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Article

Effects of Low-Volume High-Intensity Interval Training Compared to Moderate-Intensity Continuous Training on Inflammatory Profile in Women with Type 2 Diabetes

Alexis Marcotte-Chénard [1,2], Renaud Tremblay [1,2], Marie-Michelle Mony [1,2], Dominic Tremblay [1,2], Pierre Boulay [1], Martin Brochu [1,2], José A. Morais [3], Isabelle J. Dionne [1,2], Marie-France Langlois [4,5], Warner Mampuya [4], Daniel Tessier [2,4], Eléonor Riesco [1,2,*]

[1] Faculty of Physical Activity Sciences, University of Sherbrooke, Sherbrooke, QC J1K 2R1, Canada

[2] Research Centre on Aging, CIUSSS de l'Estrie-CHUS, Sherbrooke, QC J1H 4C4, Canada

[3] Research Centre of McGill University Health Centre (MUHC) and Division of Geriatric Medicine of MUHC, Montréal, QC H4A 3J1, Canada

[4] Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, QC J1H 5N4, Canada

[5] Research Centre of the CHUS, Sherbrooke, QC J1H 5N4, Canada

* Correspondence: Eléonor Riesco, Email: e.riesco@usherbrooke.ca; Tel.: +1-819-821-8000 (ext. 63337).

ABSTRACT

Background: The objective was to compare the effects of low-volume high-intensity interval training (HIIT) to moderate-intensity continuous training (MICT) on the inflammatory profile in older women with type 2 diabetes (T2D).

Methods: Thirty older physically inactive women (68 ± 5 years) with T2D were randomized in two groups: HIIT (75 min/week with 10 min/session at high intensity) or MICT (150 min/week). Inflammatory profile (IL-6, IL-10, IL-15, TNF-α, and MCP-1; Luminex), body composition (iDXA), and cardiometabolic profile (A1c, glucose, insulin, lipids) were measured in fasting state, before and after the 3-month intervention in 27 participants.

Results: While fasting levels of cytokines remained unchanged in the MICT group ($p \geq 0.18$), circulating MCP-1 levels increased (from 160.9 [IQR: 133.5–230.2] to 187.88 [155.3–237.3]) in the HIIT group ($p = 0.023$). Linear regression revealed that changes in MCP-1 concentrations were positively associated with changes in A1c (*adjusted* $R^2 = 0.203$; $p = 0.018$).

Conclusions: The results of this study suggest that 12 weeks of either low-volume HIIT or MICT do not improve inflammatory markers in older unfit women with T2D. The correlation between changes in A1c and MCP-1 levels support the role of hyperglycemia in low-grade inflammation.

KEYWORDS: HIIT; MICT; exercise; cytokines

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ABBREVIATIONS

T2D, Type 2 diabetes; MCP-1, monocyte chemoattractant protein 1; IL, interleukin; MICT, moderate-intensity continuous training; HIIT, high-intensity interval training; CPET, cardiopulmonary exercise test; HR, heart rate; HRR, heart rate reserve; BMI, body mass index

INTRODUCTION

Type 2 diabetes (T2D) is a complex metabolic disorder considered as one of the most important public health problem in the world, mainly because of its close relationship with cardiovascular diseases and premature mortality [1]. The presence of T2D in women confers a greater risk of cardiovascular complications compared to men [2], which could be caused by a worst glycemic control and less optimal control over some risk factors such as dyslipidemia and hypertension [3]. Even though more research is needed regarding sex differences in pathophysiological mechanisms leading to T2D and its complications, the literature suggests that a systemic pro-inflammatory state could be involved [4–6]. Indeed, it was reported that higher circulating levels of pro-inflammatory cytokines such as monocyte chemoattractant protein 1 (MCP-1), interleukin (IL)-6 and IL-1β are associated to a poor glycemic control as well as a greater risk of T2D-associated cardiovascular complications [7] and peripheral artery disease [8]. Furthermore, knowing the close relationship between adiposity, glucose homeostasis and inflammatory profile [9], exercise interventions that can reduce fat mass and improve glucose control could lead to a reduced pro-inflammatory profile. All together, these improvements may reduce the risk of cardiovascular diseases associated to T2D.

