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**To cite this article:** Ivan Luiz Padilha Bonfante, Daniela Bastos Vieira , Marcelo Oliveira Batista , William Ciriaco Barbosa , Renata Garbellini Duft , Keryma Chaves da Silva Mateus , Ana Paula Boito Ramkrapes , Liliane Ribeiro Vasconcelos , Milena Monfort-Pires , Celso Darío Ramos , Licio Augusto Velloso , Mara Patricia Traina Chacon-Mikahil & Cláudia Regina Cavaglieri (2025) Effects of combined training on quality of life in individuals with overweight-related type 2 diabetes: a pilot study of correlations with metabolic, inflammatory and thermogenic markers, *Annals of Medicine*, 57:1, 2530694, DOI: [10.1080/07853890.2025.2530694](https://doi.org/10.1080/07853890.2025.2530694)

**To link to this article:** <https://doi.org/10.1080/07853890.2025.2530694>



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# Effects of combined training on quality of life in individuals with overweight-related type 2 diabetes: a pilot study of correlations with metabolic, inflammatory and thermogenic markers

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## ABSTRACT

**Background:** There is still a lack of information regarding the impact of training on the domains that constitute quality of life (QoL), and the relationship between QoL with hormonal, inflammatory and pro-thermogenic/anti-inflammatory components. Thus, the present work aimed to evaluate the effects of combined training (CT) on the QoL of individuals with overweight-related type 2 diabetes mellitus (T2DM) and to correlate (baseline values and CT-induced delta percentage changes ( $\Delta\%$ )) QoL variables with hormonal, inflammatory, and pro-thermogenic/anti-inflammatory components.

**Methods:** Middle-aged individuals of both sexes and with overweight-related T2DM were assigned to either the control group (CONT group) or the combined training group (CTG). The CT consisted of strength training followed by aerobic training three times/week for 16 weeks. Pre- and post-intervention assessments included QoL perception, clinical variables, serum biochemical markers, and brown adipose tissue (BAT) activity.

**Results:** The CTG showed improvement in the perception of general QoL (20.0%) and in the physical (12.7%) and social (10.1%) domains. Significant positive correlations were observed between QoL variables with interleukin-4 (IL-4), IL-10, IL-13, IL-33, Fibroblast growth factor-21 (FGF-21), bone morphogenetic protein-4 (BMP4), irisin, and BAT activity, alongside negative correlations with IL-1, IL-2, IL-6, c reactive protein (CRP), tumor necrosis factor-alpha (TNF- $\alpha$ ) and incretin hormones at baseline and/or in the  $\Delta\%$  changes induced by training.

**Conclusion:** CT improves the perception of general QoL and the physical and social domains of individuals with overweight-related T2DM. Baseline and in the  $\Delta\%$  of CT change, QoL components are related with several clinical, hormonal, inflammatory, and pro-thermogenic/anti-inflammatory markers, besides BAT increased activity.

## ARTICLE HISTORY



Received 3 December 2024  
Revised 17 June 2025  
Accepted 27 June 2025

## KEYWORDS


Combined training; inflammation; metabolism; quality of life; thermogenesis; type 2 diabetes

## Introduction

Type 2 diabetes mellitus (T2DM) is a significant global public health problem due to its treatment costs, the large number of affected individuals, and the expected increase in incidence in the coming years [1]. The effects of T2DM on individuals are comprehensive and can negatively influence several biopsychosocial components, consequently impairing quality of life (QoL) and its associated domains [2].

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 Supplemental data for this article can be accessed online at <https://doi.org/10.1080/07853890.2025.2530694>.

**Clinical trial registration:** UTN: U1111-1202-1476 ([http://www.ensaiosclinicos.gov.br/rg/RBR-62n5qn/](http://www ensaiosclinicos.gov.br/rg/RBR-62n5qn/))

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QoL is a broad concept, referring to an individual perception of position in life in the context of the culture and value system in which the individual lives regarding their goals, expectations, standards and concerns [3]. These factors are influenced by physical health, psychological state, independence, social relationships and environmental characteristics, which are entirely susceptible to being negatively influenced by T2DM [2]. Several studies have shown that individuals with T2DM have a worse perception of their QoL compared to healthy individuals [2,4]. This is due to the effects of T2DM pathophysiology, psychological pressure and frustration with daily self-care, especially those related to disease [5,6].

Regular physical exercise is the most relevant non-pharmacological intervention for reducing cardiometabolic risk and T2DM control [7,8] and could be used as a strategy for improving QoL. The exercise training recommendation for the population with T2DM includes the practice of strength and aerobic training, i.e. combined training (CT), induces comprehensive effects on overall health and physical fitness [9,10]. A recent systematic review and meta-analysis has provided evidence that CT improves QoL in individuals with T2DM [11]. However, doubts remain regarding the influence of factors such as CT duration, intensity, and frequency on specific QoL domains (physical, psychological, social, and environmental) [11].

To better understand the relationship between QoL T2DM and training, certain clinical variables related to glucose control are evaluated [4]. However, the pathophysiology of T2DM is more complex, which justifies that new variables be evaluated in order to understand their relationships with QoL [12]. There is a limited or unavailable information on QoL associations with other important hormones related to glycemic control, inflammatory markers, thermogenic and anti-inflammatory inducers, and thermogenic activity of brown adipose tissue (BAT) [5,13,14]. All of these physiological variables have gained attention in recent years due to their importance for the prevention and treatment of cardiometabolic diseases in general, especially obesity and T2DM [1,14]. For example, dipeptidyl peptidase-4 (DPP4) inhibitors and glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) analogues are the main medications for weight loss and glycemic control at the moment [15]. Amylin/islet amyloid polypeptide (IAPP) and insulin-degrading enzyme (IDE) are associated with the development of Alzheimer's, a disease for which the T2DM population is at greater risk [16]. Among the inflammatory markers, leptin, C-reactive protein (CRP), tumor necrosis factor alpha (TNF $\alpha$ ), interleukin-1beta (IL-1b), IL-2 and IL-6 are the most associated with general inflammation and insulin resistance (IR) [17]. As for thermogenic and anti-inflammatory inducers, there are the classic markers adiponectin and IL-10, in addition to the newest ones in evidence IL-4, IL-10, IL-13, IL-33, meteorin-like, fibroblast growth factor-21 (FGF-21), bone morphogenic protein-4 (BMP-4), BMP7 and irisin [18]. Finally, increasing the thermogenic activity of BAT is considered an essential target for the prevention and treatment of cardiometabolic diseases [19].

All these variables are related to disease control and its complications, which can significantly affect health perception, QoL and its domains in individuals with T2DM [20]. In the physical domain of QoL, better metabolic control can reduce the chance of complications and comorbidities, in addition to influencing the perception of fatigue, sleep, discomfort and activities of daily living [6,11,20]. Whereas in psychosocial domains, there may be an influence on mood, self-esteem, body image, and relationships and the need for support [5,8,11]. Finally, all these biopsychosocial aspects can directly and indirectly interfere in the perception of various facets of the environmental domain, such as the perception of health and social care, opportunities to acquire new information and skills or to exercise recreation and leisure [3,8,11].

Given the need to better elucidate the effects of CT on the QoL domains of individuals with T2DM, and the lack of understanding regarding the relationships between QoL and relevant physiological markers associated with overweight-related T2DM, this pilot study had two main objectives: (1) to evaluate the effects of CT on the QoL of individuals with overweight-related T2DM; and (2) to correlate baseline values and CT-induced changes in QoL with clinical, hormonal, inflammatory, and pro-thermogenic/anti-inflammatory markers.

