ± 0.7uU/ml; EM = −2.9 ± 1.5uU/ml), but there were no group differences.

Blood pressure

Compared to baseline, SBP and DBP increased with placebo (P; $p < 0.05$). M and EP lowered SBP ($p < 0.01$), but all 3 treatments lowered DBP compared to P ($p < 0.05$; Table 2). Both M and EP decreased MAP compared to P ($p < 0.05$; Table 2) but there was no change after EM.

High-sensitivity-C-reactive protein (hs-CRP)

EP and M, but not EM, lowered CRP by approximately 20% compared to P (EP: $p < 0.05$ and M: trend $p = 0.06$; Table 4).

Triacylglycerol (TAG) and Cholesterol

Compared to baseline, exercise and/or metformin lowered TAG by approximately 13% (time effect: $p < 0.05$; Table 3), but there were no group differences. All 3 treatments raised HDL cholesterol concentrations by 8–13% compared to P (M or EP; $p < 0.05$ and EM; trend $p = 0.06$; Table 3). Each treatment also decreased the cardiac risk ratio ($p < 0.05$; Table 3).

Metabolic syndrome severity and prevalence

Exercise training and/or metformin reduced the metabolic syndrome Z-score (i.e. severity) compared to baseline (EP; trend $p = 0.07$ and EM or M; $p < 0.05$; Figure 2a). Although each treatment reversed metabolic syndrome prevalence (M = 6 to 1; EP = 7 to 4; EM 6 to 3; $p < 0.05$; Figure 2b), only EP and M reduced ATP III criteria ($p < 0.05$) compared to baseline (Figure 2c).

Correlation Analysis

Increased cardiorespiratory fitness was significantly correlated with lower fasting glucose concentrations ($r = -0.38$; $p < 0.05$) but not with any other CVD risk factor. Weight loss was correlated with lower fasting insulin concentrations ($r = 0.40$; $p < 0.05$), caloric intake ($r = 0.46$; $p < 0.05$) and waist circumference ($r = 0.60$; $p < 0.05$). Reductions in TAG concentrations were correlated with increased insulin sensitivity ($r = -0.60$; $p < 0.05$). Lower hs-CRP concentrations were correlated with decreased systolic blood pressure ($r = 0.46$; $p < 0.05$).

Discussion

Metformin is not only used to treat type 2 diabetes, but it is also suggested to reduce cardiovascular disease (CVD) risk factors in adults with impaired glucose tolerance (IGT) (23). Previous work suggested that exercise with metformin reduced CVD risk factors more than the respective treatments alone (17, 18), however, we observed no additive effect of combining exercise with metformin to reduce CVD risk factors IGT men and women. There are several possible differences between studies that may explain this. First, previous work did not systematically compare the combined treatment to either exercise (17) or metformin alone (18), thereby limiting the ability to know the effectiveness of the combined treatment on CVD risk factors. Second, recommendations to increased physical activity were not structured or supervised (18). Third, differences between HIV infected patients and IGT

pathophysiology (17) complicate comparing previous work to ours. Last, dietary manipulations (i.e. low-fat diet) confound the ability to identify the independent effect of exercise with metformin on CVD risk factors (18). Consistent with our previous work (19), the current findings suggest that metformin may blunt some of the beneficial effects of training to lower systolic blood pressure, hs-CRP and metabolic syndrome criteria.

Weight loss (i.e. fat loss) is associated with lower CVD risk. Although exercise training with ad libitum food intake has mixed effects on weight loss (24, 25), combining it with metformin has been shown to cause greater weight loss (26, 27, 28). We found that combining metformin with exercise reduced body weight by approximately 4kg more than exercise alone, however, this was not different than metformin alone. Neither metformin, alone or with exercise, affected CVD risk factors (i.e. blood lipids, blood pressure, hs-CRP) more than exercise alone. Comparable reductions in central body fat between the exercise groups may explain the similar effects of exercise at reducing blood lipids (e.g. TAG and TC) (19). However, metformin decreased blood lipids equivalently to either exercise group without a change in central fat (measured by DEXA and waist circumference). Although we report reductions in waist circumferences with metformin in this study, more direct measures of central fat (e.g. MRI or CT scan) would be needed to confirm a true change in visceral fat., Despite no strong correlation between weight loss or waist circumference and CVD risk factors, we cannot rule out the possibility that fat loss explains at least some of the metformin group outcomes. In either case, these results suggest that each treatment has distinctive mechanisms for opposing CVD development.

