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Original article

Effects of a training program at the crossover point on the cluster of metabolic abnormalities and cardiovascular risk factors

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Abstract

The present study examined the effects of a training program at a special exercise intensity—the crossover point of substrate utilization (COP)—on the metabolic abnormalities and cardiovascular risk factors in obese women with metabolic syndrome (MetS). Eighteen postmenopausal obese women with MetS (age, 54.8 ± 8.4 years; height, 160 ± 6 cm) followed a 12-week training program consisting of three 45-minute sessions/wk on a cycle ergometer. The intensity imposed during the training sessions corresponded to COP. Before and after the training program, anthropometric, biological, and blood pressure data were collected and compared. After the training program, body mass (88.4 ± 12.3 kg vs. 85.7 ± 11.1 kg), fat mass (43.2 ± 4.8% vs. 41.8 ± 4.8% body mass), body mass index (34.3 ± 3.9 kg/m^2 vs. 33.2 ± 3.6 kg/m^2), and waist circumference (105 ± 10 cm vs. 100 ± 9 cm) were significantly lower ($p < 0.01$). Moreover, fasting plasma glucose was significantly lower after the training program (114 ± 20 mg/dL vs. 107 ± 15 mg/dL; $p = 0.02$) and the quantitative insulin-sensitivity check index was significantly higher (0.58 ± 0.08 vs. 0.61 ± 0.05; $p = 0.05$). A significant reduction in systolic blood pressure was also observed (141 ± 15 mmHg vs. 129 ± 11 mmHg; $p = 0.02$). After the program, the number of patients with fasting plasma hyperglycemia and arterial hypertension was significantly decreased by 54.4% and 44.4%, respectively, and the number of patients with MetS was nonsignificantly reduced by 22.2% ($p = 0.10$). The present study shows that a training program at COP is an efficient means to treat MetS.

Keywords: Glucose and lipid metabolism; Obesity; Physical exercise; Systolic blood pressure

Introduction

Metabolic syndrome (MetS) is characterized by a cluster of metabolic abnormalities and cardiovascular risk factors, including central obesity, dyslipidemia, insulin resistance, and arterial hypertension.[1] Although the prevalence of MetS in France appears to have been declining for some years,[2] it is still too high. Indeed, in the MONA LISA study, Wagner et al[2] examined the changes in the prevalence of MetS among the French and reported that in 2006 the prevalence was still elevated, at 23.1% and 15.1% in men and women, respectively.[2] Dealing with MetS is thus a major public health issue in France.

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Several authors have demonstrated that MetS increases not only the risk of cardiovascular diseases, but also mortality from cardiovascular disease and all causes.[3–5] It is thus essential to reduce its incidence, and several authors have supported physical exercise programs as a means to achieve this goal.[6–8] However, the expected beneficial effects seem to depend on the exercise intensity[9] and, as indicated by Pérez-Martin et al,[10] the optimal exercise intensity for obese patients with MetS has not yet been determined.

Overweight and obese patients have muscular metabolic abnormalities (e.g., metabolic abnormalities in the interactions between glucose and lipid metabolisms) that may need to be taken into account for individualized physical exercise prescription.[10] The crossover point of substrate utilization (COP), which can be determined from indirect calorimetry,[11–13] can be used to evaluate the abnormal interactions between the glucose and lipid metabolisms. According to the concept of Brooks and Mercier,[14] COP is the exercise intensity at which energy from carbohydrate-derived fuels predominates over energy from lipids. At this exercise intensity, approximately 70% of the energy derives from carbohydrate and 30% from lipids.[15] The notion of exercise intensity at the COP was initially conceived in the search to identify the optimal exercise intensity for obese patients with or without type 2 diabetes.[15,16] However, to our knowledge, no study has evaluated the effects of a training program at this special exercise intensity (i.e., COP) on the abnormalities defining MetS in obese women, even though some authors consider this exercise intensity as *optimal* for patients with metabolic abnormalities.[15,16]

The purpose of the present study was therefore to examine the effects of a training program at COP on the metabolic abnormalities and cardiovascular risk factors in obese women with MetS.

