Accepted Manuscript

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Please cite this article as: Bellia Alfonso, Iellamo Ferdinando, De Carli Elisa, Andreadi Aikaterini, Padua Elvira, Lombardo Mauro, Annino Giuseppe, Campoli Francesca, Tartaglione Sara, D'Ottavio Stefano, Della-Morte David, Lauro Davide, Exercise Individualized by TRIMPi Method Reduces Arterial Stiffness in Early Onset Type 2 Diabetic Patients: A Randomized Controlled Trial with Aerobic Interval Training, *International Journal of Cardiology* (2017), doi:10.1016/j.ijcard.2017.06.065

Exercise Individualized by TRIMPi Method Reduces Arterial Stiffness in Early Onset Type 2 Diabetic Patients: a Randomized Controlled Trial with Aerobic Interval Training

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* This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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The authors report no relationships that could be construed as a conflict of interest.

Abstract

Background: Arterial stiffness (AS) and baroreflex sensitivity (BRS) are subclinical markers of vascular diseases in type 2 diabetes (T2D). We evaluated the effects of aerobic interval training (AIT), with loads prescribed according to individual heart rate and lactate profiling obtained during a baseline treadmill test (TRIMPi method), on AS and BRS in patients with early-onset T2D without cardiovascular complications.

Population study and methods: Twenty-two sedentary overweight T2D patients (aged 57 ± 7 years) were randomized to 12-weeks open-label of supervised AIT by TRIMPi (n=8) or unsupervised physical activity as per usual care (SOC) (n=11). Following parameters were evaluated (pre- and post-): anthropometrics; six-minute walking test (6MWT); fasting glucose, insulin, HbA1c; Pulse Wave Velocity (PWV) and Augmentation Index (AIxHR75) using radial approach (SphigmoCor System); BRS using Finapress method.

Results: Both interventions significantly improved distance walked during 6MWT (AIT 52 ± 21 m; SOC 39 ± 24 m, $p<0.001$ for both). PWV significantly improved with AIT ($p<0.001$) whereas did not vary with SOC ($p=0.47$). Similar trend was observed for AIxHR75. Resulting percent changes from baseline were significantly better for AIT vs SOC, in both PWV (-15.8 ± 2.1 vs $+1.50\pm3.4\%$, $p<0.001$) and AIxHR75 ($-28.9\pm3.2\%$ vs $+12.7\pm2.4\%$, $p<0.001$). BRS similarly improved in both groups ($p<0.001$ for both), as well as body weight, HbA1c and blood pressure.

Conclusion: In sedentary T2D patients, 12-weeks AIT individualized by TRIMPi method improved AS to a greater extent than usual recommendation on physical activity, whilst exerting comparable effects on exercise capacity, glycemic control and body weight. Further researches are needed to ascertain durability of these effects.

Introduction

Current guidelines largely emphasize the role of physical activity as therapeutic tool for prevention of cardiovascular diseases (CVD) in patients with type 2 diabetes (T2D) at every stage of disease [1-2]. Aerobic exercise training (and resistance as well) has been shown beneficial in ameliorating glycemic control and risk for CVD in T2D [3]. However, little is known about which exercise training modality(s) is the most effective to maximize these benefits. "Moderate-intensity physical activity (e,g., brisk walking) for at least 150 min/week" is currently the most recommended in patients with T2D [2]. Nevertheless, the optimal "dose" of exercise, defined in terms of volume and intensity of exercise, required to achieve improvements in functional capacity and prognostic parameters for these patients, still remains a crucial issue [4-6]. This is particularly true for patients with T2D, for whom hyperglycemia with its related pathophysiological derangements is demonstrated to determine macrovascular dysfunction including arterial stiffening and impaired baroreflex-sensitivity, both significantly associated with cardiovascular complications and mortality [7,8]. As with pharmacological therapy, physical activity should be tailored according to clinical characteristics and functional status of the patient, in order to improve adherence and maximize the potential benefits that exercise can exert in the long term [9]. Iellamo et al. recently proposed a new exercise training methodology that permits to account, in a single term, for both intensity and volume effects on the physiological systems on an individual basis [10-11]. This method has been referred to as individualized TRaining IMPulses (TRIMPi) and represents an integrated and individualized measure of the aerobic training load. Aerobic training according to the TRIMPi method, either with interval or continuous protocols, has been shown to significantly improve functional capacity [12], metabolic and autonomic cardiac control [13] in patients with CVD.