Blood pressure is often lowered after exercise training (11), but the effects of metformin are less consistent (13, 29, 30, 31). We found that metformin yielded little added benefit to the effects of exercise training on lowering blood pressure and this outcome is consistent with other work (18). Our data suggest that the interaction of metformin with exercise training blunts reductions in systolic blood pressure, and these results may be related to changes in cardiorespiratory fitness. Although there were no statistical differences in VO$_2$peak between the exercise groups, the attenuated rise in VO$_2$peak (EM = 10% vs. EP = 20%) is worth considering since it is consistent with our previous work in healthy adults (32). The smaller rise in VO$_2$peak is likely a result of either alterations in mitochondrial adaptations or vascular blood flow. Although we did not directly measure endothelial function, we found that exercise training or metformin alone, but not the combined treatment, reduced the vascular inflammatory marker hs-CRP by approximately 20% compared to placebo. We observed a significant correlation between the change in hs-CRP and systolic blood pressure, suggesting that reduced systolic blood pressure may be related to decreased vascular inflammation. Interestingly, metformin alone reduced both systolic blood pressure and hs-CRP, but had no effect on VO$_2$peak compared to placebo. This result strengthens the hypothesis that there is a unique interaction between metformin and exercise on the aforementioned outcomes that could have opposing effects on cardiovascular health. From this study, we cannot determine the mechanism by which the combined treatment blunted reductions in systolic blood pressure or serum hs-CRP concentrations, but it may be related to the interaction between nitric oxide synthesis and AMPK activation (33, 34). Exercise combined with metformin was previously shown to blunt AMPK activation in skeletal muscle (35). Since AMPK activation is important for nitric oxide production, it is possible

that the combined treatment blunted nitric oxide production and affected systolic blood pressure and hs-CRP concentrations.

Although combining metformin with lifestyle modification lowered TAG concentrations more than lifestyle modification alone in overweight insulin resistant adolescents (26, 28), there was no additive effect in IGT adults (18). Consistent with Andreadis et al (18), we found that exercise training and/or metformin had similar effects at lowering TAG concentrations, despite exercise increasing VO$_2$peak and reducing central body fat. The decline in TAG concentrations across treatments was associated with increased insulin sensitivity ($r = -0.60$; $p < 0.05$). Although we cannot prove causality or directionality from this correlation, a possibility is that reductions in circulating TAG lead to improved peripheral glucose uptake (36). Fasting non-esterified fatty acids (NEFA) concentrations were elevated after exercise training with metformin, which could potentially explain the blunted rise in insulin sensitivity (19). The incongruent finding between lower TAG and higher NEFA concentrations with exercise plus metformin may relate to decreased NEFA uptake in skeletal muscle and liver (37, 38) or increased lipolytic activity (39). We are not able to discern which of the mechanisms account for elevated NEFA concentrations, but our results support the beneficial effects of exercise to lower TAG and increase insulin sensitivity (40). Whether exercise and/or metformin treatments have a direct impact on reducing CVD incidence in individuals with IGT remains to be seen.

Approximately 50% of individuals with IGT have metabolic syndrome (3). Lifestyle modification or metformin decrease metabolic syndrome prevalence (3), and the combined treatment may have additive effects (18). In this study, we showed that structured exercise training and/or metformin had similar effects on reducing metabolic syndrome severity (i.e. Z-score; Figure 2a). The initial ATP III score was lower in the exercise with metformin group, compared with either treatment alone. The lower baseline may have made it more difficult to detect a significant improvement from baseline, and, only exercise training or metformin alone reduced the number of subjects meeting ATP III criteria (Figure 2c). In addition, although not statistically different, metformin decreased metabolic syndrome prevalence more than the combined treatment (Figure 2b). Since the combined treatment did not lower systolic blood pressure, an ATP III criteria factor, our findings suggest that the interaction of metformin and exercise may oppose the reversal of metabolic syndrome in IGT adults compared to metformin alone. We recognize that further work is needed given the modest sample size in this study and our inability to compare treatment groups to placebo because only 2 subjects in that group had metabolic syndrome. However, the novel observation from this study is that combining exercise with metformin may have opposing effects on cardiovascular health, which could be clinically significant (16).

In conclusion, we observed that combining metformin with structured exercise training did not have additive effects on any CVD risk factor measured in this group of IGT adults. Metformin may blunt some of the effects of exercise training on lowering systolic blood pressure and hs-C-reactive protein and consequently contribute to preventing a decrease in the number of metabolic syndrome risk factors. If our results are reproduced and generalizable to men and women with IGT then the clinical utility of recommending the combination of exercise and metformin for people with IGT may need to be re-evaluated.