As demonstrated by the meta-analysis of Hayashino et al. (2014), moderate-intensity continuous training (MICT) is among the interventions that may have this anti-inflammatory effect. After a few weeks of aerobic exercises, circulating levels of C-reactive protein and IL-6 were reduced in individuals with T2D [10]. Unfortunately, there are still some inconsistencies in the literature with previous studies that did not report any benefits of MICT on inflammatory markers in adults with T2D [11–13]. More recently, it was shown that circulating levels of IL-6, tumor factor necrosis alpha (TNF-α), leptin and adiponectin were improved by high-intensity interval training (HIIT) in adults with metabolic disorders, including T2D [14], and older women with metabolic syndrome [15]. This improvement may restore tyrosine kinase activity of insulin receptors, which will contribute to reduce insulin resistance [16].

Although interesting because it demonstrates the beneficial effect of HIIT on inflammatory profile, such high volume of HIIT (<10 min per session) could be difficult to perform for older adults with reduced physical capacities and metabolic disorders. Furthermore, a study showed that only 2–14% of older adults with T2D performed 150 min/week of moderate to vigorous exercises [17], with one of the main barrier being the perceived lack of time [18]. Therefore, the recently updated Diabetes Canada guidelines include low-volume HIIT as an alternative intervention to some risk factors such as low cardiorespiratory capacity (VO_2 max; [19]). Despite that there is no consensus in the scientific community, low-volume

HIIT is defined as any sub-maximal intensity physical effort alternating with rest period, either passive or active, with a high intensity duration of 10 min or less per session [20]. This type of training intervention requires less time commitment and could generate a greater enjoyment compared to MICT [21,22]. However, the effect of low-volume HIIT on inflammatory profile, a contributor to T2D-associated complication, remains to be established and compared to the traditional MICT.

Hence, the objective of this study was to compare the effects of a 12-week low-volume HIIT to MICT on the inflammatory profile of older women with T2D. A secondary objective was to investigate if the expected improvement of inflammatory profile would be associated to changes in body composition and glucose control.

MATERIALS AND METHODS

Study Protocol

Data presented in the manuscript are part of a previously published randomized two-arm parallel study comparing the effect of HIIT and MICT on glycaemic control (A1c)[23,24]. Participants were randomized to one of two groups: HIIT (75 min/week) or MICT (150 min/week). Participants were recruited using the research centre recruitment database and during conferences in local community organizations. After a screening phone call, participants were invited at the Research Centre on Aging for three preliminary visits. The first baseline visit consisted of the following measures: (1) resting blood pressure; (2) anthropometry and body composition; (3) 12 h-overnight fasting metabolic profile (lipid profile, glucose, insulin, A1c); (4) explanation of the 3-day dietary record and 7-day accelerometer-estimated energy expenditure. One week later, participants were invited to come back for a second visit during which a cardiopulmonary exercise test (CPET) was carried out to obtain medical clearance and determine exercise training target heart rate. During the last preliminary visit, a dietician provided individual advice for T2D management according to the current nutritional guidelines [25], focusing on low-glycemic index diet. The sole purpose of this meeting was to ensure that every participant had a similar level of knowledge on the current guideline considering that most women had their diagnosis of T2D more than 10 years ago. No food portion training was involved, and no diet regimen was enforced. All measurements were performed before and after the 12-week exercise intervention. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the Ethics Committee of the CIUSSS de l'Estrie-CHUS (2016-574-IUGS; approval date: 2015-11-05). Written informed consent was obtained from all participants before entering the study.

Participants

Thirty women with T2D, aged between 60 and 85 years old, were recruited between January 2016 and September 2019 and randomized in one of two groups: HIIT (n = 15) or MICT (n = 15). Participants had to be non-smoker, none or light drinker (≤1 alcoholic beverage/day), and physically inactive (<75 min of structured exercise/week). Exclusion

criteria were: (1) under hormonal replacement therapy; (2) insulin therapy; (3) changes in medications in the last 6 months; (4) uncontrolled hypertension (≥140/90 mmHg); (5) uncontrolled lipid profile (total cholesterol > 8 mmol/L; triglycerides > 10 mmol/L; LDL-C > 4 mmol/L); (6) unstable weight in the last 6 months (± 2.3 kg, i.e., 5 lbs); (7) physical disability limiting the capacity to perform exercises; (8) diagnosed diabetic nephropathy, retinopathy or neuropathy; (9) planned surgery during the intervention; (10) coronary artery disease without revascularization, peripheral arterial disease, venous thrombosis or pulmonary embolism and cerebrovascular diseases (stroke) in the past 3 years.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed on a treadmill using the Ball State University-Bruce ramp protocol. The VO_2 max was considered valid when at least two of the following criteria were met: (1) respiratory exchange ratio ≥ 1.10; (2) failure to increase heart rate (HR) despite an increase in workload; (3) no further increase in VO_2 (<150 mL/min) despite an increased workload [26]. Otherwise, the highest value of oxygen consumption reached was considered as the VO_2 peak. A breath-by-breath system (Ergocard; Medisoft, Sorinnes, Belgium) was used to measure gas exchange. All CPET were supervised by a clinician and an exercise physiologist [27]. Heart rate was continuously monitored with a 12-lead electrocardiogram (Quinton Q-stress, Quinton Inc., Bothell, Washington, USA) and the highest value was recorded to calculate heart rate reserve (HRR) to prescribe exercise intensity. For individuals with beta-adrenergic blocking agents, CPET were conducted in the morning at the same time of the planned exercise sessions.