In all studies conducted so far in T2D patients, the relationship between training and metabolic and cardiovascular adaptations has been investigated without regard for individual training dose. It needs to be recognized that contributions documented at the level of a patient's group may not fully apply to each member of that group even when all patients of the exercising group are exposed to

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the same volume/intensity of physical activity adjusted for their own tolerance level [12]. In this study, we tested the hypothesis that a short-term aerobic interval training program planned according to TRIMPi could improve metabolic risk factors, arterial stiffness ad autonomic cardiac control to a greater extent than that based on current, general recommendations [2] in sedentary adults with early-onset T2D.

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Methods

Participants and study design

This randomized, open label, parallel, two-arms intervention study was approved by the Independent Ethics Committee of the University Hospital "Policlinico Tor Vergata" (Rome, Italy) and conducted according to the Declaration of Helsinki. Written informed consents were obtained from all participants. Subjects were recruited among those attending the outpatient service of the Diabetology Unit of the "Policlinico Tor Vergata" University Hospital between 2014 and 2015. Eligibility criteria were as follows: (a) presence of T2D according to ADA diagnostic criteria [14] treated with metformin alone up to 2 g/daily; (b) known duration of disease below 10 years; (c) age 40-60 years; (d) body mass index (BMI) <30 with stable body weight within 12 weeks before screening; (e) glycated hemoglobine (HbA1c) <7.5% ; (f) no evidence of uncontrolled hypertension, metabolic diseases other than diabetes and no history of cardiovascular, neoplastic or other systemic diseases; (h) sedentary habits and (i) ability to perform physical activity. At baseline and study end, each patient underwent physical examination, including anthropometric measurements, six-minute walking test (6MWT), blood examinations, evaluation of arterial stiffness (AS) and autonomc cardiac control, which included baroreflex sensitivity (BRS) and time-domain heart rate variability (HRV). Pharmacological therapy was not changed throughout the study.

Physical examination and dietary counseling

Physical examination included heart rate (HR), systolic (SBP) and diastolic (DBP) pressure, height, weight and body mass index (BMI) measurements. Patients were asked not to change their dietetic habits during the study. For this purpose, they were monthly visited by a nutritional consultant and self-administered dietary questionnaires were used to check adherence to recommendations.

Six-minute walking test (6MWT)

The test was performed along a corridor of 30 m, with rigid gear surface, free of obstacles. After 10 minutes of sitting rest, patients were required to walk at the best of their ability throughout the route for six minutes. At the end of test, the distance covered (meters) were recorded.

Biochemical and metabolic assessments

Fasting glucose, total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C) and triglycerides were assessed by standard immuno-enzymatic methods. Insulin levels were measured by an immunoradiometric assay and HbA1c by high-performance liquid chromatography (HPLC). All these measurements were performed twice and the inter-assay and intra-assay coefficients of variation ranged from 1.4 to 5.1%. Insulin-resistance was estimated using the HOMA-IR index [15].

Assessment of arterial stiffness (AS)

Arterial stiffness was assessed by regional quantification of radial pulse wave velocity, which represents the speed of a pressure wave propagating down the blood vessel, related in turn with the vessel elastic modulus [16, 17]. Increased pulse wave velocity as a consequence of peripheral arterial stiffening is the basis for further indices of aortic stiffness, as described below. Evaluations were performed in the early morning after a 10-min rest period. After blood pressure measurement, an arterial pressure waveform was non invasively recorded by applanating the radial artery with a hand-held tonometer (Sphygmocor apparatus by ATCOR Medical, Sydney, Australia). Resulting data were registered into a dedicated laptop. Central waveform used for assessments was derived by the integral software after 20 sequential waveforms had been acquired. Central aortic pressure waveforms were derived from the radial artery waveforms by using a transfer function. The following parameters were measured: (i) augmentation pressure (AP), which is the difference between the second reflected and the first (primary) wave; (ii) augmentation index (AIx@75), which is the difference between the second and the first peaks of the central aortic waveform

expressed as a percentage of the aortic pulse pressure (adjusted for standard heart rate of 75 bpm); (iii) aortic systolic and diastolic pressures; (iv) aortic pulse pressure; (v) pulse wave velocity (PWV), which is the travel time (m/sec) of a pressure wave from common carotid to radial artery, as measure of aortic compliance [18].

