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Metabolic and anti-inflammatory effects of a home-based programme of aerobic physical exercise

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SUMMARY

Aims: Regular exercise demonstrated the ability to provide enormous benefits to many diseases, atherosclerotic-based, degenerative and neoplastic, but also to grant anti-inflammatory actions, assessed by various authors in different populations. Despite of these clear benefits, many patients are unable to attain long-term results through chronic physical activity for different causes. On this basis, the aim of our study was to assess the metabolic and anti-inflammatory effects of a home-based programme of fast walking in patients affected by metabolic syndrome (MS). **Materials and methods:** We enrolled 176 subjects with MS as stated by ATP III criteria. Patients were invited to walk for 1 h every day 5 days a week for 24 weeks. The walking velocity was required higher than the one retained 'comfortable' by the patient, previously assessed in the run-in visit. Monitoring of physical activity was carried out through an OMRON step counter type Walking Style II. All the subjects enrolled completed the training period. **Results:** After the 24 weeks of intervention body mass index changed from 31.59 to 29.23 ($p < 0.001$); mean waist circumference passed from 105.19 to 100.06 cm ($p < 0.001$); mean fasting glucose changed from 119.76 to 114.32 mg/dl ($p < 0.001$); for diabetic population ($n = 70$) mean glicated haemoglobin levels changed from 7.38% to 6.86% ($p < 0.001$); total cholesterol levels from 192.15 to 185.78 mg/dl ($p < 0.001$); HDL cholesterol levels raised from 44.03 to 47.63 mg/dl ($p < 0.001$); triglycerides levels lowered from 148.29 to 135.20 mg/dl ($p < 0.001$); WBC changed from 7361.08 to 7022.56/mm^3 ($p < 0.001$); hs-CRP from 0.55 to 0.28 mg/dl ($p < 0.001$); fibrinogen serum levels lowered from 339.68 to 314.86 mg/dl ($p < 0.001$). **Conclusions:** A long-term home-based programme of aerobic physical activity improves metabolic asset and reduces systemic inflammation in sedentary people.

What's known

This topic has been the subject of many studies in recent years, some of which also conducted using home monitoring using a pedometer.

The results were not unequivocal as a result of the heterogeneity of the populations studied, of different types of exercise proposed, different intensity and different duration of protocols

What's new

To our knowledge, no study has evaluated in a explicit manner the effectiveness of a programme of home-based exercise as that proposed by us with the aim to test first the compliance, and hence the effectiveness towards the biomarkers of systemic inflammation and of the major cardiovascular risk factors associated with the metabolic syndrome.

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Disclosure
All the authors declare no conflict of interest.

Introduction

It is well established that regular exercise is a non-pharmacological therapeutic intervention with an enormous range of benefits, including reduced morbidity and mortality of atherosclerotic disease (1), heart failure (2); type 2 diabetes (3), and chronic obstructive pulmonary disease (4), as well as many other age-related chronic disorders (5). Among the different types of exercise, the aerobic training, when habitually performed, clearly showed to provide several favourable metabolic effects against the main cardiovascular (CV) risk factors (6).

The main well known mechanisms by which physical training exerts its beneficial efficacy helping to improve the health status are the favourable effects on the CV risk factors; the enhancement of muscular exercise tolerance and improvement of physical fitness; the enhancement of myocardial and peripheral perfusion; the augmented well-being of the individual (7). But many other mechanisms responsible for the protective effects of regular exercise remain to date unexplained or not completely clear.

Chronic low-grade systemic inflammation, defined as modest (two to fourfold) elevations in circulating levels of pro-inflammatory and anti-inflammatory cytokines, natural occurring cytokine antagonists, and acute-phase proteins, as well as minor increases in counts of neutrophils and natural killer cells (8) seem to be clearly involved in the development and

progression of atherosclerosis, and may be found strictly linked to several other chronic pathological conditions.

Furthermore, chronic subclinical inflammation has been recently recognized as firmly related to the metabolic pathways involved in the insulin resistance, a key player in the pathogenesis of the metabolic syndrome (MS) (9). The finding that increased levels of C-reactive protein (CRP), the prototypic marker of inflammation, but also of fibrinogen and leukocyte count have been associated with the MS and to the elements of which is compounded (10), confirms the association between inflammation and MS also when considered the possible confounding factors.

In this point of view, the promotion of regular physical activity should be emphasised also to take advantage of its anti-inflammatory properties (11).