Despite metformin alone reducing CVD risk factors comparably to exercise alone, the improvements in cardiorespiratory fitness after exercise is one of the best predictors of CVD and early mortality. As a result, our findings highlight the overall positive effects of exercise on lowering CVD risk in adults with IGT.

Acknowledgments

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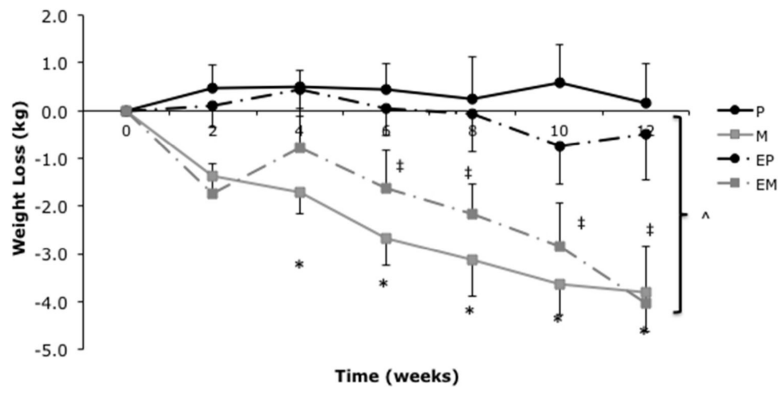
Figure 1a.

Change in body weight over the 12 week protocol. ^Significant effect of M and EM compared to P (p < 0.05). Significant effect of M(*) and EM(‡) compared to baseline (p < 0.05). Data are mean ± standard error of the mean.
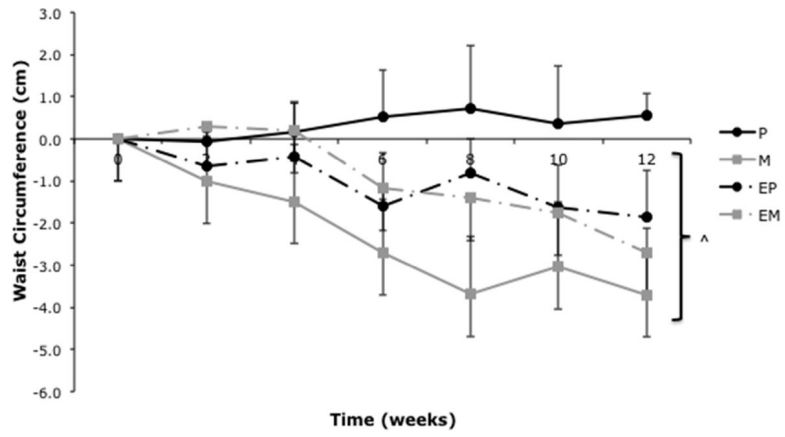
Figure 1b.
Change in waist circumference over the 12 week intervention. *Significant effect of time (p < 0.05). Data are mean ± standard error of the mean.
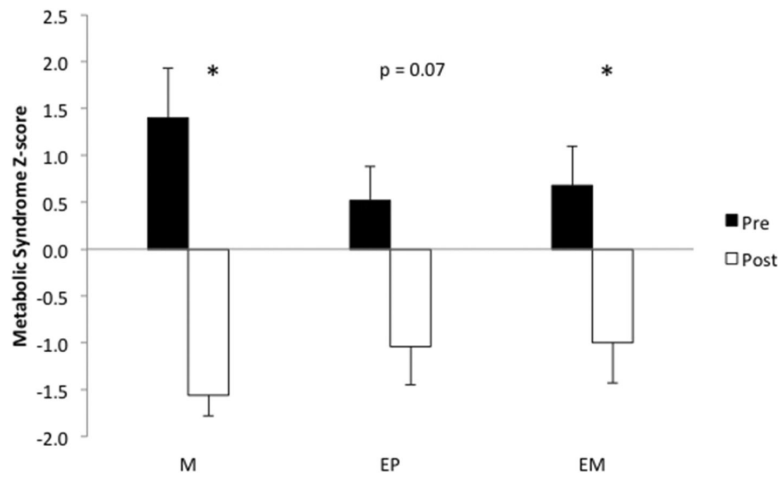
Figure 2a.