Materials and methods

Participants

Eighteen obese women [age, 54.8 ± 8.4 years; body mass, 88.4 ± 12.3 kg; height, 160 ± 6 cm; body mass index (BMI), 34.3 ± 3.9 kg/m^2] with MetS, which was diagnosed according to the criteria proposed by the National Cholesterol Education Program,[17] volunteered to take part in this study. All participants signed a consent form after being informed of the investigation purposes and procedures. This experiment was also approved by the local ethics committee for participants' protection in clinical research and the technical committee for clinical hospital research (CP 09-49).

Materials

Body mass (kg) and percentage of fat mass were assessed using a multifrequency bioelectrical impedance meter (BC-418 MA; Tanita, Arlington Heights, IL, USA).

The blood lipid concentrations (triglycerides, total cholesterol, and high-density lipoprotein cholesterol) were determined using an Architect C4000 system (Abbott, Rungis, France). The low-density lipoprotein cholesterol (LDL-C) concentrations were computed using Friedewald et al's[18] formula. The blood glucose concentrations were determined by an automated hexokinase method (AU5800 analyzer; Beckman-Coulter, Villepinte, France), and the glycosylated hemoglobin (HbA_{1c}) was measured by high-performance liquid chromatography (HLV-723 G7; Tosoh, Lyon, France).

To evaluate insulin resistance, blood insulin and leptin concentrations were measured using an immunoradiometric assay (Bi-INS-IRMA; Cisbio Bioassays, Codolet, France) and a radioimmunoassay assay (human leptin RIA kit; Millipore, Billerica, MA, USA), respectively.

Resting systolic blood pressure (SBP; mmHg) and diastolic blood pressure (DBP; mmHg) were measured using a noninvasive blood pressure monitor (Carescape V100; GE Healthcare, Chalfont Saint Giles, Bucks, UK).

Respiratory gas analysis was carried out through indirect calorimetry via a breath-by-breath system with an open-circuit metabolic card (Ergocard; Medisoft, Sorinnes, Belgium). This respiratory gas analysis system was calibrated in accordance with the manufacturer's guidelines.

The indirect calorimetry and the training sessions were conducted on an electromagnetically braked cycle ergometer (Excalibur Sport; Lode, Groningen, The Netherlands), which maintained the set power output by adjusting the resistance with variations in pedal rate.

Procedures

The purpose and procedures of the study were explained to the participants during the first session. Anthropometric data were also collected at this time. BMI was calculated as body mass (kg) divided by the square of height (m). An average of three readings, measured to the nearest cm, was taken.

Fasting blood samples were collected at rest (before the indirect calorimetry) from an antecubital vein after an overnight fast by an experienced nurse. The blood samples were coded and subsequently assayed. Insulin resistance was evaluated from the homeostasis model assessment of insulin resistance (HOMA-IR) index using the following equation[19]:

$$\text{HOMA} - \text{IR} = \text{insulinemia} \times \text{glycemia} \div 22.5$$

In this equation, the insulinemia and glycemia are expressed in μU/mL and mM, respectively. Moreover, to quantify insulin sensitivity, the quantitative insulin-sensitivity check index (QUICKI) was also calculated[20]:

$$\text{QUICKI} = 1 \div (\text{loginsulinemia} + \text{logglycemia})$$

In this equation, the insulinemia and glycemia are expressed in μU/mL and mM, respectively.

Resting SBP and DBP were determined from the left arm of the seated participant after 5 minutes rest. Three separate measurements were taken at 1-minute intervals, and the mean of the three readings was recorded.

The women then performed a graded exercise test in order to determine maximal aerobic power (MAP; power output at the last completed workload). This exercise test was carried out on a cycle ergometer, with an initial resistance set at 10 W (for 1 minute) followed by increments of 10 W/min until volitional exhaustion. The participants were instructed to develop the highest possible level of power.