Unfortunately, despite of this great range of benefits, several patients are unable to attend to long-term physical activity programmes for different reasons: first of all the presence of comorbidities, but also the lack of facilities, lack of motivation, or perception of too hard training.

Home-based activities seem to be associated with higher adherence than facility-based activities. Activities such as walking, jogging, or cycling can easily be incorporated into routine daily life, whereas facility-based activities typically require more intentional effort and planning (12), even if the superiority of home-based programmes is clearer in the long term.

On this basis, we designed a study aimed to test the hypothesis that a long-term home-based programme of physical exercise based on fast walking might be able to improve the metabolic asset, the blood pressure levels and the main laboratoristic markers of inflammation in sedentary subjects affected by MS assessed by the ATP III criteria.

Methods

We enrolled 176 subjects (95 men and 81 women, mean age 59.1 $\pm$ 13.6 years) among those who were referred to the Hospital Units of Medicina Vascolare and Medicina Interna e Cardioangiologia of the University of Palermo for ambulatory examination in the period between 01/09/2007 and 31/06/2011. During this period were evaluated approximately 800 possible candidates; 176 patients actually enrolled in addition to meeting the inclusion criteria of the study provided significant guarantees of compliance to the proposed treatment. All subjects were previously informed about the characteristics of non-pharmacological intervention that was the object of study, as well as the duration and methods of implementation of the clinical, laboratory and instrumental monitoring. The study design was approved by the local ethics committee.

Main inclusion criterion was the presence of at least three findings of MS as stated by ATP III criteria (13).

Exclusion criteria were:

- Age > 80 years
- End-stage renal disease (Stage 5 chronic kidney disease – GFR <15 ml/min/1.73 m^2).
- Every pathologic condition resulting in a limitation of the physical activity of the subject.
- Every CV and/or cerebrovascular event in the last 6 months. The presence of previous CV events (more than 6 months) did not constitute an exclusion criterion in subjects maintaining their normal physical and working activities.
- Presence of electrocardiographic evidence of cardiac arrhythmias, or clinical and/or echocardiographic evidence of cardiac heart failure (EF < 50%)
- In hypertensives, presence of secondary hypertension.

The initial study procedure included, for all subjects, a comprehensive medical history with complete physical examination and specific consideration of CV risk profile, assessment of body mass index (BMI) calculated as the individual's body weight divided by the square of his or her height, waist circumference and assessment of drug treatment.

At baseline, we evaluated the following blood tests: total cholesterol, HDL cholesterol, triglyceride, creatinine, fibrinogen, haemocromocitometric count, fasting glucose, CRP; furthermore, we performed in all subjects an ECG and a 24-h ambulatory blood pressure monitoring (ABPM).

The assessment of the level of physical activity was performed by administration of a specific questionnaire (International Physical Activity Questionnaire). Only subjects who were being sedentary to the questionnaire were enrolled.

Cardiovascular risk factors were evaluated on the basis of the criteria shown below. Hypercholesterolaemia, hypocholesterolaemia HDL and hypertriglyceridaemia were defined as reported in ATP III criteria (13).

Hypertension was defined as present if subjects had been previously diagnosed according the World Health Organization/International Society of Hypertension guidelines and were routinely receiving antihypertensive therapy (14).

Patients were defined as type 2 diabetics if they had known diabetes treated by diet, oral hypoglycaemic drugs or insulin.

Previous cerebrovascular disease (TIA/ischemic stroke) was assessed by history, specific neurological

examination performed by specialists, and hospital or radiological (brain computed tomography or brain magnetic resonance) records of definite previous stroke.

The ABPM was performed using a Recorder type TM – 2430 by A & D Company Limited of Tokyo, Japan. This device provides an oscillometric record. Our recorders had previously been validated and recommended for clinical use (15). The monitoring equipment was arbitrarily applied at 8.00 A.M. The cuff was fixed to the non-dominant arm, and three blood pressure readings were taken concomitantly with sphygmomanometer measurements to ensure that the average of the two sets of values did not differ by > 5 mmHg. The device was set to measure blood pressure at 15 min intervals during the day (6 a.m. to 10 p.m.) and at 30 min intervals during the night (10 p.m. to 6 a.m.). During the 24 h of examination, the patient was informed to hold the arm immobile at the time of measurements, to keep a diary of daily activities and to return to the hospital 24 h later. The monitoring was always performed on a working day and during the normal intake of the usual anti-hypertensive treatment. The patients had no access to the ambulatory blood pressure values.