Exercise Interventions

Exercise interventions were performed on treadmill (Life Fitness, Club Series, FlexDeck®; Rosemont, Illinois, USA), usually 1 h after breakfast on non-consecutive days, three times per week for a total of 12 weeks. All exercise sessions were performed in the dedicated training room at the Research Centre on Aging and were supervised by an exercise physiologist. All details on HIIT and MICT training protocol were previously reported following the Consensus on Exercise Reporting Template [23,24]. Briefly, women in the HIIT group performed 75 min/week of HIIT (6 × 1 min at 90% HRR/session with active 2-min recovery at 45% HRR), while women in the MICT group performed 150 min/week (45 min at 60% HRR/session). The HIIT protocol was developed to elicit half the workload compared to MICT as it was also half of the time commitment. HR was continuously monitored with a Polar H7 Bluetooth HR monitor paired with the Polar Club app (Polar, Kempele, Finland) on an IPad (Apple, Cupertino, CA, USA) during all training sessions.

Inflammatory Profile

Fasting inflammatory profile was obtained (12 h fast) from blood samples collected in the ante-cubital vein in EDTA tubes (Vacutainer, K2

EDTA 7.2 mg) by a qualified research nurse. Blood samples were then centrifuged during 10 minutes at 4 °C at 1000 × *g*. Plasma was aliquoted and subsequently frozen at −80 °C until analysis. Pro-inflammatory cytokines (IL-6, IL-1β, IL-15, MCP-1, TNF-α) and anti-inflammatory cytokines (IL-10, IL-1ra) were measured before and after the 12-week intervention. Circulating cytokines concentrations were determined using human-specific multiplex cytokine immunoassays (EMD Millipore Milliplex, HCYTOMAG-60K) on a Luminex^{200} with xMAP (multi-analyte platform) technology systems (Luminex Corporation, Austin, TX) according to the manufacturer's instructions. All measurements were performed in duplicate and averaged, with pre- and post-intervention samples measurements performed within the same plate. The intra-assay coefficients of variation were between 0.67% and 1.56% for all cytokines.

Anthropometrics and Body Composition

Body weight (± 0.2 kg) and height (± 0.1 cm) were measured with an electronic scale (SECA 707, Hamburg, Germany) and a wall stadiometer (Takei, Tokyo, Japan), respectively. Lean body mass, fat mass and visceral adipose tissue were estimated by using body dual X-ray absorptiometry (iDXA, GE Healthcare, Chicago, IL, USA) with the EnCORE Version 16 software. In our laboratory, test-retest coefficient of variation is 1.9% for fat mass and 1.2% for lean body mass in 100 individuals. Finally, waist circumference was assessed at the midpoint between the inferior costal border and the iliac crest [28].

Fasting Cardiometabolic Profile

A total of 12 mL of blood was collected to measure A1c, insulin, glucose, and lipid profile, and were analyzed by the CHUS biochemistry laboratory using enzymatic and immunologic methods. All blood samples were obtained after a 12-h overnight fast and at least 72 h after the last training session at the end of the intervention. Participants were asked to restrict themselves from exercising and moderate-to-vigorous physical activity in the previous 24 h and from consuming alcohol in the previous 48 h. Systolic and diastolic blood pressure were measured with an automatic blood pressure monitor (Spot Vital Signs LXi, Welch Allyn Inc., NY, USA) on the left arm. The measure was taken after 5 min of rest in a sitting position.

Macronutrient Intakes

Participants were asked to complete a 3-day dietary diary with the use of a food scale the week before and after the intervention to assess dietary habits [29]. Estimated total energy, carbohydrate, lipid, protein, and fiber intakes were estimated by using Nutrific software (Laval University, Sainte-Foy, Quebec, Canada).