Assessment of cardiac autonomic control

BRS was assessed by means of sequences technique by analyzing simultaneous recordings of non-invasive finger beat-by-beat BP (Finapres, Ohmeda 2350, Englewood CO, USA) and electrocardiographic trace from a precordial lead at a sampling rate of 250 Hz (REP 10, Marazza, Italy), as described previously [19]. The sequences method allows a quantification of the baroreceptor-cardiac reflex sensitivity at the current prevailing levels of arterial pressure and R-R interval and reflects vagally mediated baroreflex responses. Heart rate variability considered in the present study was the standard deviation of mean R–R interval. The experiments were performed in the morning in a room at ambient temperature (22 °C to 24 °C) with the patient laying supine for 15 min before experiments to relax in the room made dark and noiseless. Subjects were required not to eat or drink caffeinate beverages for at least 3 h. After instrumentation, blood pressure (BP) was measured twice by sphygmomanometry and subsequent continuous data acquisition was performed for 10 min. All post-training assessments were performed at least 24-h after the last exercise session.

Exercise test

At baseline, all patients underwent progressive incremental treadmill test until volitional fatigue, using a modified Bruce protocol, for the assessment of individual blood-lactate concentration profile and maximal HR. Capillary blood samples were taken from the ear lobe with a sterile lancet 1 min before the test, each 3 min during the test and 3 min after the end. The blood sample (about 5 μl) was immediately analyzed to assess blood-lactate concentration using an electro-enzymatic

technique (Lactate Pro-YSI 1500 Sport, Yellow Springs Instruments, Yellow Springs, OH, USA). Before each exercise test, the analyzer was calibrated following the instructions of the manufacturer using standard lactate solutions of 0, 5, 15, and 30 mmol L−1. The highest HR measured during the maximal incremental test was used as maximum reference value (HRmax). Blood lactate concentrations were plotted against running speeds and fractional HR elevation (ΔHR), and individual blood-lactate concentration profiles were identified via exponential interpolation [11].

TRIMPi calculation

As previously reported [12], the training impulse method (TRIMP) is based on the ΔHR (HRexercise−HRrest/HRmax−HRrest) as main exercise variable. The duration of any specific training session is multiplied by the average ΔHR achieved during that session. To avoid giving a disproportionate importance to long-duration activity at low ΔHR levels compared with intense but short-duration activity, the ΔHR is weighted by a multiplying individual factor (y), in a way that reflects the intensity of effort. This y factor is based upon the exponential rise of blood lactate levels with the fractional elevation of exercise above resting HR [12]. This factor serves to equate the TRIMP scores of exercises of long duration and relatively low HR with exercises of short duration and high HR. Thus, overall:

TRIMP = time (min) · ΔHR · *y*

where *y* is a nonlinear coefficient given by the equation: $y = 0.64e^{1.92x}$

with e = base of the Napierian logarithms and x = ΔHR

This TRIMP method utilizes the mean exercise HR during an exercise bout, and the multiplying factor y is computed using two constants in the equation (b, c) that are equal for all subjects. The use of the mean exercise HR and the same multiplying factor y potentially miss to reflect the individual physiological demands of each training session [10], introducing an individual weighting factor (y_i) for each subject. This y_i reflects the profile of a typical blood lactate response curve to increasing exercise intensity. Individual y_i values are calculated for each subject with the best fitting

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method using exponential models [10] so that, with increasing exercise intensity as indicated by the HR response, the weighting factor y_i increases exponentially. Thus, for each training session, an individualised TRIMP (TRIMP$_i$) can be calculated at any time as the area under the curve represented by the pseudo-integral of all ΔHR data points [10].

Exercise training/physical activity interventions

Patients randomized to individualised aerobic interval training (AIT), exercised on treadmill according to the following program:

Warm up: 10 'at 40-60% of HRmax. *Workout*: 4 minutes walk to 75-80% of the HRmax reference to be repeated 2 to 4 times per training session interspersed with active 3-minute recovery to 45-50% of the HRmax. Workload (speed, incline and serial number) was gradually adapted to the level of efficiency achieved by the subject (the training impulse method –TRIMP-). *Cool down*: 10' at 40-50% of HRmax.