Metabolic syndrome severity before and after the 12 week intervention. *Pre to post was statistically different by paired t-test; $p < 0.05$. $^\$p = 0.07$. Data are mean ± standard error of the mean.
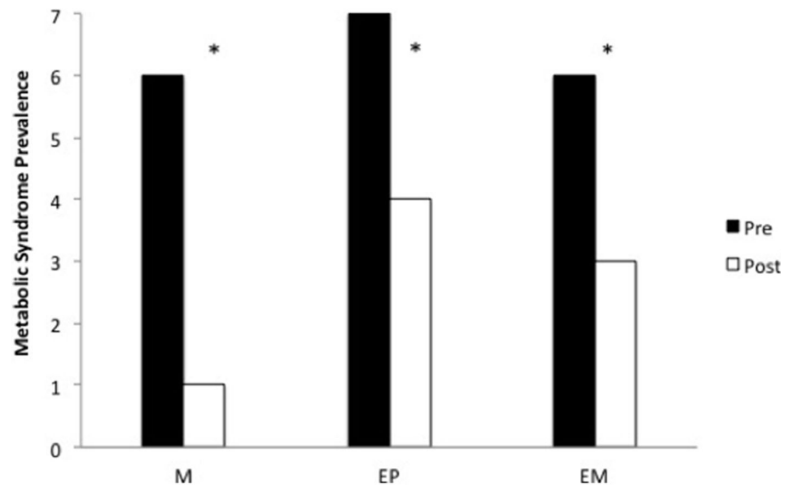
Figure 2b.
Metabolic syndrome prevalence before and after the 12 week intervention. Prevalence refers to the fraction of individuals with metabolic syndrome pre and post. *Pre to post was statistically different by McNemar; p < 0.05. Data are frequency.
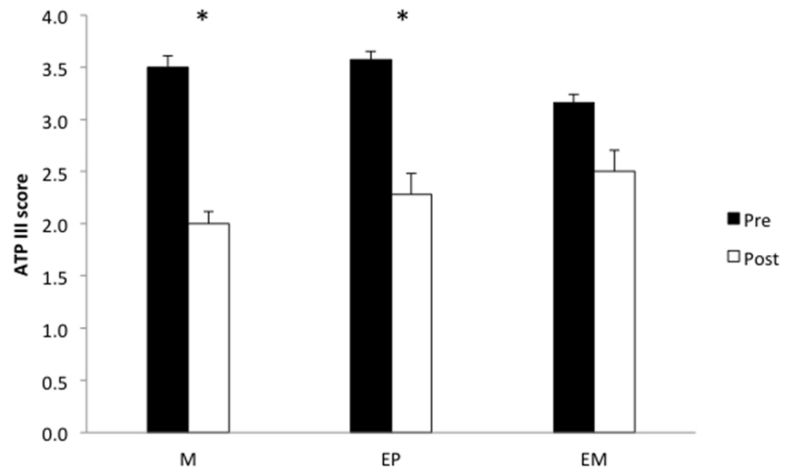
Figure 2c.
ATP III score before and after the 12 week intervention. *Pre to post was statistically different by paired t-test; $p < 0.05$. Data are mean ± standard error of the mean.

Table 1

Subject Characteristics.

	P	M	EP	EM
Sex	6F/2M	4F/4M	5F/3M	5F/3M
Age (year)	49.8 ± 10.9	45.0 ± 7.5	45.4 ± 8.0	49.1 ± 6.6
BMI (kg/m^2)	34.0 ± 6.3	33.9 ± 5.2	33.5 ± 4.1	31.2 ± 5.3
Body weight (kg)	93.5 ± 6.0	101.5 ± 5.8	95.5 ± 5.1	94.1 ± 6.5
VO$_2$ peak (ml/kg-ffm/min)	41.2 ± 8.2	43.4 ± 10.3	45.7 ± 9.4	48.2 ± 4.9
Fasting Glucose (mM)	5.79 ± 0.57	5.58 ± 0.61	5.42 ± 0.42	5.46 ± 0.80
2-hour Glucose (mM)	9.38 ± 1.33	9.28 ± 1.53	10.23 ± 1.02	9.46 ± 1.70
Steps per day	4983.9 ± 2104.9	5028.1 ± 2047.7	5871.7 ± 1912.8	6444.6 ± 1529.9

No significant differences were observed between conditions.

Data are mean ± standard deviation.

Table 2

Effect of exercise and/or metformin on blood pressure.