## Methods

### Volunteers

This pilot study presents the results of secondary analyses (QoL variables) of individuals with overweight-related T2DM from the randomized controlled trial, Universal Trial Number (UTN):

U1111-1202-1476, (<http://www.ensaiosclinicos.gov.br/rg/RBR-62n5qn/>) complying with clinical trial registration guidelines. Primary results from this trial have been previously published, evaluating the effects of combined training on thermogenic activity of adipocytes and incretin hormones [21,22]. The study period with individuals with T2DM was between July 2016 and July 2017. The study was approved by the Research Ethics Committee of the University of Campinas and was based on the principles of the Declaration of Helsinki. All volunteers were informed of the purpose of this study and consent was obtained by signed the Free and Informed Consent Form.

Volunteers of both sexes were recruited according to the following inclusion criteria: previous diagnosis of T2DM; age, between 40 and 60 years; BMI, 25–35 kg/m<sup>2</sup>; sedentary; no training and/or diet program in the 12 months preceding inclusion. Exclusion criteria included: diagnosis of cardiac arrhythmia, ischemia, coronary artery disease, severe hypertension, chronic obstructive pulmonary disease, anaemia, uncontrolled hypothyroidism, limiting osteoarticular diseases, or severe T2DM complications. Subjects using exogenous insulin, thiazolidinediones, beta-blockers, anticoagulants, anti-inflammatories, or medications that could interfere with physiological responses, and those who failed to complete the QoL questionnaires were also excluded. Discontinuation criteria included: lack of motivation or availability to attend sessions; attendance below 85% or more than three consecutive absences; and changes in medication types or dosages during the study. A total of 29 volunteers completed the study, 13 in the combined training group (CTG) and 16 in the control group (CONT group). The number of subjects in each group differs from the primary studies because not all volunteers answered the QoL questionnaires pre- and post-intervention [21,22].

As mentioned previously, this study was part of a larger trial and the a priori power calculation was conducted for other variables. Therefore, a posteriori power calculation for pre-post QoL variables in the CTG is presented. The power was calculated using G\*Power 3.2.1 software (University of Kiel, Kiel, Germany), using a study design of an f test with  $p < 0.05$  and 95% power. The power were the following: general perception of QoL = 0.99; general perception of health = 1.0; physical domain = 0.99; psychological domain = 0.53; social domain = 0.20; environment domain = 0.25; and total points = 0.86. Thus, it is observed that most variables present a strong power, above 0.80.

### **Experimental design**

Both the CTG and CONT group filled out the World Health Organization Quality of Life – (WHOQOL-BREF) questionnaire. In addition, anthropometric and body composition measurements, physical fitness variables, blood samples and feeding behaviour data were collected. A 48–72 h interval was provided between tests requiring abstinence from physical activity. Volunteers were instructed to avoid alcohol for 24 h and caffeine or stimulating drinks for 12 h prior to each test. Ten volunteers of CTG also underwent positron emission tomography coupled with computed tomography (PET-CT) in pre- and post-experimental periods (to assess the BAT activity). All assessments were performed before and after the experimental period.

The experimental period was conducted over 16 weeks in 2017, with two additional weeks for pre-assessments and another week for post-assessments. Volunteers were instructed not to change their medications (dosage/types) or their eating pattern during the experimental period. The control group was not submitted to any training protocol and was followed up monthly by telephone during the experimental period.

### **Quality of life questionnaire**

We apply the WHOQOL-BREF questionnaire in Portuguese, which has been validated to the Brazilian population [3]. This instrument from the World Health Organization in Brazil is managed by the Brazilian Centre for Quality of Life Group and is available for free use for academic purposes and by non-profit organizations [3].

The WHOQOL-BREF assesses four domains: physical (7 questions), psychological (6 questions), social (3 questions), and environmental (8 questions), totalling 24 questions. Additionally, it includes two questions on overall QoL and general health perception. For analysis, scores for questions 3, 4, and 26 were

recoded ((1=5), (2=4), (3=3), (4=2), (5=1)). Scores were then calculated for each domain, and a total QoL score was obtained by summing the domain scores [3].

### ***Anthropometry, body composition, functional variables and nutritional assessment***

Body weight and height were measured with a calibrated manual scale (Filizola, São Paulo, Brazil) and with a wall-mounted stadiometer. BMI was calculated from the weight and height values. Waist circumference (WC) was measured at standard anatomical landmarks. Body composition was evaluated by whole-body plethysmography (BOD POD, COSMED, USA) [21].

The determination of resting metabolic rate (RMR) was performed using oxygen consumption and carbon dioxide production, using a gas analyzer, with continuous collection of expired gases breath to breath (CPX Ultima, MedGraphics, USA), and Weir equation. Before of RMR, baseline heart rate and blood pressure were measured after 5 min of rest (seated). Cardiorespiratory fitness was assessed using a progressive treadmill test with gas analysis, with VO<sub>2</sub> max determined from the last 30 s of exercise. Strength was assessed *via* one-repetition maximum (1RM) tests for bench press and leg press [23].

The volunteers were requested not to change their diet. To ensure that food behavior was being followed, the volunteers were routinely alerted to this aspect and even filled out FR. The FRs were analyzed semi-quantitatively, delimiting the macronutrient and total caloric intake [21].

### ***Blood collections and biochemical analyses***

Early in the morning after a 12-hour fast, about 40 ml blood samples were collected from each volunteer. Part of the samples was promptly sent for analysis in a clinical analysis laboratory; an aliquot was also centrifuged and stored in a -80°C freezer for further analysis.

Biochemical and hormonal measurements were performed using automated methods. The serum samples were used to analyze: insulin, C-peptide, thyroid-stimulating hormone (TSH) (chemiluminescence method), triglycerides, TC (enzyme-trind method), HDL cholesterol (accelerator-selective detergent method), VLDL cholesterol, and LDL cholesterol (Friedewald formula method). Whole blood was used to measure glycated haemoglobin (HbA1c) (high-performance liquid chromatography method) and blood cell count (automated method and microscopy).

The following indices were calculated using biochemical variables: homeostatic model assessment beta functionality and IR (HOMA-B and HOMA-IR equations) [24]. IR was also verified by the TYG index using the equation (fasting triglycerides (mg/dl) x fasting glucose (mg/dl)/2) [25]. The metabolic syndrome (MS) z score was calculated for each variable using individual subject data, and standard deviations of data for the entire group at baseline. Gender-specific MS z score equations were used following the Adult Treatment Panel III criteria [26]. The equation for MS z score calculation was as follows: SM z score = [(40 or 50 - HDL)/16.74 + (Triglycerides - 150)/73.61] + [(glucose - 100)/45.15] + [(waist - 94 or 102)/8.66] + [medium blood pressure - 100]/10.64].

Serum concentrations of adiponectin, leptin, CRP, TNF $\alpha$ , IL-1b, IL-2, IL-4, IL-6, IL-10, IL-13, IL-33, meteorin-like, FGF-21, BMP-4, BMP7 (R&D System/USA), irisin (US Biological/USA), natriuretic peptides, GIP, GLP-1, IDE, amylin/IAPP and DPP-4 (Aviva Systems Biology/USA) were performed using the Enzyme-Linked Immunosorbent Assay (ELISA) method, according to the specifications of the manufacturers.

### ***PET-CT and BAT activity***

BAT activity was evaluated with radiopharmaceutical [18F]-fluorodeoxyglucose (18F-FDG) and PET/CT scan after mild cold exposure. Before the PET/CT scan, volunteers underwent an individualized cooling protocol, in which they were kept in a mild cold exposure room (17–18°C) for two hours. Subjects remained seated in a comfortable reclining armchair located in a small room with thermometers and a digital air conditioner, which was switched on an hour before the assessment. After one hour of cold exposure, volunteers were injected with 4.0 MBq/kg of 18F-FDG and calorimetry was repeated. During the second hour, volunteers were instructed to ingest water. The volunteers were monitored throughout

the period to ensure they did not shiver. In the case of incipient shivering or tense musculature, the room temperature was increased by 1°C until comfort was re-established [21,27,28].