Weekly attendance: (i) 2 times a week for the first and the second week, for 2 reps; (ii) 3 times a week for the third and fourth week x 2 reps; (iii) 3 times a week for the fifth and sixth week x 3 reps; (iv) 3 times a week from the seventh onwards x 4 reps.

Subjects were instructed on rating self-perceived exertion according to the Borg scale [20]**.** All training sessions were performed in the morning and supervised by a physical therapist. Adherence was defined as attending to ≥80% of planned sessions.

Patients in the control group (SOC) were provided with a pedometer and asked to perform at least 10,000 steps per day or 70,000 steps per week of non-supervised brisk walking, as reported elsewhere [21]. Patients were allowed to visualize the number of steps in order to reach the daily or weekly targets. A daily report of physical activity was provided by the device and used to monitor adherence to recommended physical activity. Adherence was defined as performing ≥ 80% of recommended amount of weekly physical activity.

Statistical analysis

Normality of distribution was assessed by the Kolmogorov-Smirnov test. Between groups differences in baseline characteristics were evaluated by χ^2 test and unpaired t-test. Within groups changes in the reported variables were evaluated by the paired-*t* test or Wilcoxon signed ranks test, as appropriate. Between groups changes were evaluated by the unpaired *t*-test and Mann-Whitney rank sum test, as appropriate. All these analyses were performed in the *per protocol* population, namely those patients who fulfilled the protocol in the terms of adherence to intervention and outcome assessments. Results are expressed as means ± SD for normally-distributed variables whereas skewed variables were expressed as median and interquartile range (25-75%). A *p* value <0.05 was considered statistically significant. All analyses were performed using SPSS software for Windows version 15.0 (SPSS, Chicago, IL).

Results

Fig. 1A shows the flow diagram of the study. Nine individuals out of 38 patients assessed for eligibility were excluded because they did not fully meet eligibility criteria or declined to participate. Twenty-nine patients were randomly assigned to AIT according to TRIMPi method (n=15) or usual recommendations as per standard of care (SOC) (n=14). Overall, seven subjects were discontinued from the study because of low adherence to interventions. Therefore, twenty-two patients completed the study and were included in the final analysis. Table 1 shows main clinical features of the study population, stratified by treatment groups. At study entry, patients had suboptimal glycemic control (mean HbA1c >6.5%) according to current guidelines [2]. Most of them were overweight/obese (mean BMI >27) and hypertensive (15 out of 22 patients). Overall, main clinical features did not differ between groups at baseline, except for the higher number of hypertensive patients in the SOC group (10/11) compared to AIT group (5/10). However, both mean SBP and DBP were not significantly different between groups. Of note, baseline exercise capacity was superimposable between AIT and SOC groups, as indicated by the distance walked at

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the 6MWT (600±43 vs 572±24 m, respectively, p=0.31). After 12 weeks, both interventions significantly improved exercise capacity and HbA1c levels without significant differences between the two groups (Fig. 1B and Table 2). As shown in Table 2, both AIT and SOC programs induced a significant improvement in metabolic parameters and blood pressure levels, as well as in body weight, but without significant differences between training programs. On the other hand, no significant changes from baseline were observed in fasting glucose, insulin, HOMA-IR and lipid profile, in both groups.

The effects of AIT and SOC on arterial stiffness and neural cardiac regulation are reported in Table 3. Patients in the AIT experienced significant improvements in AIx@75 and PWV. As shown in Figure 1C, percent changes from baseline in Aix@75 were -26.9±3.2% for AIT and +7.1±2.4% for SOC, respectively (p<0.001 for difference between groups), whereas percent changes from baseline in PWV were -21.2±2.1% and +1.5±3.4%, respectively (p<0.001 for difference between groups). Finally, BRS increased significantly from baseline with both AIT and SOC, without, however, significant differences in the magnitude of changes between the two training programs (Figure 1D). The same trend was observed for HRV (data not shown).

Discussion

The main findings of the present study are that a structured, individualized, short-term aerobic exercise training program can improve arterial function in patients with uncomplicated, early-onset, type 2 diabetes. These findings should be placed in the context of the growing evidence indicating that exercise training should be individually tailored according to patient's clinical and functional status. To our knowledge, this is the first study reporting that an actual individualized aerobic training program induces a significantly improvement in augmentation index (Aix) and pulse wave velocity (PWV) in comparison to a generally recommended, yet controlled (in this study), physical activity program in diabetic patients.