Estimated Physical Activity and Energy Expenditure Levels

Physical activity levels were estimated using the Physical Activity Scale for the Elderly questionnaire [30]. This self-administered questionnaire

uses a scoring between 0 and 793 to evaluate occupational, leisure and physical activity levels. A higher score means a higher level of physical activity. Participants were also asked to wear an accelerometer (Actical Philips Respironics, Bend, OR, USA) for 7 consecutive days during the week before and after the intervention. Data were collected at a sampling rate of 30 Hz using a 15-s epoch length. To be considered valid, the accelerometer had to be waist-worn at the left anterior axillary line with data collected for at least 5 days with a wear time of over 10 h per day. A physical activity log was also filled out by the participants during this same period for control purposes. Energy expenditure was estimated from accelerometer data, using Actical's Z software (Actical Philips Respironics, Bend, OR, USA), which converted activity count data into minute-by-minute energy expenditure.

Statistical Analyses

Statistical power calculation was based on A1c changes rather than in inflammatory profile considering that the main objective of the previously published study was to assess the effect of a 12-week intervention of either HIIT or MICT on glycemic control (A1c). The normality of data was assessed with visual inspection of the quartile histograms and Q-Q plots as well as the Shapiro-Wilk test in total sample and in both groups separately. The baseline comparison between HIIT and MICT was performed using independent T-tests or Mann-Whitney U tests when data were not normally distributed. Inflammatory profile and glycemic control (A1c) were analyzed using non-parametric procedures. Wilcoxon tests were used to assess the effect of the 12-week intervention in each group and Mann-Whitney U tests to compared changes (delta; Δ = post-intervention value − pre-intervention value) between groups. Spearman Rho correlations were used to investigate the association between inflammatory profile, body composition (total fat mass) and glycemic control (A1c). Linear regression was also performed to assess the proportion of variance explained by independent variables. Other normally distributed variables (body composition, energy intake and expenditure as well as macronutrient intake) were analyzed using repeated measures ANOVA (2 groups × 2 measures). Mauchly's test of sphericity was automatically respected because there are only two levels of comparison. Analyses were performed using SPSS IBM 22.0 and the significance threshold was set at $p \leq 0.05$. Nevertheless, the *p*-value was not be solely interpreted as a dichotomous manner (significant or not), but rather as a continuous value [31]. Data are presented as medians [interquartile range; IQR], unless mentioned otherwise.

RESULTS

Participant's Characteristics

A total of 27 participants completed the study and had available data for the inflammatory profile (HIIT: $n = 13$ and MICT: $n = 14$; **Figure 1**). At baseline, both groups had similar characteristics (all $p > 0.05$; **Table 1**), apart from a higher fasting glucose in the MICT group ($p = 0.015$).

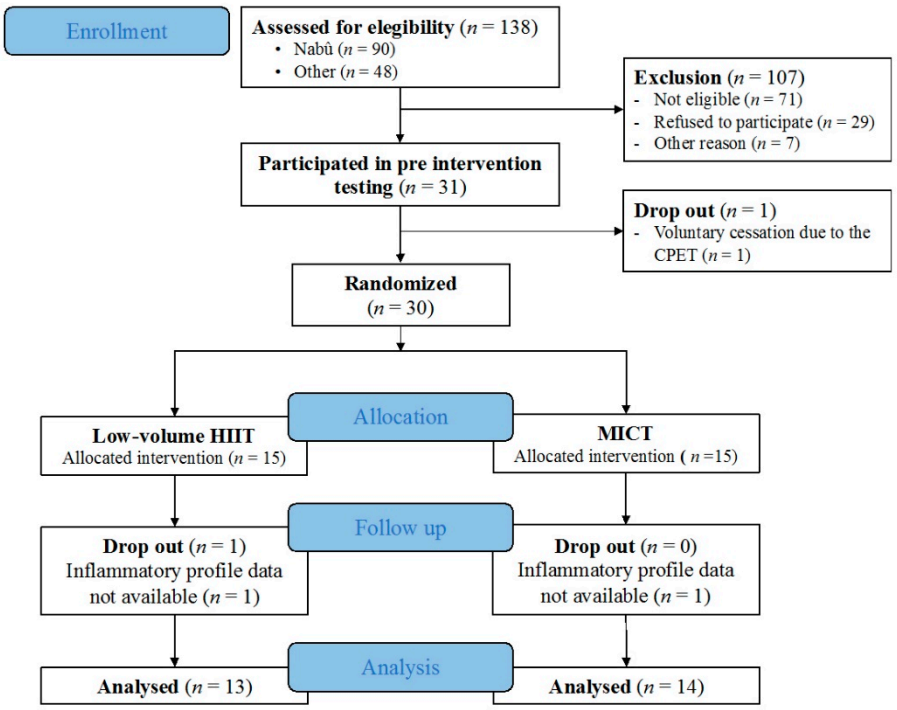

Figure 1. The CONSORT flow chart (from screening to the study analyses). CPET= cardiopulmonary exercise testing; HIIT= high-intensity interval training; MICT= moderate intensity continuous training.