After 2-h of cold exposure, volunteers were moved to the PET/CT room, where PET/CT static images were acquired and processed on a Siemens Biograph mCT 40 TruePoint Device (Siemens Medical Solutions Inc., IL, USA), always in the direction of the proximal region from the thigh to the craniocaudal area of the head. PET images were reconstructed using a standard iterative algorithm (3D ordered subsets expectation maximization [OSEM], with point-spread function (PSF) and time-of-flight (TOF) with two iterations and 21 subsets), with the computerized tomography data utilized for attenuation correction and image fusion [21,28].

Carimas® software (Version 2.9/Turku PET Centre, Finland) was used to calculate BAT activity as mean standard uptake value (SUV) of the region of interest (ROI) analyzed. For the calculations, axial and coronal images of the <sup>18</sup>F-FDG PET scan were used in combination with computed tomography for anatomical reference. All values were adjusted for the individual's body weight [29]. The BAT ROI were drawn in the supraclavicular and cervical regions (in the axial and coronal planes) on both sides (right and left), with the average value of the two measurements being used as the mean SUV [21].

### Combined training protocol

The CT protocol consisted of a 5 min warm-up on an exercise bike and subsequent performance of strength training (ST), followed by aerobic training (AT) in the same session performed on Mondays, Wednesdays and Fridays for 16 weeks. The strength training consisted of (37–44 min, 3 sets of 10–12 submaximal repetitions, and 1 to 1.15 min interval) followed by aerobic training (35 min at 50–70% of VO<sub>2</sub>max) in the same session. The training periods were divided into two stages of 8 weeks each with progressive load adjustments and followed the recommendations of exercises for subjects with T2D [9]. More details about the training are in Table 1.

### Statistical analysis

Normality was assessed using the Kolmogorov–Smirnov test. Non-normally distributed data were log-transformed (Ln). Between-group differences in pre- and Δ% change values were analyzed using independent Student's *t* tests. Two-way repeated-measures ANOVA was applied to detect time×group

**Table 1.** Details of combined training protocol.

Weeks	1–8 wk	9–16 wk
<b>Warm-up (min)</b>	5	5
<b>Strength training</b>		
Leg press 45 <sup>oa</sup>	3×12	3×10
Leg extension <sup>a</sup>	3×12	3×10
Seated Leg Curl <sup>a</sup>	3×12	3×10
Bench press <sup>a</sup>	3×12	3×10
Lat Pulldown Machine <sup>a</sup>	3×12	3×10
Barbell Bicep Curl <sup>b</sup>	3×12	3×10
Triceps cable extension <sup>b</sup>	3×12	3×10
Smith Machine Shoulder Press <sup>b</sup>	3×12	3×10
Calf extension <sup>c</sup>	3×12	3×10
Crunches <sup>c</sup>	3×12	3×10
Rest (s) interval between sets and exercises	60	75
Intensity (submaximal repetitions)	10–12	10–12
Total duration strength training (min)	37–42	39–44
<b>Aerobic training</b>		
50–55 % VO <sub>2</sub> max (min)	3.5	–
50–60 % VO <sub>2</sub> max (min)	–	3.5
55–60 % VO <sub>2</sub> max (min)	14	–
60–65 % VO <sub>2</sub> max (min)	14	14
65–70 % VO <sub>2</sub> max (min)	–	14
50–60 % VO <sub>2</sub> max (min)	–	3.5
50–55% VO <sub>2</sub> max (min)	3.5	–
Total duration aerobic training (min)	35	35
<b>Total training session duration (min)</b>	77–82	79–84

<sup>a</sup>Performed on Monday, Wednesday, and Friday.

<sup>b</sup>Performed on Monday and Friday.

<sup>c</sup>Performed on Wednesday.

interactions. Tukey's post hoc test was used if significant interactions in a two-way ANOVA were found. Pearson's correlation coefficient was also used to assess the relation of the pre (all subjects) and  $\Delta\%$  (only training group) of QoL with the other pre and  $\Delta\%$  variables. Spearman's correlation coefficient was used to verify the relation of perception of general health and QoL with the other variables only in pre moment because these variables have discrete characteristics. The level of significance used was alpha ( $\alpha$ )  $\leq$  0.05. All analyses were conducted using Statistica 6.0 software.

## Results

### Baseline characteristics and primary results

Table 2 presents data regarding the characteristics of the sample, demographic variables and clinical markers in the pre-intervention period (baseline) of CTG and CONT group.

As previously described, the intervention promoted improvements in body composition, physical fitness, glycemic and lipid metabolism, in addition to a decrease in leptin and an increase in serum anti-inflammatory and pro-thermogenic markers (adiponectin, IL-33, irisin, natriuretic peptides and BMP-4) in the CTG group. Moreover, thermogenic gene expression (TMEM26, EPST11) increased in the subcutaneous waist adipose tissue whereas autophagic genes (ULK1, LC3, ATG4) decreased after intervention. Alongside, energy expenditure and metabolic activity increased in both brown adipose tissue and other trunk adipose compartments upon cold exposure [21].

### Pre-post QoL variables

Figure 1 and Supplementary Table 1 present the pre-post-intervention and  $\Delta\%$  results of the perception of QoL obtained by the WHOQOL-BREF questionnaire. A significant increase in the physical domain was

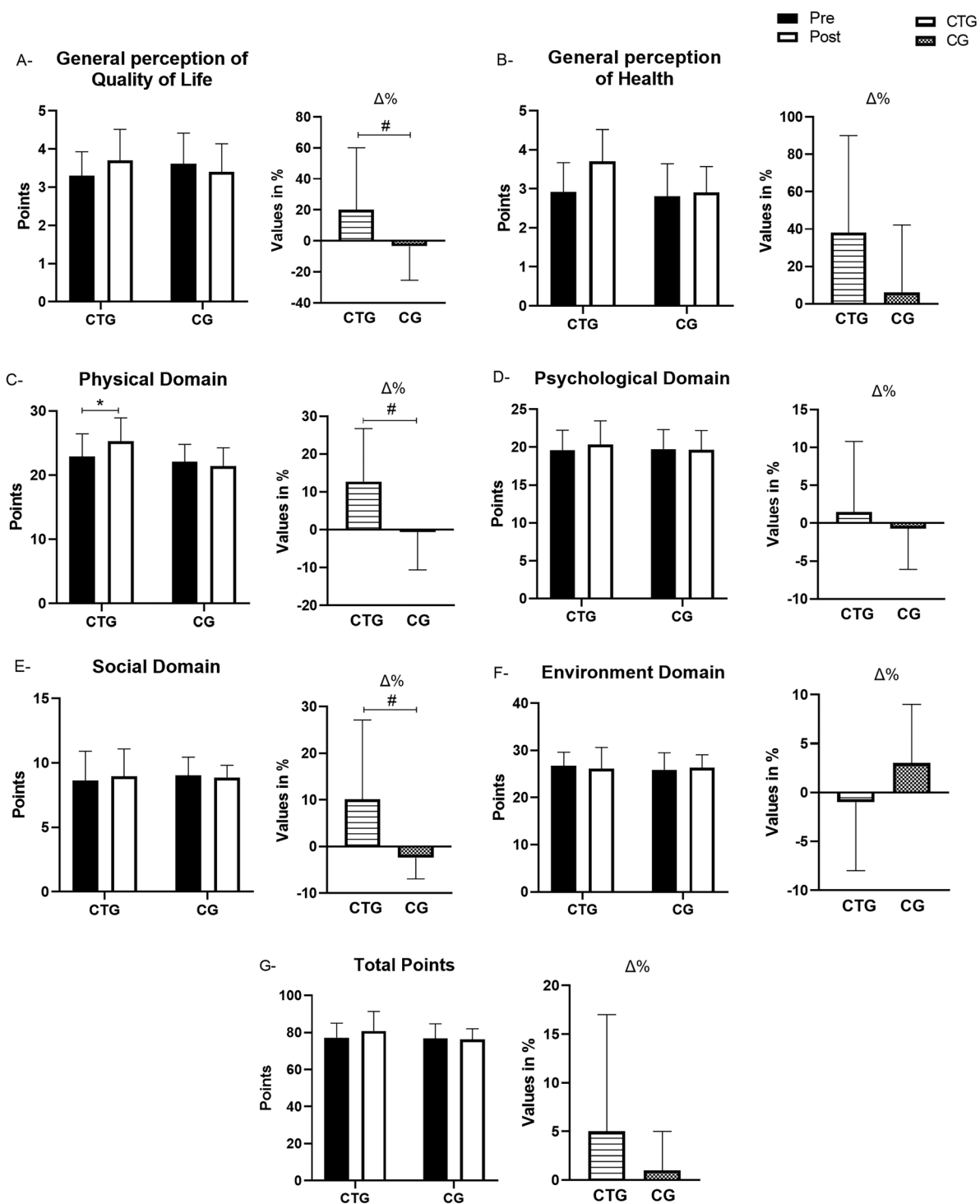
**Table 2.** Characterization of the sample-demographic variables and clinical markers in pre-experimental period (baseline).