After a period of 2–4 days, indirect calorimetry was performed. This exercise test was always executed in the morning (8:00–10:00 AM) after at least 12 hours of fasting. Moreover, it was carried out under medical supervision in an air-conditioned room of the hospital (temperature, 20–22°C). The test consisted of five 6-minute workloads, as initially proposed by Brooks and Mercier[14] and recently recommended by Brun et al.[21] Before the exercise test, the seat and handlebar heights of the electromagnetically braked cycle ergometer were set according to each participant's preference. After 3 minutes of rest, the participant began to pedal at an initial workload set at 20% MAP for 6 minutes (Fig. 1) and then continued pedaling at imposed workloads corresponding to 30%, 40%, 50%, and 60% MAP. Throughout the exercise test, the participants were asked to pedal at a rate between 60 rpm and 70 rpm. The participants breathed through a mouthpiece, and their respiratory variables (i.e., oxygen uptake: $\dot{V}O_2$ and carbon dioxide output: $\dot{V}CO_2$) were recorded breath-by-breath, then averaged during the last 15 seconds of each workload. As proposed by Brun et al,[21] these values were used to calculate the respective oxidation rates of carbohydrates and lipids by applying the classical stoichiometric equations of indirect calorimetry:

$$\text{Carbohydrate oxidation} = 4.5850\dot{V}CO_2 - 3.2255\dot{V}O_2$$

$$\text{Lipid oxidation} = -1.7012\dot{V}CO_2 + 1.6946\dot{V}O_2$$

In these equations, carbohydrate and lipid oxidations are expressed in mg/min, whereas $\dot{V}CO_2$ and $\dot{V}O_2$ are expressed in mL/min.

The obtained values were then converted into kcal (i.e., lipids providing approximately 9 kcal/g and carbohydrates providing only 4 kcal/g). Thus, the percentages of carbohydrates and lipids participating in total energy expenditure were determined. Then, to determine COP, the percentages of oxidized carbohydrates and lipids were indicated on the same graph according to the power output over five points. The crossover of the two curves corresponded to COP.

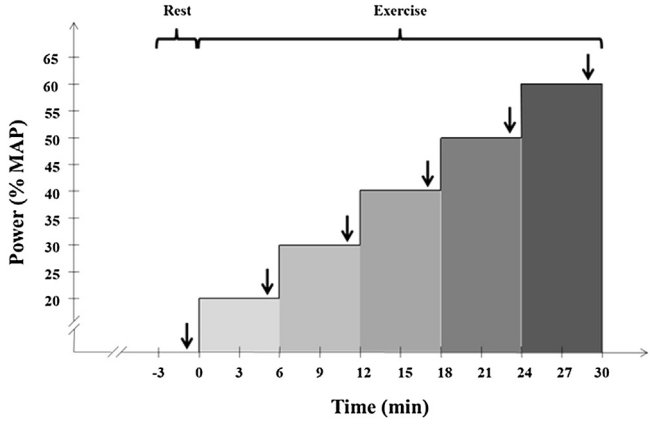

Fig. 1. Indirect calorimetry test performed by patients to determine the crossover point of substrate utilization.

After indirect calorimetry, all participants followed a training program for 12 weeks. The program consisted of three 45-minute sessions/wk on an electromagnetically braked cycle ergometer. The intensity imposed during the training sessions corresponded to COP. After the 12 weeks of training, all anthropometric and biological data, blood pressure measures and COP were again collected for comparison with pretraining values.

Statistical analysis

Data are expressed as the mean ± standard deviation for continuous variables. For categorical data, the frequencies are presented. The normal Gaussian distribution of the continuous data was verified by the Shapiro–Wilk test.

A Student paired samples t test was used for normally distributed continuous data to evaluate the training program effect. When these data did not pass the test for normality, a Wilcoxon signed-rank test was used. For categorical data, the frequencies were compared using Pearson's Chi-square test or Fisher's exact test when appropriate. All statistical analyses were performed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). A p-value ≤ 0.05 was considered statistically significant.

Results

The means and standard deviations of the anthropometric and biological data, as well as the blood pressures and COP measured before and after the training program, are presented in Table 1. All anthropometric data (except height) were significantly different after the training program ($p < 0.01$; Table 1). Moreover, concerning the biological data, fasting plasma glucose (FPG) was significantly lower after the training program ($p = 0.02$), whereas QUICKI was significantly higher ($p = 0.05$; Table 1). A significant reduction in SBP was also noted after the training program ($p = 0.02$; Table 1). Finally, COP was increased after the training program ($p < 0.05$; Table 1).