Table 1. Participants baseline characteristics.

Baseline characteristics	**Total sample** (*n* = 27)	
	HIIT (*n* = 13)	**MICT** (*n* = 14)
Age (years)	67.8 [64.5–70.8]	68.2 [64.5–70.4]
Duration of T2D (years)	10.0 [7.0–16.0]	10.0 [3.5–12.0]
BMI (kg/m^2)	31.5 [28.2–38.8]	33.0 [27.8–40.5]
Waist circumference (cm)	105.5 [99.1–110.0]	113.5 [99.3–120.1]
Fasting glucose (mmol/L)	7.0 [5.8–8.2]	8.2 [6.1–9.5] †
A1c (%)	6.6 [6.1–7.4]	7.0 [6.4–7.5]
Total cholesterol (mmol/L)	4.01 [3.19–4.14]	3.55 [3.34–4.43]
LDL-cholesterol (mmol/L)	1.94 [1.34–2.42]	1.64 [1.38–2.49]
HDL-cholesterol (mmol/L)	1.26 [1.03–1.68]	1.06 [0.98–1.54]
TG (mmol/L)	1.13 [0.71–1.48]	1.53 [1.24–2.19]
Systolic BP (mmHg)	128.0 [116.5–135.5]	129.5 [122.0–137.5]
Diastolic BP (mmHg)	77 [73.0–78.5]	77.5 [72.8–79.8]
VO_2 peak (mL/kg/min)	17.8 [15.3–20.6]	17.8 [15.3–19.8]
Medication (*n*)	6.0 [4.0–9.0]	6.0 [4.0–7.0]
Glucose lowering medication [*n* (%)]	13 (100)	14 (100)
Hypotensive medication [*n* (%)]	13 (100)	14 (100)
Lipid lowering medication [*n* (%)]	13 (100)	14 (100)

Data are presented as median [interquartile range] and *N* (%) for the medication; BMI = body mass index; HIIT = high intensity interval training; MICT= moderate intensity continuous training; A1c = glycated hemoglobin; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglycerides; BP = blood pressure. † Significant difference between HIIT and MICT for fasting glucose (p = 0.015).

Table 2. Energy intake and macronutrient consumption before and after intervention for HIIT and MICT.

Energy intake and expenditure	**HIIT** (*N* = 13)		**MICT** (*N* = 11)		***p*-value**	***p*-value**
	Before	**After**	**Before**	**After**	**Time**	**Time × Group**
Total energy intake (kcal)	1570 ± 326	1539 ± 386	1662 ± 313	1657 ± 193	0.801	0.854
Carbohydrate (g)	185 ± 54	183 ± 44	181 ± 50	187 ± 47	0.881	0.736
Fat (g)	64 ± 14	61 ± 21	74 ± 17	70 ± 18	0.381	0.951
Protein (g)	69 ± 11	71 ± 17	75 ± 15	73 ± 19	0.951	0.660
Fiber (g)	21 ± 11	22 ± 8	20 ± 8	20 ± 10	0.527	0.730
Energy expenditure (kcal) *	352 ± 260	336 ± 152	360 ± 121	438 ± 108	0.679	0.537

Data are presented mean ± SD; Value are the mean of the 3 days of dietary record; * data for accelerometer were only available for 10 individuals (HIIT = 6; MICT = 4).

Table 3. Inflammatory profile before and after HIIT and MICT intervention.