Measurements recorded during the 24 h were stored on a personal computer and screened as follows: a 24 h record was rejected for analysis if more than one third of potential day and night measurements were absent or invalid. The ambulatory BP values used for statistical analysis are expressed as 24-h average systolic and diastolic pressures, and 24-h average heart rate.

Patients enrolled initiated a programme of home-based physical activity centred on fast walking. Patients were invited to walk for 1 h every day for 5 days a week. The walking velocity was required to be constant and higher than the one retained 'comfortable' by the patient, previously assessed in the run-in visit inviting the patient to walk 'normally' in a 10-m walkway under chronometric control. To every subject enrolled was asked to register in a diary the daily activity, indicating the time of start and end of fast walking.

The level of daily physical activity and the adherence to the protocol were assessed through the periodic analysis of data registered by a step counter provided to every patient. We used an OMRON step counter type Walking Style II. This device, besides the function of step counter, also features aerobic steps. Aerobic steps are counted separately when walking more than 60 steps per minute and more than 10 min consecutively. Data about total number of steps, total number of aerobic steps, total distance walked, total aerobic distance walked, total energy expenditure (calories) are stored in the internal memory of step counter every day for a week maximum. Every 7 days data should be transferred to PC and the step counter resetted.

Every week, during the periodic visit because of data input and storage for the later analysis, was performed a comparison between patient's diary of physical activity and speed counter data.

Walking velocity during training period was obtained analysing the separate aerobic distance covered recorded by step counter and comparing it with the time spent walking aerobically as reported in the patient's diary. Weekly, during the periodic control of data, patients enrolled were required to modify walking velocity and/or walking distance to adhere the protocol.

In subjects who were taking medication, during the entire monitoring period was maintained the best possible therapy. Changes in the drug treatment administered were not permitted during the study except for the requirements related to glycemic control in diabetics to avoid the risk of hypoglycaemia, exacerbated by the increase in the level of daily physical activity.

The total duration of home-based fast walking programme was set in 24 weeks.

All the subjects enrolled completed the 24 weeks of training period.

At the end of the training period were repeated blood tests, were reassessed anthropometric parameters and was repeated a ABPM.

Statistical analysis

Statistical analysis of quantitative and qualitative data, included descriptive statistics, was performed for all the items. Continuous data were expressed as mean ± standard deviation, unless otherwise specified. The paired samples Student's *t*-test procedure was used to compare the mean differences in continuous anthropometric and laboratoristic variables before and after the intervention.

Discrete variables were analysed using the χ^2 and Fisher's exact test, as needed.

The McNemar–Bowker analysis was used to test for symmetry between the dipping and MS pattern before and after training period. Data were analysed by the Epi info software (version 6.0, CDC, Atlanta, GA) and the Spss Software 14.0 version (SPSS, Inc., Chicago, IL). All p-values were two-sided and p-values less than 0.05 were considered to indicate statistical significance.

Results

Anthropometric, clinical, anamnestic and metabolic parameters assessed at baseline are reported in Table 1.

Table 1 Main anthropometric, clinical and laboratoristic variables on admission and after 24 weeks of home-based regular exercise in the trained group

	Admission	After intervention	p
Number of patients enrolled	176		
M/F (n)	95/81		
Age (years)	59.1 ± 7.47		
Weight (kg)	86.04 ± 4.73	79.58 ± 3.32	0.0001
BMI	31.59 ± 4.84	29.23 ± 3.79	0.0001
Waist circumference (cm)	105.19 ± 11.78	100.06 ± 9.67	0.0001
Hypertension (n/%)	158 (89.77)		
Diabetes (n/%)	64 (36.36)		
Glucose blood levels (mg/dl)	119.76 ± 38.38	114.32 ± 28.63	0.0001
HbA1c (diabetics only) (%)	7.38 ± 1.19	6.86 ± 0.67	0.0001
Creatinin (mg/dl)	1.03 ± 0.54		
Cr Cl (ml/min)	99.50 ± 40.93		
Fibrinogen blood levels (mg/dl)	339.68 ± 63.19	314.86 ± 39.71	0.0001
hs-CRP (mg/dl)	0.55 ± 0.87	0.28 ± 0.27	0.0001
White blood cells (mm^3)	7361.08 ± 1659.62	7022.56 ± 1007.86	0.0001
Total Cholesterol blood levels (mg/dl)	192.15 ± 38.61	185.78 ± 37.37	0.001
HDL Cholesterol blood levels (mg/dl)	44.03 ± 10.44	47.63 ± 9.13	0.0001
Triglycerides blood levels (mg/dl)	148.29 ± 57.73	135.2 ± 34.48	0.0001
24-h SBP (mmHg)	133.06 ± 15.23	129.47 ± 11.88	0.0001
24-h DBP (mmHg)	76.62 ± 9.74	74.04 ± 7.83	0.0001
24-h HR (bpm)	71.86 ± 8.99	70.12 ± 7.19	0.0001
Anamnestic cerebrovascular event (n/%)	23 (13.1)		
Anamnestic CHD (n/%)	31 (17.6)		
Anamnestic PAD (n/%)	10 (5.7)		
Liver steatosis (n/%)	122 (69.32)		
COPD (n/%)	9 (5.1)		
Current smokers (n/%)	32 (18.2)		
Statin use (n/%)	62 (35.2)		