Arterial stiffness, measured as PWV in the aorta, is a strong predictor of cardiovascular risk and mortality in people with hypertension, metabolic syndrome and diabetes mellitus [22-25]. Similarly, AIx is a measure of vascular function, possibly representing an early indicator of vascular damage [26]. Hence, their improvement by exercise training early in the course of the disease could carry a protective effect in the long term. Indeed, some studies reported beneficial effects of exercise training on arterial stiffness in terms of lowering PWV in patients with T2D [26, 27], but these findings might have been confounded by the presence of several comorbidities [27] and the lack of control groups [26], factors that have been carefully considered in our study. Interestingly, improvement in arterial stiffness with supervised AIT occurred without a concomitant significant difference in the improvement of functional capacity between AIT and SOC, having this parameter increased to a comparable extent in both groups. These findings indicate that individualized exercise training can reverse arterial stiffening in uncomplicated T2D, before the occurrence of overt vascular complications, independently of other benefits on cardiovascular function and exercise tolerance [27]. This result would support the concept that protective effects of exercise on vascular structure are more likely to occur as the intervention is started early during the natural course of diabetes.

Mechanism(s) responsible for the improvement of vascular function cannot be elucidated by this study. It is possible that repeated increases in shear stress induced by interval training, with the resultant activation of the nitric oxide pathways [28], may have a crucial role in this scenario. In addition, diabetes has been shown to accelerate vascular aging [29] through non-enzymatic glycation, leading to formation of increased collagen crosslinks resulting in increased arterial stiffness [30]. Thus, it is possible that pulsatile stretching of collagen fibers during aerobic exercise can break these collagen crosslinks, potentially reversing the arterial stiffening process [31]. Results of the present study fulfilled only in part our hypothesis, since individualized training program did not improve autonomic cardiac control and metabolic risk factors to a greater extent than that occurring with a generally-recommended, unstructured, physical activity plan. It could be argued

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that physical activity as recommended by usual standards of care, when combined with strong adherence to prescription, as indicated in this study by pedometric data, is as effective at improving glucose metabolism and cardiac autonomic control as an individualized, structured, aerobic exercise training program. However, this explanation, although likely, fits only in part with the divergent finding between metabolic/autonomic and vascular responses. It could be that the more subtle molecular and biochemical changes at the level of vessels wall require a more structured and individualized exercise training regimen to manifest in comparison to the metabolic and autonomic responses, these latter reflecting more generalized adaptations to training. Indeed, there is general consensus on the beneficial effects of any kind of aerobic physical activity on glucose and lipid metabolism and autonomic control, whereas the benefits at molecular and biochemical level possibly leading to changes in vascular functioning (not addressed in this study) are less recognized [32]. This is not a subtle point, since vascular dysfunction is considered one of the earliest pathophysiological processes in the progression to atherosclerosis associated with metabolic disease [33].

Strengths of this study are the use of a HR monitoring device and therapist's supervision in all training sessions in the AIT group, which allowed us to verify full adherence of patients to prescribed training protocols, not just attendance, and the objectively measured amount of actually performed physical activity according to current recommendations in the SOC group, through the use of pedometers. Furthermore, we compared the effects of two exercise regimens in the same, homogenuous population of diabetic patients rather than comparing patients vs healthy subjects. This makes us more confident on the actual effectiveness of the interventions in a given patients population.

The main limitation of the present investigation is the small sample size. As such, the study should be regarded as a "proof-of-concept" study. Second, autonomic evaluation was essentially based on the assessment of heart rate variability by standard deviation of R-R interval, which has been largely validated in literature. Whilst we cannot rule out the hypothesis, we do not believe our

results would have been different by using other additional indicators of autonomic regulation. There may be also sex differences in the effects of exercise training on arterial stiffness that could not be detected, given the small number of male vs. female subjects. It will also be important to conduct longitudinal studies to identify whether the beneficial effects of short-term exercise training on lowering arterial stiffness is maintained, and whether persistent, individualized exercise training can delay or prevent worsening of diabetes and its CV complications. Indeed, we cannot comment on clinical outcomes. However, clinical outcome was not the focus of the study, and, as such, any uncertainty relating to clinical outcomes should not detract from the novelty of the study.