Inflammatory profile	**HIIT (*N* = 13)**		**MICT (*N* = 14)**		**Time effect *p*-value**	**Delta comparison *p*-value**
	Before	**After**	**Before**	**After**		
MCP-1 (pg/mL)	**160.9 [133.5–230.2] (176.9 ± 51.3)**	**187.88 [155.3–237.3] (212.0 ± 93.1)**	188.9 [122.6–276.2] (199.2 ± 87.6)	190.2 [144.4–241.6] (201.1 ± 95.2)	**HIIT: 0.023** MICT: 0.594	**0.031**
IL-6 (pg/mL)	0.40 [0.27–0.92] (0.94 ± 1.33)	1.04 [0.46–1.41] (1.14 ± 0.85)	0.80 [0.38–1.80] (1.14 ± 1.0)	0.66 [0.36–1.75] (1.18 ± 1.14)	HIIT: 0.388 MICT: 0.753	0.462
IL-8 (pg/mL)	0.56 [0.30–1.19] (0.75 ± 0.60)	0.49 [0.35–2.37] (1.35 ± 1.64)	0.74 [0.29–3.37] (1.77 ± 1.66)	0.65 [0.36–2.77] (1.76 ± 2.19)	HIIT: 0.594 MICT: 0.917	0.733
IL-10 (pg/mL)	0.81 [0.00–13.27] (6.02 ± 9.01)	0.71 [0.00–5.95] (3.32 ± 5.34)	6.46 [0.50–15.82] (12.08 ± 18.28)	1.34 [0.00–13.22] (8.99 ± 14.13)	HIIT: 0.401 MICT: 0.182	0.769
IL-15 (pg/mL)	4.62 [0.68–9.84] (5.48 ± 5.43)	0.81 [0.24–6.48] (3.65 ± 5.22)	4.08 [1.96–8.05] (5.76 ± 5.94)	3.77 [2.08–10.28] (5.77 ± 4.85)	HIIT: 0.484 MICT: 0.672	0.867
IL-1ra (pg/mL)	22.66 [7.27–50.57] (48.64 ± 79.29)	12.53 [5.83–44.96] (45.33 ± 80.92)	37.66 [13.29–37.66] (109.4 ± 167.4)	41.70 [12.90–171.50] (102.1 ± 155.3)	HIIT: 0.196 MICT: 0.221	0.830
IL-1β (pg/mL)	1.31 [0.000–4.89] (2.49 ± 3.46)	0.34 [0.00–1.69] (1.61 ± 3.65)	0.78 [0.29–4.02] (3.30 ± 5.47)	0.78 [0.24–5.34] (4.40 ± 7.60)	HIIT: 0.674 MICT: 0.203	0.225
TNF-α (pg/mL)	5.92 [4.33–18.81] (12.41 ± 13.47)	11.03 [4.10–22.99] (15.19 ± 15.49)	9.71 [5.52–19.33] (12.85 ± 8.76)	8.13 [5.71–18.76] (12.15 ± 8.86)	HIIT: 0.753 MICT: 0.753	0.583

Data are presented as median [interquartile range] and (mean ± SD) below; HIIT= high intensity interval training; MICT = moderate intensity continuous training; MCP1 = monocyte chemoattractant protein 1; IL = interleukin; TNF-α = tumor necrosis factor alpha. Bold= significant difference.

Change in Body Composition, Glycemic Control and in Energy Intake and Expenditure

Full data on body composition and glycemic control changes can be found elsewhere [23]. Total fat mass (FM) significantly decreased compared to baseline value (MICT = 33.6 [26.4–43.6] to 31.6 [26.2–44.0] kg; HIIT = 32.1 [26.9–42.3] to 29.4 [26.1–41.0] kg; $p = 0.006$), without interaction between groups ($p = 0.799$). Estimated visceral adipose tissue and total lean body mass remained unchanged ($p \geq 0.299$). Glycemic control, measured by A1c, significantly decreased after the intervention in MICT (7.0 [6.4–7.5] to 6.7 [5.9–7.2]%; $p = 0.014$); while it did not reach significance in HIIT (6.5 [6.0–7.5] to 6.3 [5.8–7.4]%; $p = 0.411$). There was no change in estimated total energy expenditure, total energy intake or macronutrient intake after the intervention ($p > 0.38$), and no interaction between groups ($p > 0.54$; **Table 2**).

Effect of HIIT and MICT on Fasting Inflammatory Profile

At baseline, fasting inflammatory profile was not different between groups ($p > 0.190$). As shown in **Table 3**, fasting cytokine levels remained unchanged in MICT ($p > 0.182$), while an increase in fasting MCP-1 concentrations was observed in HIIT group ($p = 0.023$). Comparison of changes (Δ) in MCP-1 levels showed a significant difference between groups ($p = 0.031$), with an increase in HIIT only (+ 27.2 [−10.1–75.1] pg/mL).

Association between Changes in Body Composition, Metabolic Profile, and Inflammatory Profile

There was no correlation between ΔMCP-1 levels and Δ total fat mass ($r = 0.12$; $p = 0.57$) or Δ estimated visceral adipose tissue ($r = -0.07$; $p = 0.78$). A positive correlation was observed between ΔA1c and Δ MCP-1 ($r = 0.49$; $p = 0.018$), meaning that a greater reduction in A1c was associated to a higher reduction of MCP-1 concentrations. Linear regression showed a positive association between Δ MCP-1 and ΔA1c (adjusted $r^2 = 0.20$, $p = 0.018$; **Figure 2**). After including Δ FM in the model, A1c remained statistically significant (*adjusted* $r^2 = 0.11$, $p = 0.048$), while FM was not ($p = 0.987$).