Regarding the cluster of metabolic abnormalities and cardiovascular risk factors defining MetS, the number of patients with FPG $\geq$ 110 mg/dL ($p = 0.04$) and arterial hypertension ($p = 0.02$) was significantly lower after the training program (Fig. 2). Indeed, although 18 patients had arterial hypertension before the training program, only 10 patients remained hypertensive after training (44.4%). Similarly, after the training program, six patients (among 11 patients before the training program) did not have FPG $\geq$ 110 mg/dL (54.5%).

Although four patients did not have MetS after the training program (22.2%; $p = 0.10$), no significant difference in the number of MetS parameters was noted (Fig. 3).

Table 1
Means and standard deviations of the anthropometrical and biological data, and blood pressures measured before and after the training program.

	Before		After	
	Mean	Standard deviation	Mean	Standard deviation
Anthropometrical data				
Body mass (kg)	88.4	12.3	85.7*	11.1
Fat mass (% body mass)	43.2	4.8	41.8*	4.8
Body mass index (kg/m^2)	34.3	3.9	33.2*	3.6
Waist circumference (cm)	105	10	100*	9
Biological data				
Triglycerides (mg/dL)	151	67	151	63
Total cholesterol (mg/dL)	207	48	203	53
High-density lipoprotein cholesterol (mg/dL)	44	12	44	11
Low-density lipoprotein cholesterol (mg/dL)	132	35	130	41
Glycosylated hemoglobin (%)	6.2	0.6	6.2	0.7
Glucose (mg/dL)	114	20	107**	15
Insulin (μU/L)	8.9	4.2	8.4	4.1
Leptin (ng/mL)	31.9	16.1	28.4	6.8
Homeostasis model assessment insulin-resistance index	2.73	1.06	2.16	0.81
Quantitative insulin-sensitivity check index	0.58	0.08	0.61**	0.05
Blood pressure				
Systolic (mmHg)	141	15	129**	11
Diastolic (mmHg)	82	12	77	7
Crossover point				
Workload (W)	39	16	49**	14
Oxygen uptake (mL/kg/min)	10.0	2.2	11.1	2.5

* $p < 0.01$; ** $p < 0.05$.

Discussion

The purpose of the present study was to examine the effects of a training program at COP on the metabolic abnormalities and cardiovascular risk factors in obese women with MetS.

The results demonstrate that the training program at COP significantly reduced body mass (−3.1%), fat mass (−3.2%), BMI (−3.2%), and waist circumference (−4.8%) in these women (Table 1). To our knowledge, no other study has assessed the efficacy of this type of training program in this population. However, Dumortier et al[22] proposed an individualized exercise intensity based on indirect calorimetry that corresponds to the point of maximal fat oxidation rate, LIPOX$_{max}$,[21] as a means to reverse the metabolic abnormalities characterizing MetS. They recruited 39 patients with MetS for their study: 28 patients followed an 8-week training program (cycling at LIPOX$_{max}$) during three 40-minute training sessions/wk and 11 patients were untrained. The experiment showed that the training program at LIPOX$_{max}$ produced a significant reduction in body mass (−3.0%), fat mass (−3.4%), BMI (−3.0%), and waist circumference (−4.2%) in the trained patients,[22] with results very close to those observed in the present study. An improvement in the anthropometric data in patients with MetS may therefore be obtained by training programs at LIPOX$_{max}$ or COP.

The present study revealed no significant difference in lipids or lipoproteins after the training program at COP. In 2005, Kelley et al[23] performed a meta-analysis of 13 studies (including 613 participants: 348 trained and 265 untrained) to examine the effects of training programs on lipid and lipoprotein concentrations in overweight or obese adults. They found that physical exercise significantly decreased only the triglyceride concentration in the trained individuals, which differs from our finding. However, the studies in Kelley et al's meta-analysis[23] proposed training programs with an average of four 42-minute training sessions/wk (at 64% maximal $\dot{V}O_2$) for 20 weeks. It is therefore possible that the training program of the present study was not long enough, did not schedule exercise sessions often enough, or was not intense enough to yield a significant decrease in the triglyceride concentration.