In conclusion, the present study indicates that individually-tailored aerobic exercise training is an effective tool to reduce arterial stiffening in addition to improve CV risk profiles in patients with early-onset, uncomplicated, T2D. The TRIMPi method could represent a step forward in the individualization of an aerobic training tailored to the patient's clinical and functional status within the wide armamentarium of life-style changes and pharmacological therapy, although these finding must be confirmed by larger, active-controlled studies.

Figures Legend

Figure 1: (A) Flow chart of the study. **(B)** Distance covered during 6MWT at baseline (white bars) and after exercise interventions (black bars) in individualized aerobic interval training (AIT) and physical activity as per standard of care (SOC) groups. * $p < 0.05$ vs relative baseline. **(C)** Percentage changes in heart rate-adjusted augmentation index (AIx@75) and pulse wave velocity (PWV), induced by individualized aerobic interval training (AIT, white bars) and physical activity as per standard of care (SOC, black bars). **(D)** Baroreflex sensitivity (BRS) at baseline (white bars) and after (black bars) individualized aerobic interval training (AIT) and physical activity as per standard of care (SOC).

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Fig. 1

A

B

C

34.
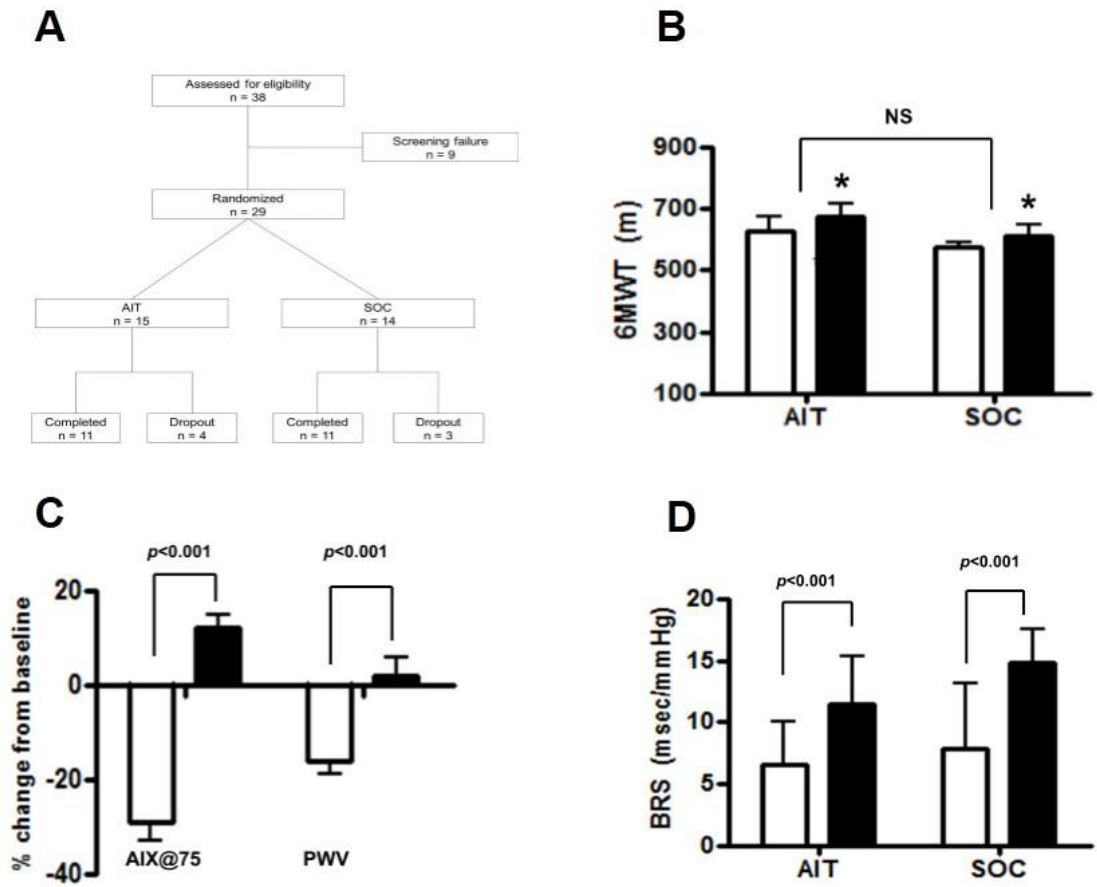
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Table 1. Baseline characteristics of patients stratified by groups