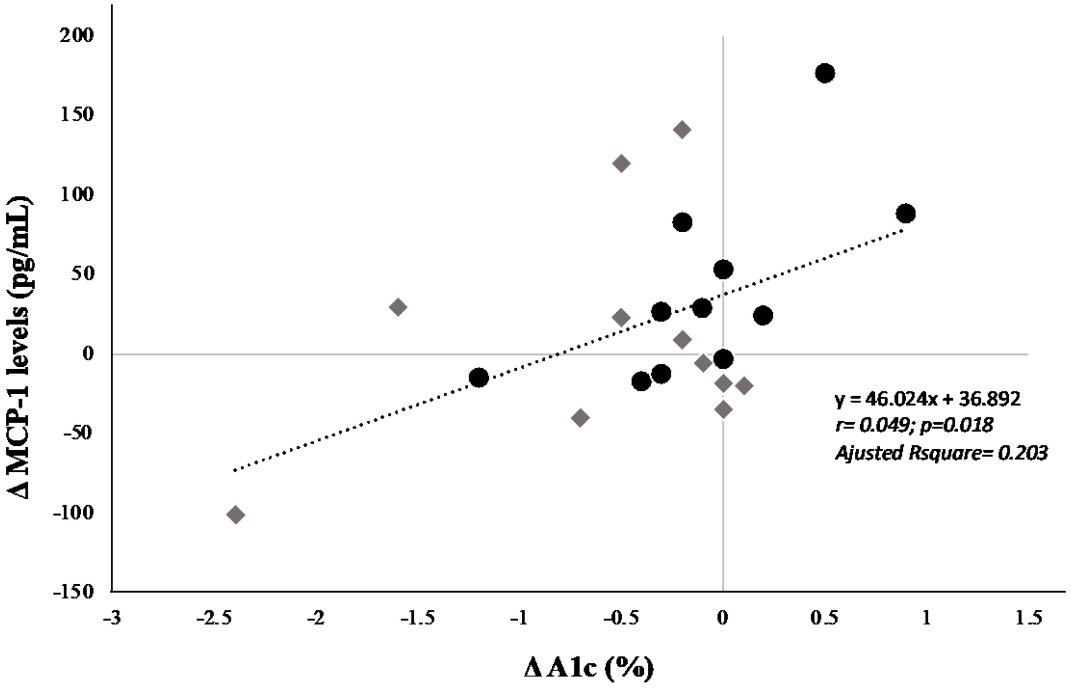

Figure 2. Correlation between A1c change and MCP-1 change. A1c = glycated hemoglobin; MCP-1 = Monocyte chemoattractant protein 1. Individuals outside of the blue section reached the Minimal Clinically Important Difference (MCID) for A1c (0.3%); Grey diamond dot = MICT; Black circle dot = HIIT.

DISCUSSION

The objective of this study was to compare a 12-week low-volume HIIT and MICT on inflammatory profile markers in older unfit women with T2D and determine if it would be associated with changes in body composition and glucose control. Despite a reduction in fat mass and A1c, no change was observed in inflammatory profile, except for an increase in MCP-1 levels in the HIIT group. Although the effectiveness of HIIT (either low or high volume) to modify systemic levels of inflammatory markers remains unclear in T2D individuals, the results of this study differ from the global improvement reported in response to HIIT in adults with metabolic disorders [14]. The main difference with these studies is either the volume or the intensity. As an example, a reduction of fasting IL-6 concentrations was reported after 10 weeks of low-volume sprint interval training (4 × 30 s/3 days per week) performed at maximal intensity [32] or after 24 weeks of high volume HIIT (3 series of 10 × 60 s/3 days per week) in middle age individuals with T2D and obesity [33]. This discrepancy suggests that low-volume HIIT may not represent a sufficient stimulus to reduce pro-inflammatory cytokines concentrations. Knowing the previously reported role of the selected cytokines in T2D pathogenesis (IL-6, IL1β, IL-8, IL-10, and IL-15 [7,34–36]) or their association with a poor glycemic control (MCP-1 [8]), low-grade inflammation was expected in our study population. However, participants baseline IL-6 and MCP-1 concentrations were similar to what was reported by Banitalebi et al. [32] after low-volume sprint interval training (≈1.20 pg/mL and 200 pg/mL, respectively), suggesting an absence of low-grade inflammation at baseline, and therefore, a limited potential for improvement. This hypothesis is also

supported by the fact that participants of the present study had a less deteriorated lipid profile compared to the study of Zadeh et al. [33], which is a known factor that contribute to the risk of chronic inflammation [37].