	Combined training group	Control group
Female/male	7/6	8/8
T2DM diagnosis (years)	5.03 $\pm$ 2.58	4.75 $\pm$ 3.04
Age (years)	50.53 $\pm$ 3.55	52.18 $\pm$ 4.49
Weight (kg)	84.00 $\pm$ 12.64	84.61 $\pm$ 9.77
BMI (kg/m <sup>2</sup> )	29.62 $\pm$ 3.59	29.58 $\pm$ 3.29
Waist circ. (cm)	97.00 $\pm$ 11.34	97.18 $\pm$ 7.58
Lean mass (kg)	53.42 $\pm$ 11.19	54.83 $\pm$ 10.95
Fat mass (%)	35.27 $\pm$ 5.43	35.38 $\pm$ 7.25
VO <sub>2</sub> max. (ml/kg/min)	21.75 $\pm$ 4.26	22.41 $\pm$ 5.15
Leg Press 1 RM (kg)	190.15 $\pm$ 83.22	233.68 $\pm$ 90.89
Bench press 1RM (kg)	28.50 $\pm$ 15.22	37.66 $\pm$ 19.58
RMR (kcal/day)	1292.43 $\pm$ 307.63	1369.17 $\pm$ 391.52
Systolic BP (mmHg)	114.15 $\pm$ 13.62	123.37 $\pm$ 12.51
Diastolic BP (mmHg)	76.30 $\pm$ 11.54	77.62 $\pm$ 11.22
Heart Rate (bpm)	82.76 $\pm$ 11.56	79.62 $\pm$ 11.98
Carbohydrate (g/day)	316.38 $\pm$ 91.10	370.25 $\pm$ 72.04
Lipid (g/day)	54.59 $\pm$ 19.95	68.57 $\pm$ 17.20
Protein (g/day)	71.00 $\pm$ 21.93	92.44 $\pm$ 19.73
Calories (kcal/day)	1681.04 $\pm$ 455.37	1973.85 $\pm$ 385.89
Insulin ( $\mu$ U/mL)	14.33 $\pm$ 7.32	10.85 $\pm$ 5.28
Glucose (mg/dL)	154.07 $\pm$ 60.63	119.25 $\pm$ 26.97
HbA1c (%)	7.98 $\pm$ 2.59	6.70 $\pm$ 0.81
HOMA-B (%)	77.38 $\pm$ 48.32	85.89 $\pm$ 55.64
HOMA-IR (%)	5.29 $\pm$ 2.76	3.21 $\pm$ 1.72*
Triglycerides (mg/dL)	169.07 $\pm$ 82.63	138.93 $\pm$ 70.01
Cholesterol (mg/dL)	175.53 $\pm$ 36.44	186.31 $\pm$ 42.12
HDL-c (mg/dL)	38.00 $\pm$ 11.20	47.12 $\pm$ 18.78
LDL-c (mg/dL)	102.30 $\pm$ 24.57	111.37 $\pm$ 32.48
VLDL-c (mg/dL)	33.84 $\pm$ 16.47	27.81 $\pm$ 13.95
TSH (IU/ml)	2.21 $\pm$ 3.41	1.83 $\pm$ 2.14

Values are in mean  $\pm$  standard deviation.

BMI, Body mass index; BP, Blood pressure; HbA1c, glycated hemoglobin; HDL-c, High-density lipoprotein cholesterol; HOMA, Homeostasis model assessment; LDL-c, Low-density lipoprotein cholesterol; RMR, Resting metabolic rate; T2DM, Type 2 diabetes mellitus; TSH, Thyroid-stimulating hormone; VLDL-c, Very-low density lipoprotein cholesterol.

\*Difference between groups in pre moment.



**Figure 1.** Pre and post perception of quality of life obtained by Whoqol-Bref. Abbreviations: CTG, Combined training group; CG, Control group; Total points: sum of physical, psychological, social and environmental domain. Black bars=pre; White bars=post; Bars with lines =  $\Delta\%$  of CTG; bars with dots =  $\Delta\%$  of Control group; \* $p < 0.05$  difference between the CTG and control group in Tukey post hoc; # $p < 0.05$  difference between CTG and Control group  $\Delta\%$  in  $t$  independent test.

observed in the CTG in ANOVA ( $p=0.001$ ) followed by Tukey post hoc ( $p=0.01$ ) and consequently between the  $\Delta\%$  ( $p=0.01$ ) of the CTG and CONT group Regarding general QoL perception and the social domain, significant differences in  $\Delta\%$  changes were also found between the CTG and CONT groups ( $p=0.04$  for both), with the CTG demonstrating greater increases. In the analysis of the effect size (E.S), the CTG stands out, presenting in the pre-post comparison a moderate effect for the perception of general QoL (E.S.= 0.54) and physical domain (E.S. 0.68), alongside a strong effect for the perception of general health (E.S. 0.99).

### Significant correlations at baseline: QoL variables with clinical, hormonal, inflammatory, and thermogenic markers

Table 3 presents the significant correlations between the perception of QoL variables with clinical, hormonal, inflammatory and pro-thermogenic/anti-inflammatory variables in the pre-experimental period (data from the training and control groups together). Negative correlations were observed between the perception of general QoL with glucose, HOMA-IR, TYG index, triglycerides, amylin, and TNF- $\alpha$ , and alongside positive relations with IL-4, IL-13 and IL-33. Also, negative correlations between the physical domain and BMI, LDL and leptin, and positive relations with DPP-4 and Erythrocytes. Negative correlations between the psychological domain and waist circumference, total cholesterol, LDL and IL-2, and positive relation with FGF-21. Negative correlations between social domain with body weight, waist circumference and glucose. Environmental domain was negatively associated with IL-1  $\beta$  and CRP, and positively related with DPP-4 and BMP-4. Lastly, negative correlations between total points with IL-1 $\beta$ , and IL-2, and positive relation with DPP-4.

**Table 3.** Significant correlations between quality of life variables with anthropometric, body composition, functional, biochemical and molecular factors in the pre-experimental period.