Condition	Test	P	M	EP	EM
SBP (mmHg)	Pre	126.1 ± 3.1	134.0 ± 3.8	136.8 ± 2.4	126.8 ± 5.6
	Post	134.5 ± 5.4*	123.9 ± 2.7*^	128.0 ± 3.9^	126.3 ± 5.1
	(%)	6.5 ± 2.7*	−7.3 ± 2.0^	−6.3 ± 3.1^	0.0 ± 3.0
DBP (mmHg)	Pre	76.8 ± 2.8	82.9 ± 2.9	88.1 ± 2.1$	82.1 ± 2.9
	Post	82.9 ± 2.3*	78.9 ± 1.7^	81.4 ± 2.0^*	78.5 ± 2.5^
	(%)	8.3 ± 1.9*	−4.1 ± 3.7^	−7.5 ± 1.9^**	−3.9 ± 3.5
MAP (mmHg)	Pre	92.3 ± 0.85	98.9 ± 1.2	103.3 ± 0.7	96.0 ± 1.3
	Post	99.1 ± 1.2	92.9 ± 0.6^	95.9 ± 1.0*^	93.3 ± 1.2
	(%)	7.3 ± 1.3	−5.6 ± 2.8^	−7.1 ± 2.1*^	−2.3 ± 3.1

SBP (systolic blood pressure), DBP (diastolic blood pressure), and MAP (mean arterial pressure).

Data are mean ± standard error of the mean.

$Significant compared to P at pre-testing. Co-varying for baseline DBP did not alter the results.

*Significant compared to baseline; p < 0.05.

^Compared to P (p < 0.05).

Table 3

Effect of exercise and/or metformin on blood lipids and inflammation.

Condition	Test	P	M	EP	EM
TC (mM)	Pre	4.43 ± 0.22	4.76 ± 0.31	4.86 ± 0.25	4.85 ± 0.48
	Post	4.51 ± 0.17	4.48 ± 0.35	4.68 ± 0.26	4.49 ± 0.34
	(%)	3.5 ± 6.7	−5.4 ± 5.0	−3.7 ± 2.4	−5.5 ± 3.8
LDL (mM)	Pre	2.33 ± 0.21	2.18 ± 0.41	2.13 ± 0.13	2.4 ± 0.5
	Post	2.48 ± 0.19	1.92 ± 0.27	2.00 ± 0.20	2.1 ± 0.3
	(%)	2.1 ± 11.8	−1.6 ± 14.0	−6.9 ± 6.9	−6.1 ± 8.5
HDL (mM)	Pre	1.46 ± 0.11	1.50 ± 0.11	1.61 ± 0.12	1.54 ± 0.07
	Post	1.36 ± 0.11	1.68 ± 0.13[^]	1.74 ± 0.13[^]	1.65 ± 0.07[*$]
	(%)	−7.1 ± 2.5	13.0 ± 7.0	8.2 ± 3.8	7.6 ± 2.1
CRR	Pre	3.11 ± 0.20	3.26 ± 0.25	3.10 ± 0.21	3.22 ± 0.37
	Post	3.43 ± 0.24	2.70 ± 0.15[^]	2.79 ± 0.24[*]	2.77 ± 0.25[*^]
	(%)	11.1 ± 5.6	−14.3 ± 6.4	−10.3 ± 3.7	−11.8 ± 4.4
TAG (mM)$^{\psi}$	Pre	1.40 ± 0.18	2.36 ± 0.40	2.45 ± 0.25	1.93 ± 0.36
	Post	1.46 ± 0.16	1.92 ± 0.28	2.05 ± 0.29	1.63 ± 0.29
	(%)	3.1 ± 11.6	−13.8 ± 7.3	−13.5 ± 10.2	−12.0 ± 7.0
hs-CRP (ng/ml)	Pre	90.2 ± 20.8	100.4 ± 19.3	72.0 ± 19.9	64.0 ± 17.1
	Post	114.3 ± 33.2	94.5 ± 30.2[$]	55.7 ± 22.0[*^]	58.5 ± 15.2
	(%)	16.4 ± 14.2	−20.1 ± 18.7[$]	−27.4 ± 8.7[*^]	−8.4 ± 10.8

TC (total cholesterol), LDL (low-density lipoprotein), HDL, (high density lipoprotein), TAG (triacylglycerol), hs-CRP (high sensitive C-reactive protein), CRR (cardiac risk ratio = TC/HDL). = Post- Pre change.

Data are mean ± standard error of the mean.

[*] Significant compared to baseline; p < 0.05.

$^{\psi}$ Significant effect of test; p < 0.05.

[^] Compared to P (p < 0.05).

[$] Compared to P (p =0.06).