Based on the National Cholesterol Education Program definition of MetS,[17] Balkau et al[24] reported that respectively 12% and 6% of French men and women with MetS have fasting hyperglycemia. This frequent metabolic abnormality is

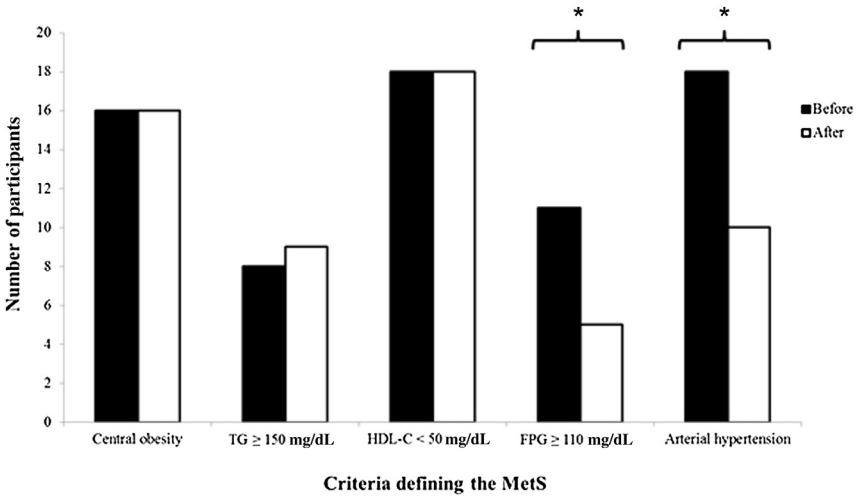

Fig. 2. Training program effects on the criteria defining metabolic syndrome (MetS). * $p < 0.05$. FPG = fasting plasma glucose; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.

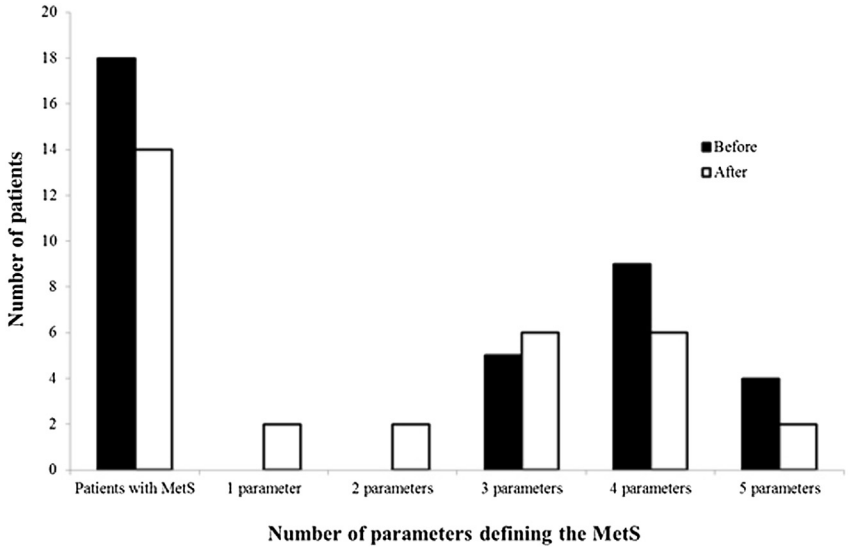

Fig. 3. Effects of a training program on metabolic syndrome (MetS) and the number of parameters defining MetS.

linked to insulin resistance in these patients.[25] Although the factors involved in insulin resistance and their underlying mechanisms are not fully understood,[26] evidence suggests that insulin resistance is at least partially linked to skeletal muscle abnormalities.[27] However, studies have shown that physical exercise may counteract these abnormalities and thus enhance insulin sensitivity.[28–30] Indeed, physical exercise improves insulin sensitivity by inducing increases in muscle fiber size, capillary density, glycogen and glycogen synthase contents, as well as by increasing the translocation of glucose transporters (GLUT4) to the cellular membrane.[31] The present study showed a significant decrease in FPG after the training program, associated with a nonsignificant decrease in insulin concentration and resistance (assessed by HOMA-IR; Table 1). Moreover, insulin sensitivity (measured by QUICKI) was increased after the program (Table 1). These results thus suggest that a training program at COP reduces fasting hyperglycemia by improving insulin sensitivity, probably due to skeletal muscle adaptations such as the increased translocation of GLUT4. However, further studies of these skeletal muscle adaptations are needed to better understand the mechanisms of the improved insulin sensitivity and glucose homeostasis in response to physical exercise at COP in patients with MetS.