	General perception of QoL	Physical domain	Psycho. domain	Social domain	Envir. domain	Total points
BMI (kg/m <sup>2</sup> )	NS	$r = -0.45$ $p = 0.04$	NS	NS	NS	NS
Weight (kg)	NS	NS	NS	$r = -0.59$ $p = 0.01$	NS	NS
Waist (cm)	NS	NS	$r = -0.53$ $p = 0.02$	$r = -0.64$ $p = 0.04$	NS	NS
Glucose (mg/dL)	$r = -0.35$ $p = 0.03$	NS	NS	$r = -0.72$ $p = 0.01$	NS	NS
HOMA-IR (%)	$r = -0.34$ $p = 0.03$	NS	NS	NS	NS	NS
TYG index (mg/ml)	$r = -0.33$ $p = 0.04$	NS	NS	NS	NS	NS
Amylin (pg/ml)	$r = -0.32$ $p = 0.04$	NS	NS	NS	NS	NS
DPP-4 (ng/ml)	NS	$r = 0.49$ $p = 0.01$	NS	NS	$r = 0.39$ $p = 0.03$	$r = 0.42$ $p = 0.02$
Total Cholesterol (mg/dL)	NS	NS	$r = -0.48$ $p = 0.04$	NS	NS	NS
Triglycerides (mg/dL)	$r = -0.31$ $p = 0.05$	NS	NS	NS	NS	NS
LDL (mg/dL)	NS	$r = -0.71$ $p = 0.04$	$r = -0.51$ $p = 0.001$	NS	NS	NS
VLDL (mg/dL)	NS	NS	NS	NS	NS	NS
Erythrocytes (mil/mm <sup>3</sup> )	NS	$r = 0.52$ $p = 0.02$	NS	NS	NS	NS
IL-1 $\beta$ (pg/ml)	NS	NS	NS	NS	$r = -0.71$ $p = 0.04$	$r = -0.71$ $p = 0.01$
IL-2 (pg/ml)	NS	NS	$r = -0.70$ $p = 0.04$	NS	NS	$r = -0.77$ $p = 0.02$
TNF- $\alpha$ (pg/ml)	$r = -0.35$ $p = 0.04$	NS	NS	NS	NS	NS
CRP (ug/ml)	NS	NS	NS	NS	$r = -0.39$ $p = 0.03$	NS
Leptin (ng/ml)	NS	$r = -0.50$ $p = 0.03$	NS	NS	NS	NS
IL-4 (pg/ml)	$r = 0.48$ $p = 0.01$	NS	NS	NS	NS	NS
IL-13 (pg/ml)	$r = 0.39$ $p = 0.04$	NS	NS	NS	NS	NS
IL-33 (pg/ml)	$r = 0.38$ $p = 0.04$	NS	NS	NS	NS	NS
FGF-21 (pg/ml)	NS	NS	$r = 0.38$ $p = 0.04$	NS	NS	NS
BMP-4 (pg/ml)	NS	NS	NS	NS	$r = 0.48$ $p = 0.01$	NS

BMP-4, Bone Morphogenic Protein 4; BMI, body mass index; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase 4; Envir. Domain, Environment Domain; FGF-21, Fibroblast growth factor; HOMA-IR, Homeostasis model assessment - Insulin resistance; IL, Interleukin; Psycho. Domain, Psychological domain; QoL, Quality of life; RMR, Rest metabolic rate. Total points, sum of the physical, psychological, social and environmental domain; NS=not statistically significant.

Only significant correlations were presented ( $p \leq 0.05$ ).

### Significant correlations between $\Delta\%$ changes in QoL and $\Delta\%$ changes in clinical, hormonal, inflammatory, and thermogenic markers in CTG

Finally, Table 4 shows the significant relationships between the  $\Delta\%$  of pre-post CTG variables of QoL changes with the  $\Delta\%$  with the same other variables analysed in the pre-training. Negative correlations were observed between the perception of general QoL with waist circumference, C-peptide, GLP-1, GIP, basophils, and IL-6, beside of positive relations with the haemoglobin and IL-10 were detected. Positive correlations between general perception of health with irisin and BAT and negative correlations between

**Table 4.** Significant correlations between CTG  $\Delta\%$  of change in quality of life variables with anthropometric, body composition, functional, biochemical and molecular factors.

	General perception of QoL	General perception of Health	Physical domain	Psycho. domain	Social domain	Envir. domain	Total points
BMI (kg/m <sup>2</sup> )	NS	NS	$r - 0.86$ $p = 0.02$	NS	NS	NS	NS
Weight (kg)	NS	NS	$r - 0.86$ $p = 0.02$	NS	NS	NS	NS
Waist (cm)	$r - 0.8243$ $p = 0.02$	NS	NS	NS	NS	NS	NS
VO <sub>2</sub> max.(mL/kg/min)	NS	NS	$r 0.98$ $p = 0.01$	$r 0.97$ $p = 0.02$	$r 0.91$ $p = 0.04$	NS	$r 0.97$ $p = 0.02$
Strength Leg press (kg)	NS	NS	$r 0.97$ $p = 0.02$	$r 0.96$ $p = 0.03$	NS	$r 0.73$ $p = 0.02$	$r 0.96$ $p = 0.03$
DP (mm/hg)	NS	NS	$r - 0.99$ $p = 0.01$	NS	NS	NS	NS
Hemoglobin (g/dL)	$r 0.99$ $p = 0.03$	NS	NS	NS	NS	NS	NS
Insulin ( $\mu$ U/mL)	NS	NS	NS	NS	NS	$r - 0.55$ $p = 0.04$	NS
C-peptide (ng/ml)	$r - 0.68$ $p = 0.04$	NS	NS	NS	NS	NS	NS
IDE (ng/ml)	NS	NS	$r - 0.99$ $p = 0.01$	$r - 0.99$ $p = 0.03$	NS	NS	NS
Glucose (mg/dL)	NS	NS	NS	NS	NS	$r - 0.63$ $p = 0.02$	NS
HbA1c (%)	NS	NS	$r - 0.99$ $p = 0.01$	$r - 0.99$ $p = 0.04$	NS	NS	$r - 0.99$ $p = 0.03$
TYG index (mg/dL)	NS	NS	NS	NS	NS	$r - 0.95$ $p = 0.001$	NS
GLP-1 (pg/ml)	$r - 0.94$ $p = 0.01$	NS	NS	NS	NS	NS	NS
GIP (pg/ml)	$r - 0.90$ $p = 0.03$	NS	NS	NS	NS	NS	NS
TG (mg/dL)	NS	NS	NS	NS	NS	$r - 0.93$ $p = 0.001$	NS
VLDL (mg/dL)	NS	NS	NS	NS	NS	$r - 0.92$ $p = 0.001$	NS
Basophils (mil/mm <sup>3</sup> )	$r - 0.55$ $p = 0.04$	NS	$r - 0.99$ $p = 0.01$	NS	NS	NS	NS
Lymphocyte (mil/mm <sup>3</sup> )	NS	NS	$r - 0.99$ $p = 0.02$	NS	NS	NS	NS
Platelets (mil/mm <sup>3</sup> )	NS	NS	NS	NS	NS	NS	$r - 0.99$ $p = 0.04$
CRP ( $\mu$ g/ml)	NS	NS	NS	$r - 0.99$ $p = 0.03$	NS	NS	NS
IL-1 $\beta$ (pg/ml)	NS	NS	NS	NS	NS	$r - 0.95$ $p = 0.04$	$r - 0.99$ $p = 0.04$
IL-6 (pg/ml)	$r - 0.92$ $p = 0.02$	NS	NS	NS	NS	NS	NS
IL-10 (pg/ml)	$r 0.99$ $p = 0.04$	NS	NS	NS	NS	NS	NS
Irisin ( $\mu$ g/ml)	NS	$r 0.91$ $p = 0.02$	NS	NS	NS	NS	NS
BMP-4 (pg/ml)	NS	NS	NS	$r 0.67$ $p = 0.04$	$r 0.96$ $p = 0.03$	NS	NS
BAT activity (g/ml)	NS	$r 0.90$ $p = 0.01$	NS	NS	NS	NS	NS