Data are presented as mean value ± SD. BMI, Body Mass Index; Cr Cl, creatinine clearance (calculated through Cockroft and Gault formule); hs-CRP, high sensitivity C-reactive protein; CHD, coronary heart disease; PAD, peripheral artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

After the 24 weeks of intervention in the trained group, BMI changed from 31.59 to 29.23 ($p < 0.0001$); mean waist circumference passed from 105.19 to 100.06 cm ($p < 0.0001$); mean fasting glucose changed from 119.76 to 114.32 mg/dl ($p < 0.001$); for diabetic population ($n = 64$) mean glicated haemoglobin levels changed from 7.38% to 6.86% ($p < 0.0001$); total cholesterol levels from 192.15 to 185.78 mg/dl ($p < 0.001$); HDL cholesterol levels raised significantly from 44.03 to 47.63 mg/dl ($p < 0.0001$); triglycerides levels lowered from 148.29 to 135.20 mg/dl ($p < 0.0001$); white blood count changed from 7361.08 to 7022.56/mm^3 ($p < 0.001$); CRP from 0.55 to 0.28 mg/dl ($p < 0.001$); fibrinogen serum levels lowered from 339.68 to 314.86 mg/dl.

Evaluation of the data collected through the pedometer (see Table 2) shows already at 12 weeks but more at 24 weeks, a significant increase in physical activity levels of the subjects at home. Mean total number of steps walked day was reported of 8851 ± 921 at 12 weeks and 9224 ± 771 at 24 weeks. Mean total number of aerobic steps (evaluated

Table 2 Pedometer data in the trained group

	12 weeks	24 weeks
Total number of steps/day	8851 ± 921	9224 ± 771
Total number of aerobic steps/day	6988 ± 574	7234 ± 610
Total distance walked (km/day)	6.63 ± 0.69	7.05 ± 0.77
Total aerobic distance walked (km/day)	5.12 ± 0.44	5.36 ± 0.52
Estimated total energy expenditure (kcal/day)	425 ± 52	459 ± 68

Data are presented as mean value ± SD.

separately from the pedometer for a walking velocity higher than 60 steps per minute and more than 10 min consecutively) was 6988 ± 574 at 12 weeks and 7234 ± 610 at 24 weeks. The mean total distance covered every day at 12 weeks was of 6.63 ± 0.69 km of which 5.12 ± 0.44 km aerobic (attributable to fast walking); at 24 weeks mean total distance covered every day was of 7.05 ± 0.77 km of which 5.36 ± 0.52 km aerobic. The estimated total energy expenditure/day because of steps walked was of 425 ± 52 kcal at 12 weeks and 459 ± 68 kcal at the end of the training period.

Discussion

Over the past decade, until the first description provided by Ross (16), an impressive amount of evidences has accumulated about the relationship between systemic inflammation, the atherosclerotic disease, the CV risk factors, the MS and the endothelial dysfunction (8,9,17).

Although it is yet to be proven whether inflammation is the cause rather than an effect of the mechanism underlying development of the features of MS in healthy individuals in these years is strongly affirming the conviction that a state of subclinical inflammation represents a pathological background of several pathologic conditions. It is well established that inflammatory markers predict the development of diabetes and glucose disorders (18) and that CRP appears to be independently associated with incident isolated systolic hypertension in healthy population (19). So, relationship between chronic low-grade systemic inflammation, as defined before (8) and the main findings of MS is very close.