No significant difference in HbA_{1c} was observed after the training program, but given that this biological factor reflects the average plasma glucose concentration over the previous 3 months and that the training program lasted 3 months, this lack of change is unsurprising (Table 1). Indeed, the training program duration was probably too short.

Leptin is an adipocyte-secreted hormone in direct proportion to the amount of energy stored in adipose tissue. Obese patients have higher leptin concentrations than lean individuals but are resistant to its effects.[32] Therefore, leptin, which has a central role in regulating energy homeostasis,[33,34] does not have a beneficial effect in obese patients (e.g., leptin stimulates energy expenditure and promotes satiety). Dyck,[35] however, suggested that dieting and physical exercise may partially reverse leptin resistance. The present 12-week training program at COP did not significantly reduce the leptin concentration (Table 1). Reseland et al[36] examined the influence of different interventions (diet, physical exercise or a combination of the two) on the leptin concentration in a large cohort of men with MetS. Their results showed that dieting alone reduced the leptin concentration but that this reduction was greater when physical exercise (3 sessions/wk for 1 year) was associated. Interestingly, no significant effect was noted for physical exercise alone. The reduction in leptin concentration may therefore be principally linked to diet and potentiated by physical exercise in adults with MetS. This hypothesis would thus explain the lack of significant difference in the present study.

Our results reveal that the training program lowered blood pressure (significantly for SBP). Several mechanisms could explain this reduction.[37] First, physical exercise increases the vascular expression of endothelial nitric oxide synthase, an enzyme that oxidizes L-arginine to generate L-citrulline and nitric oxide, in humans.[38] As nitric oxide has a vasodilator effect,[39] endothelial nitric oxide synthase production through physical exercise may reduce blood pressure. Another possible mechanism is the exercise-induced modification in blood vessel morphology and function to improve blood flow.[37] Indeed, physical exercise may induce angiogenesis (i.e., an expansion of the capillary network by the formation of new blood vessels) and arteriogenesis (i.e., an enlargement of existing vessels),[40] both of which would reduce blood pressure.

After the training program, the number of patients with MetS was 22.2% lower, although this drop was insignificant ($p = 0.10$; Fig. 3). As suggested in Fig. 2, this decrease may be due to the significant 44.4% reduction in the number of patients with arterial hypertension after the training program or the significant 54.5% decrease in the number of patients with

hyperglycemia ($p < 0.05$). Several earlier studies have already indicated a significant reduction in the prevalence of MetS after training programs, partially explained by a significant decrease in blood pressure and/or FPG.[6,8] For example, Tjønna et al[8] compared a training program with constant intensity exercises and a program including intermittent intensity exercise in patients with MetS. The exercise durations differed in order to ensure the same energetic expenditure, but both programs included three training sessions/wk for 16 weeks. The results showed a significant reduction in the number of patients with MetS for both programs, but the reduction was greater for intermittent intensity exercise (−37% and −46% for constant and intermittent intensity exercises, respectively). Also, although the two training programs similarly improved body mass, BMI, waist circumference, SBP, and DBP (with a decrease of approximately 12 mmHg and 5 mmHg for SBP and DBP, respectively), the intermittent intensity program improved some of the biological and physiological data more than the constant intensity program.[8] Although the present study shows that constant intensity exercise at COP was efficient to treat MetS, it may be more appropriate to propose intermittent intensity exercise.

The current study presents an essential limit. Indeed, this preliminary study has not included a control group (i.e., with untrained patients). Consequently, it is not possible to know with certainty if the noticed beneficial effects were linked to only our training program at COP. Indeed, it is possible that few patients have increased their daily physical activities' level or decreased their food intake. Nevertheless, the sedentary effects are well known, and we can suppose that a stagnation of all measured parameters would have been noted in a control group. However, further studies must be conducted to confirm this hypothesis.

Conclusion

The present study revealed that a training program at COP had beneficial effects on body mass, fat mass, BMI, waist circumference, FPG, QUICKI, and SBP in obese women with MetS. In addition to these improvements, there were fewer patients with MetS after the training program (22.2%), which was probably due to the significant 44.4% reduction in the number of patients with arterial hypertension and/or the significant 54.5% decrease in the number of patients with hyperglycemia.

Conflicts of interest

The authors declare no conflicts of interest.

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