BMP-4, Bone Morphogenic Protein 4; CRP, C-reactive protein; DP, Diastolic pressure; Envir. Domain, Environment Domain; HOMA-IR Homeostasis model assessment-Insulin resistance; HbA1c, glycated hemoglobin; IL-Interleukin; Psycho. Domain, Psychological domain; QoL, Quality of life; Total points, sum of the physical, psychological, social and environmental domain; TG, Triglycerides; TYG index, Triglycerides/glucose index; VLDL, Very low density lipoprotein; VO<sub>2</sub>max., maximum volume of oxygen; NS = not statistically significant. Only significant correlations were presented ( $p \leq 0.05$ ).

physical domain with body weight, BMI, diastolic pressure, IDE, glycated haemoglobin, basophils, and lymphocytes were observed, along with positive relations with VO<sub>2</sub>max. and strength (leg press). Negative correlations between the psychological domain with IDE, glycated haemoglobin and CRP, and positive associations with VO<sub>2</sub> max., strength (leg press) and BMP-4 were detected. The social domain presented positive correlations with VO<sub>2</sub>max. and BMP-4., while the environmental domain showed negative relations with insulin, glucose, TYG index, triglycerides, VLDL and IL-1  $\beta$ , and positive association with strength (leg press). Lastly, negative correlations between total points of QoL with glycated haemoglobin, platelets, and IL-1  $\beta$  were observed, alongside positive relations with VO<sub>2</sub>max. and strength (leg press).

## Discussion

The present study aimed to evaluate the effects of CT on the QoL of individuals with overweight-related T2DM and to examine the correlations between baseline and training-induced changes in QoL domains with a wide range of physiological variables. As main findings, we observed that CT improves the perception of general QoL and the physical and social domains of individuals with overweight-related T2DM. In addition, QoL and its domains were associated at baseline and in the changes induced by CT with several physiological variables here analysed, which increases understanding and importance of the interrelationships between individual perception of well-being with metabolic control, inflammation and thermogenesis.

The observed improvements in QoL following CT are consistent with previous findings that document the benefits of exercise, particularly aerobic and combined modalities, on the QoL of individuals with T2DM [8,11,30]. On the other hand, the present work observes an increase in QoL related to the social domain, which is not always observed when studying individuals with diabetes, as identified in a recent meta-analysis [8,11]. One of the points that may explain the divergence is that part of the studies that evaluate QoL use the SF-36 questionnaire, which analyses only the physical and mental domains. On the other hand, the social component is included in the mental domain with other variables related to QoL. Furthermore, in addition to several physiological components that were improved by CT and could indirectly influence the social context, it is essential to highlight that all training sessions were carried out in person, in groups and accompanied by researchers and instructors, which might have beneficially influenced volunteers in their perception of social QoL. This is supported by findings that group training can be more effective in protecting against isolation and depression [31].

At baseline, negative associations were found between key cardiometabolic risk factors—including body weight, BMI, waist circumference, glucose, HOMA-IR, triglycerides, total cholesterol, and LDL cholesterol—with QoL and health measures. These associations are in line with existing literature [8,11,30]. It is also expected that CT, due to its already known metabolic effects [9], could influence part of these relationships. Indeed, this was confirmed by inverse correlations between the  $\Delta\%$  change of weight, BMI, waist circumference, glucose and VLDL with those related to QoL. Additionally, CT also interferes with negative relationships between the  $\Delta\%$  change in QoL and its components with other clinical variables, such as diastolic blood pressure, insulin and glycated haemoglobin, part of these associations also being found in the literature [11].

Beyond classical metabolic markers, this study identified novel associations between QoL and variables related to glycemic metabolism, such as the TyG index, C-peptide, amylin, and IDE, alongside positive correlations with DPP-4. These findings are noteworthy, given the established links between these markers and IR [25], as well as the association of IDE and amylin with an increased risk of neurodegenerative diseases [16], whereas DPP-4, a key regulator of incretin hormones, is integral to metabolic regulation and may indirectly influence QoL by enhancing glycemic control [16]. Together, these results show that alongside the well-known effects of physical training on glycaemic control (increased insulin sensitivity and glucose tolerance through various mechanisms such as improved body composition, inflammation, lipid profile, myokine secretion, GLUT-4 translocation independent of insulin, etc.) [9], other variables involved in the regulation of glycemic metabolism also contributed to the overall metabolic improvement and consequently to the perception of QoL.

Direct and indirect components of physical fitness present positive correlations with several QoL variables baseline. Erythrocytes were correlated to the physical domain, while the  $\Delta\%$  of change of hemoglobin associated with the perception of general QoL, and leg press strength, and VO<sub>2</sub>max. are positively

correlated with several QoL components. Strength and aerobic physical fitness were reported to correlate to the QoL in different populations [7,32]. Additionally, haemoglobin and erythrocytes can be considered indirect markers of aerobic physical fitness [33], and the relations here observed have not been reported before. Interestingly, the percentage improvement in the physical fitness components of the CTG ( $VO_{2max}$ : 13.8%; strength in leg press: 30.3%; and strength in bench press: 29.4%) are very close to that observed in the perception of general QoL, health, and in the physical and social domains, which reinforces the importance of maintaining/improving physical fitness to improve QoL.

Another variable in the blood count that shows inverse relationships between the total points are platelets, a result that can also be considered beneficial, since an increase in the number of these coagulation elements has been related to increased cardiovascular risk [34]. Considering the effects of CT on the parameters previously reported [21], as well as the effects on QoL and correlations observed in the present study, we can infer a global cardiometabolic improvement related to the improvement in QoL and its domains. These findings are in agreements with a recent study that observed such benefits in elderly people with T2DM undergoing aerobic training [35].

Although some studies already provided important evidence that QoL could be negatively affected by subclinical inflammation caused by excess body fat and cardiometabolic diseases, these studies focused on the analysis of CRP or blood count parameters through leukocyte count [2,5,6]. The present work, in addition to observing this inverse relationship of QoL components with CRP, lymphocytes and basophils, brings a wide range of findings, which gives a broader perspective on inflammation with the associations found here. At baseline, QoL and its domains are inversely related to the inflammatory markers CRP, IL-1, IL-2, TNF, and Leptin, while in the  $\Delta\%$  change induced by CT, negative correlations are observed again between CRP and IL-1 and IL-6. It is important to highlight that IL-1, IL-6 and TNF are the main stimulators of CRP and largely responsible for causing IR [36]. On the other hand, important relationships were detected between QoL and its domains with several anti-inflammatory and pro-thermogenic markers (IL-4, IL-10, IL-13, IL-33, FGF-21 and BMP-4) at baseline, and with the  $\Delta\%$  changes in irisin and in BMP-4. Notably, IL-10 is one of the best-known anti-inflammatory signals and tends to increase following inflammatory responses, showing higher levels in healthy individuals than those with cardiometabolic diseases [21,37]. IL-4, IL-13 and IL-33, in addition to being associated with anti-inflammatory stimuli, also play a significant role on adipocyte thermogenesis [38,39]. Additionally, FGF-21, irisin and BMP-4, in addition to thermogenic induction, have significant effects on improving IR and general metabolic homeostasis [40]. Both inflammatory and pro-thermogenic anti-inflammatory markers can interfere in metabolic control and various symptoms associated with low-grade subclinical inflammation, such as fatigue, weakness, skin problems, joint pain and stiffness, digestive problems, recurrent infections, among others [5,6,17]. All of these symptoms can significantly affect quality of life and may explain the observed correlations.