	AIT	SOC	*p*
	(n = 11)	(n = 11)	
Age (years)	58.8±7.9	56.3±6.4	0.42
Duration of diabetes (years)	5.9±4.4	3.4±3.7	0.16
Men/Women (n)	9/2	7/4	0.41
Hypertension (n)	5	10	0.001
Weight (kg)	76.8±11.2	81.0±12.7	0.42
BMI (kg/m²)	27.7±2.8	29.9±3.4	0.06
Total cholesterol (mg/dl)	165±30	179±31	0.32
HDL cholesterol (mg/dl)	55±11	51±15	0.54
LDL cholesterol (mg/dl)	88±30	97±27	0.47
Triglycerides (mg/dl)	104 (83-131)	111 (82-138)	0.82
Fasting glucose (mg/dl)	133±17	125±25	0.41
Fasting insulin (µU/ml)	10.7 (9.8-18.4)	16.5 (11.6-27.4)	0.08
HbA$_{1c}$ (%)	6.9±0.3	6.8±0.9	0.74

HOMA-IR	3.42 (3.00-6.35)	5.08 (2.9-8.4)	0.39
SBP (mmHg)	131±11	133±10	0.63
DBP (mmHg)	79±6	80±6	0.87

Data are expressed by means±SD or median (interquartile range) according to normality distribution.

AIT, individualized aerobic interval training; SOC, physical activity as per standard of care.

Table 2. Changes in weight, metabolic parameters and blood pressure by treatment groups

	AIT (n = 11)	SOC (n = 11)	*p*
Body weight (Kg)	-1.9 (-0.3;-3.5)	-1.7 (-0.2; -3.3)	0.89
HbA1c (%)	-0.3 (-0.4; -0.7)	-0.4 (-0.07; -0.8)	0.72
Fasting glucose (mg/dl)	1 (-14; 15)	10 (-6; 27)	0.34
Fasting insulin (μU/ml)	0.3 (-3.5; 4.2)	2.8 (-3.8; 4.6)	0.47
HOMA-IR	0.11 (-1.28; 1.50)	0.89 (-1.63; 2.11)	0.39
Total cholesterol (mg/dl)	11 (-3; 25)	-3 (-16; 11)	0.14
HDL cholesterol (mg/dl)	4 (-2; 9)	2 (-4; 7)	0.63
LDL cholesterol (mg/dl)	4 (-5; 14)	-4 (-18; 10)	0.28
Triglycerides (mg/dl)	13 (-27; 54)	-3 (-65; 59)	0.62
SBP (mmHg)	-7 (-14; 1)	-5 (-11; 2)	0.65
DBP (mmHg)	-3 (-7; 3)	-2 (-7; 4)	0.71

Data are expressed as median and interquartile range. AIT, individualized aerobic interval training; SOC, physical activity as per standard of care; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Changes in arterial stiffness parameters by treatment groups.

	AIT (n = 11)		SOC (n = 11)	
	PRE	POST	PRE	POST
Aortic Pulse Pressure (mmHg)	39 (35; 48)	37 (33; 49)	44 (33; 50)	42 (37; 46)
Aortic Systolic Pressure (mmHg)	117 (112; 125)	120 (113; 129)	122 (111; 131)	125 (117; 130)
Aortic Diastolic Pressure(mmHg)	75 (71; 81)	76 (71; 81)	81 (77; 82)	78 (70; 90)
AIx@75 (%)	26 (23; 28)	19 (16; 24)*	28 (23; 31)	30 (23; 37)
AP (mmHg)	15 (8; 17)	12 (9; 14)	14 (8; 17)	14 (8; 21)
PWV (m/s)	7.4 (6.9; 8.9)	4.8 (3.2; 6.6)†	7.5 (6.8; 7.9)	7.6 (6.4; 8.4)

Data are expressed as median (interquartile range). AIT, individualized aerobic interval training; SOC, physical activity as per standard of care. AIx@75 (%), augmetation index; AP, augmentation pressure; PWV, pulse wave velocity. * $p<0.01$, † $p<0.001$ vs relative baseline value.