Although not expected, an increase in MCP-1 levels was observed after 12 weeks of low-volume HIIT. It was previously reported that a single-bout of low-volume HIIT (8 × 60 s) can increase MCP-1 levels in the following hours [38], therefore blood samples were collected at least 72 h after the last exercise session to limit the risk of an acute effect of exercise. However, post-intervention MCP-1 levels in the HIIT group were similar to the baseline levels of the MICT group. Moreover, these values are considered in the normal range of what could be expected in healthy individuals [39]. As a result, we hypothesized that the rise in MCP-1 levels in the HIIT group might simply be attributable to natural variation, which allows the value to return in normal range.

Because MCP-1 concentration was previously associated to body mass index (BMI) and acts as a potent chemoattractant for pro-inflammatory monocytes, it has a key role in low-grade inflammation in adipose tissue, a condition suggested to be involved in the T2D pathophysiology [7]. Therefore, it was expected that MCP-1 levels would be associated to fat mass in women with T2D. The fact that we did not observe low-grade inflammation, albeit all women had T2D, suggests that there was no inflammation in adipose tissue, and thus probably a low gene expression of MCP-1. While the absence of low-grade inflammation in T2D individuals could be surprising, it may explain the absence of association between MCP-1 levels and fat mass, which is usually more the reflection of abdominal adipose tissue dysfunction (i.e., meta-inflammation) often observed in individuals with T2D.

Further analyses indicated that changes in A1c was positively associated with changes in MCP-1 levels, meaning that an A1c decrease is associated with a reduced MCP-1 concentrations. Changes in A1c explained 20.3% of the variance of MCP-1 concentrations, while including total fat mass in the model reduced the percentage of the variance explained in our statistical model to 11.3%. These results are in line with other studies showing that MCP-1 concentrations are closely associated to glycemic control and hyperglycemia [8,40–42]. Therefore, in individuals with T2D displaying higher risk of cardiovascular disease, finding the optimal exercise modalities that can improve glycemic control and reduce hyperglycemia to a greater extend is important.

A recent meta-analysis including five randomized controlled trials revealed that IL-6 concentrations can be reduced by −0.91 pg/mL (95% CI; −1.47 to −0.35 pg/mL; I^2 = 89.8%) in response to MICT. Most of the inter-individual variability observed could be explained by the total number of sessions performed and weekly exercise volume [10]. Combined with the absence of low-grade inflammation, the shorter intervention duration (36 sessions) of the present study could partially explain the absence of change in different inflammatory makers. It is critical to draw attention to the fact that the women in this study had poor aerobic capacity. Therefore, the lower absolute physiological stress of exercise during the intervention in both groups could also partially explained the lack of improvement. Other

limitations such as the smaller sample size and the exclusion of men should also be noted when interpreting the result, which may limit the generalizability of these data.

Despite this limitation, this study was strengthened by the use of a walking protocol and submaximal intensity (<100% VO_2 peak) compared to most of the studies that have used sprint interval training on ergocycle. Knowing that walking is considered one of the favorite activity by the elderly [43] and that submaximal intensity is associated with a greater affective valence compared to supra-maximal exercise intensity [44,45], further studies investigating different walking HIIT protocol modalities are needed. HIIT protocol modalities are needed to establish what the minimal number of sessions and HIIT volume are required to reduce inflammatory profile in older women with uncontrolled T2D.

CONCLUSIONS

In older women with controlled T2D and no low-grade inflammation, a 12-week intervention of low-volume HIIT or MICT did not modify the fasting inflammatory profile. The increase in systemic MCP-1 levels and its association with glycemic control suggest that exercise modalities that could improve A1c should be prioritized considering that it could mitigate T2D-related inflammation in aging women. These findings contribute to the growing body of scientific evidence suggesting that low-grade inflammation is not a systematic phenomenon that occur in the elderly population, even in the presence of comorbidities like T2D and obesity.

AUTHOR CONTRIBUTIONS

PB, MB, JAM, IJD, M-FL and ER designed the study. AM-C, RT, MM-M and DT were in charge of data collection and trained all the participants during the intervention. DT, PB and WM were overseeing the cardiopulmonary exercise testing for the medical clearance. M-FL was the endocrinologist in charge of supporting the research team with more complex cases. RT and ER performed the lab analysis for the inflammatory profile. AM-C analyzed the data and wrote the paper. All authors reviewed the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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