The positive correlations observed between the  $\Delta\%$  change in BAT activity with the general perception of health in the CTG strengthen the association of organic adaptations for heat production and increased energy expenditure with QoL and physical exercise. BAT is the main thermogenic tissue linked to improved health and protection against cardiometabolic diseases and there is evidence showing that increased BAT activity is significantly associated with cardiometabolic improvement and protection against obesity, T2DM, dyslipidaemia, coronary artery disease, atrial fibrillation, heart failure, hypertension and cerebrovascular diseases [19,40]. These effects of BAT are mainly due to the increase in energy expenditure, and consequent improvement in lipid and glycemic metabolism, attenuating the adverse effects and symptoms that metabolic dysfunction and low-grade subclinical inflammation normally present in low BAT activity can cause and consequently affect the QoL [5,40].

Although the present study brings new and significant findings regarding the relationship between QoL, CT and several metabolic and molecular factors, new studies should focus on better understanding certain relations, especially psychosocial and environmental components. In addition, the associations observed between the environmental domain with CT effects may be more difficult to establish. However, the presence of some facets in the environmental domain can help explain this context, for example, 'health and social care: availability and quality', 'opportunities to acquire new information and skills' and 'participation in recreation and leisure opportunities' can be related to the practice of physical activity [3].

As the present work is a pilot study, future research should aim to confirm and expand these findings in larger and more diverse populations, including individuals with longer disease duration and complications, as well as healthy individuals. Particular emphasis should be placed on further exploring the

mechanistic roles of inflammatory and thermogenic markers—such as IL-4, IL-10, IL-13, FGF-21, irisin, BMP-4, and BAT activity—in mediating changes in quality of life. Although our work provides initial correlations, more in-depth physiological, molecular, and longitudinal analyses are essential to determine causal pathways and understand how these biomarkers interact with psychosocial and clinical domains of QoL and health in individuals with T2DM. Finally, new work on the topic should advance through interdisciplinary collaboration based on these initial findings.

The present work has some limitations. The first is the number of subjects evaluated, especially in the training group. Therefore, the work is defined as a pilot study and should be used to explore new perspectives and base work on a larger number of evaluated subjects. Although some studies with training and QoL in individuals with T2DM have a sample size close to the present study, most studies on the subject present samples with more than 20 subjects [11]. However, the result of the power calculated a posteriori for most of the QoL variables and the large number of metabolic and molecular variables used in correlation analyses strengthen the work. Another limitation is having subjects of both sexes as physiological differences between men and women could affect the results. Nonetheless, the age range of the sample (CTG: 45–56 years; CONT group: 46–58 years), as well as the low number of pre-menopausal women in CT ( $n=1$ ), must have minimised this effect. The time since diagnosis of T2DM (between 1 and 10 years – average of ~5 years) and the non-inclusion of individuals using exogenous insulin and with complications of the disease, means that the results should be observed with caution before extrapolating to the population with T2DM in general. In addition to the effects of training, the socialization that was provided to the CTG during the training sessions is a factor that may have influenced the QoL results.

## Conclusion

CT improves the perception of general QoL, the physical and social domains in individuals with overweight-related T2DM. The correlations observed at baseline and the improvements stimulated by CT between QoL components and various physiological parameters underscore the importance of enhancing physical fitness, reducing IR and inflammation, and promoting thermogenesis to improve perceptions of well-being. These findings highlight the multidimensional benefits of CT beyond traditional metabolic outcomes. Future studies with larger samples, including individuals with advanced T2DM complications and those using exogenous insulin, are warranted to validate and expand upon these results and to further explore the physiological determinants of QoL improvements in this population.

## Ethics approval

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the University of Campinas (Approval Number: 1.597.626; approved on May 30, 2016).

## Consent to participate

All volunteers were informed of the purpose of this study, and the consent was written by signed the Free and Informed Consent Form.

## Consent to publish

The authors affirm that human research participants provided informed consent for publication of the data (Figure 1 and Tables 1–4).

## Acknowledgments

The authors thank the participants; Obesity and Comorbidities Research Center – University of Campinas; Faculty of Physical Education – University of Campinas; Integrated Teaching, Research and Extension Laboratory – School of Physical Education – University of Campinas. Finally, we thank the funding agencies, cited mentioned below.

## Authors contributions

CRedit: **Ivan Luiz Padilha Bonfante**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing; **Daniela Bastos Vieira**: Investigation, Writing – original draft, Writing – review & editing; **Marcelo Oliveira Batista**: Investigation, Writing – original draft, Writing – review & editing; **William Ciriaco Barbosa**: Investigation, Writing – original draft, Writing – review & editing; **Renata Garbellini Duft**: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing; **Keryma Chaves da Silva Mateus**: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing; **Ana Paula Boito Ramkrapes**: Investigation, Methodology, Writing – original draft, Writing – review & editing; **Liliane Ribeiro Vasconcelos**: Investigation, Methodology, Writing – original draft, Writing – review & editing; **Milena Monfort-Pires**: Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing; **Celso Darío Ramos**: Conceptualization, Resources, Writing – original draft, Writing – review & editing; **Lício Augusto Velloso**: Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing; **Mara Patricia Traina Chacon-Mikahil**: Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing; **Cláudia Regina Cavaglieri**: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

## Disclosure statement

The authors declare no conflicts of interest.

## Data availability

The data that support the findings of this study may be made available from the corresponding author upon reasonable request, depending on confidentiality level of the requested data.

## Funding

The study was supported by São Paulo Research Foundation (FAPESP) – São Paulo/Brazil – Regular Research Grants – Process: 2016/08751-3; Coordination for the Improvement of Higher Education Personnel (CAPES)-Brazil – Financing Code 001; National Council for Scientific and Technological Development (CNPQ) – Brazil-Financing Code 307985/2022-9.

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## References

- [1] Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2022;183:109119. doi:10.1016/j.diabetes.2021.109119.
- [2] Slagter SN, van Vliet-Ostaptchouk JV, van Beek AP, et al. Health-related quality of life in relation to obesity grade, type 2 diabetes, metabolic syndrome and inflammation. *PLoS One.* 2015;10(10):e0140599. doi:10.1371/journal.pone.0140599.
- [3] Fleck MP, Louzada S, Xavier M, et al. [Application of the Portuguese version of the abbreviated instrument of quality life WHOQOL-bref]. *Rev Saude Publica.* 2000;34(2):178–183. doi:10.1590/s0034-89102000000200012.
- [4] Jing X, Chen J, Dong Y, et al. Related factors of quality of life of type 2 diabetes patients: a systematic review and meta-analysis. *Health Qual Life Outcomes.* 2018;16(1):189. doi:10.1186/s12955-018-1021-9.
- [5] Kim JR, Kim HN, Song SW. Associations among inflammation, mental health, and quality of life in adults with metabolic syndrome. *Diabetol Metab Syndr.* 2018;10(1):66. doi:10.1186/s13098-018-0367-9.
- [6] Bozdemir-Ozel C, Arikan H, Calik-Kutucu E, et al. Subclinical inflammation is associated with reductions in muscle oxygenation, exercise capacity and quality of life in adults with type 2 diabetes. *Can J Diabetes.* 2020;44(5):422–427. doi:10.1016/j.jcjd.2020.02.007.
- [7] Kell RT, Bell G, Quinney A. Musculoskeletal fitness, health outcomes and quality of life. *Sports Med.* 2001;31(12):863–873. doi:10.2165/00007256-200131120-00003.
- [8] Myers VH, McVay MA, Brashear MM, et al. Exercise training and quality of life in individuals with type 2 diabetes: a randomized controlled trial. *Diabetes Care.* 2013;36(7):1884–1890. doi:10.2337/dc12-1153.