Effectiveness of regular physical exercise against the main CV risk factors, obtaining a whole anti-atherosclerotic effect, is well established (4,6,7). The attempt to explain the systemic effects of muscular contraction lead to the recent evidence that contracting human skeletal muscle releases significant amounts of cytokines and chemokines, called 'myokines' (20). These myokines interact not only with the immune system, but are supposed also to exert several metabolic ways, giving a possible explanation of the metabolic changes following chronic regular exercise (21). Several of the myokines, released from the muscle fibres during contraction (Il-6, IL-10, IL-15, Il-1 receptor antagonis (IL-1ra), soluble TNF-α receptor (sTNFr), unrelated to muscular damage, seems to have anti-inflammatory properties (11).

On this basis, several authors tried to demonstrate that physical exercise has an anti-inflammatory activity per sè, by acting through several mechanisms involving inhibition of pro-inflammatory, and stimulation of anti-inflammatory pathways. Balducci et al. (22) recently assessed that physical exercise in type 2 diabetic patients with the MS is associated with a significant reduction in hs-CRP and other inflammatory and insulin resistance biomarkers, independent of weight loss.

Similar assessments were made in non-diabetic hypertensives and in other populations at high levels of CV risk by extending the analysis not only to the main biomarkers of systemic inflammation but also to pro-inflammatory cytokines such as IL-6, TNF, IL-1, etc. (23–25). Although the mechanisms by which the exercise exerts its anti-inflammatory action are clear only in part, the many existing studies confirm for different types of exercise, different intensities and in different populations the anti-inflammatory effect in addition to the improvement of the control of CV risk factors, agreeing that only programmes for medium-long term are proven to be effective in achieving these goals.

In this frame, in addition to what is already known about this topic, our study provides convincing evidence that a light-to-moderate long-term home-based programme of aerobic physical activity performed on sedentary adults with MS can help control the main CV risk factors, providing furthermore a down-regulation of the systemic inflammation.

Our patients did not reach the threshold of 10,000 steps daily (26), but our aim was to shift the focus from the number of total steps to the number of aerobic steps, namely the importance of walking for a long period of time at a constant speed and higher than to that considered normal by the patient.

Our data, although not supported by the assessment of changes in serum levels of inflammatory cytokines, appear to confirm as evidenced by previous report (25), demonstrating that a home-based exercise programme conducted in sedentary subjects can lead to a significant improvement both of the BP profile and of the other indices linked to MS, showing also an anti-inflammatory effect as demonstrated by the reduction in the main indices of systemic inflammation. But in addition to what was previously observed, our study provides evidence that these metabolic improvements added to a reduction in the main markers of chronic subclinical inflammation could be obtained without resorting to heavy programmes, associated with a very low rate of long-term adherence (12).

In our series, no patients left the study before its completion. The common experience tells us that compliance is one of the main problems of physical activity programmes, and in fact in our study only a strict preselection has allowed us to achieve a result

so significant, but this really encouraging result confirms that a home-based physical activity programme centred on fast walking, monitored through the use of a pedometer, could be well accepted by patients who are adequately motivated by the doctor. In our experience, the use of a pedometer may prove to be an effective tool for promoting healthy lifestyle changes that include daily physical activity and self-monitoring of therapeutic goals, as reported elsewhere (27). This tool is a possible solution to the problem of poor compliance (28) shown by many patients against types of exercise that involve expensive equipment or are not easily accessible.

About the 64 diabetic patients enrolled in our study, it should be noted that approximately half were treated with insulin while others taking oral antidiabetic drugs. In 19 of these (10 treated with insulin, 9 under oral antidiabetic drugs), it was necessary to reduce the dose of the medication as a secondary consequence of the reduction in blood glucose levels under exercise. It should be noted that also in this subgroup of patients at the end of the study, there was a statistically significant reduction in blood glucose and glycosylated haemoglobin levels, and that this improvement in glycemic control was achieved despite the reduction in the dosage of antidiabetic therapy carried out in some of them.

In conclusion, a home-based programme of aerobic physical activity centred on fast walking monitored through the use of a pedometer provides both metabolic and anti-inflammatory properties in sedentary adults with MS.

Author contributions

D. Di Raimondo, C. Buttà, G. Miceli, L. Giarrusso enrolled patients, followed the exercise programme, collected data. D. Di Raimondo designed the study, wrote the article, performed data analysis and interpretation. A. Tuttolomondo revised the article and revised English language. A. Casuccio performed statistical analysis. G. Licata and A. Pinto critically revised the article.

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