- [9] Colberg SR, Albright AL, Blissmer BJ, American College of Sports, M., & American Diabetes, A., et al. Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. *Exercise and type 2 diabetes*. *Med Sci Sports Exerc*. 2010;42(12):2282–2303.
- [10] Zaki S, Sharma S, Vats H. Effectiveness of concurrent exercise training in people with type 2 diabetes: a systematic review and meta-analysis. *Physiother Theory Pract*. 2024;40(9):2094–2115. doi:10.1080/09593985.2023.2225717.
- [11] Sabag A, Chang CR, Francois ME, et al. The effect of exercise on quality of life in type 2 diabetes: a systematic review and meta-analysis. *Med Sci Sports Exerc*. 2023;55(8):1353–1365. doi:10.1249/MSS.0000000000003172.
- [12] Galicia-García U, Benito-Vicente A, Jebari S, et al. Pathophysiology of type 2 diabetes mellitus. *Int J Mol Sci*. 2020;21(17):6275. doi:10.3390/ijms21176275.
- [13] Fuller NJ, Sawyer MB, Coward WA, et al. Components of total energy expenditure in free-living elderly men (over 75 years of age): measurement, predictability and relationship to quality-of-life indices. *Br J Nutr*. 1996;75(2):161–173. doi:10.1079/bjn19960122.
- [14] Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*. 2019;15(5):288–298. doi:10.1038/s41574-019-0176-8.
- [15] Grespan E, Guolo A, Muscelli E, et al. Loss of the incretin effect in type 2 diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2022;107(7):2092–2100. doi:10.1210/clinem/dgac213.
- [16] Martínez-Valbuena I, Valenti-Azcarate R, Amat-Villegas I, et al. Amylin as a potential link between type 2 diabetes and Alzheimer disease. *Ann Neurol*. 2019;86(4):539–551. doi:10.1002/ana.25570.
- [17] Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. *Am J Physiol Cell Physiol*. 2021;320(3):C375–C391. doi:10.1152/ajpcell.00379.2020.
- [18] Bonfante ILP, Duft RG, Mateus K, et al. Acute/chronic responses of combined training on serum pro-thermogenic/anti-inflammatory inducers and its relation with fed and fasting state in overweight type 2 diabetic individuals. *Front Physiol*. 2021;12:736244. doi:10.3389/fphys.2021.736244.
- [19] Becher T, Palanisamy S, Kramer DJ, et al. Brown adipose tissue is associated with cardiometabolic health. *Nat Med*. 2021;27(1):58–65. doi:10.1038/s41591-020-1126-7.
- [20] Zaki S, Alam MF, Sharma S, et al. Impact of concurrent exercise training on cardiac autonomic modulation, metabolic profile, body composition, cardiorespiratory fitness, and quality of life in type 2 diabetes with cardiac autonomic neuropathy: a randomized controlled trial. *J Clin Med*. 2024;13(13):3910. doi:10.3390/jcm13133910.
- [21] Bonfante ILP, Monfort-Pires M, Duft RG, et al. Combined training increases thermogenic fat activity in patients with overweight and type 2 diabetes. *Int J Obes (Lond)*. 2022;46(6):1145–1154. doi:10.1038/s41366-022-01086-3.
- [22] Bonfante ILP, Duft RG, Mateus KCdS, et al. Combined training and hormones/enzymes with insulinotropic actions in individuals with overweight and type 2 diabetes mellitus: A randomized controlled trial. *Eur J Sport Sci*. 2024;24(1):97–106. doi:10.1002/ejsc.12057.
- [23] Brunelli DT, Chacon-Mikahil MP, Gaspari AF, et al. Combined training reduces subclinical inflammation in obese middle-age men. *Med Sci Sports Exerc*. 2015;47(10):2207–2215. doi:10.1249/MSS.0000000000000658.
- [24] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–419. doi:10.1007/BF00280883.
- [25] Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord*. 2008;6(4):299–304. doi:10.1089/met.2008.0034.
- [26] Conceição MS, Bonganha V, Vechin FC, et al. Sixteen weeks of resistance training can decrease the risk of metabolic syndrome in healthy postmenopausal women. *Clin Interv Aging*. 2013;8:1221–1228. doi:10.2147/CLIA.S44245.
- [27] Chen KY, Cypess AM, Laughlin MR, et al. Brown Adipose Reporting Criteria in Imaging Studies (BARCIST 1.0): Recommendations for Standardized FDG-PET/CT experiments in humans. *Cell Metab*. 2016;24(2):210–222. doi:10.1016/j.cmet.2016.07.014.
- [28] de-Lima-Junior JC, Souza GF, Moura-Assis A, et al. Abnormal brown adipose tissue mitochondrial structure and function in IL10 deficiency. *EBioMedicine*. 2019;39:436–447. doi:10.1016/j.ebiom.2018.11.041.
- [29] Lahesmaa M, Eriksson O, Gnad T, et al. Cannabinoid type 1 receptors are upregulated during acute activation of brown adipose tissue. *Diabetes*. 2018;67(7):1226–1236. doi:10.2337/db17-1366.
- [30] Cai H, Li G, Zhang P, et al. Effect of exercise on the quality of life in type 2 diabetes mellitus: a systematic review. *Q Life Res*. 2017;26(3):515–530. doi:10.1007/s11136-016-1481-5.
- [31] Stevens M, Lieschke J, Cruwys T, et al. Better together: how group-based physical activity protects against depression. *Soc Sci Med*. 2021;286:114337. doi:10.1016/j.socscimed.2021.114337.
- [32] Perez-Cruzado D, Cuesta-Vargas AI, Vera-García E, et al. The relationship between quality of life and physical fitness in people with severe mental illness. *Health Q Life Outcomes*. 2018;16(1):82. doi:10.1186/s12955-018-0909-8.
- [33] Hellsten Y, Nyberg M. Cardiovascular adaptations to exercise training. *Compr Physiol*. 2016;6(1):1–32. doi:10.1002/j.2040-4603.2016.tb00672.x.
- [34] Renga B, Scavizzi F. Platelets and cardiovascular risk. *Acta Cardiol*. 2017;72(1):2–8. doi:10.1080/00015385.2017.1281560.

- [35] Della Guardia L, Carnevale Pellino V, Filipas L, et al. Nordic walking improves cardiometabolic parameters, fitness performance, and quality of life in older adults with type 2 diabetes. *Endocr Pract.* 2023;29(2):135–140. doi:[10.1016/j.eprac.2022.11.007](https://doi.org/10.1016/j.eprac.2022.11.007).
- [36] Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* (1985). 2005;98(4):1154–1162. doi:[10.1152/jappphysiol.00164.2004](https://doi.org/10.1152/jappphysiol.00164.2004).
- [37] Eckardt K, Görgens SW, Raschke S, et al. Myokines in insulin resistance and type 2 diabetes. *Diabetologia.* 2014;57(6):1087–1099. doi:[10.1007/s00125-014-3224-x](https://doi.org/10.1007/s00125-014-3224-x).
- [38] Brestoff JR, Kim BS, Saenz SA, et al. Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature.* 2015;519(7542):242–246. doi:[10.1038/nature14115](https://doi.org/10.1038/nature14115).
- [39] Rao RR, Long JZ, White JP, et al. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell.* 2014;157(6):1279–1291. doi:[10.1016/j.cell.2014.03.065](https://doi.org/10.1016/j.cell.2014.03.065).
- [40] Kajimura S, Saito M. A new era in brown adipose tissue biology: molecular control of brown fat development and energy homeostasis. *Annu Rev Physiol.* 2014;76(1):225–249. doi:[10.1146/annurev-physiol-021113-170252](https://doi.org/10.1146/annurev-physiol-021113-170252).