Effects of Nonperiodized and Linear Periodized Combined Exercise Training on Insulin Resistance Indicators in Adults With Obesity: A Randomized Controlled Trial

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Abstract

Background

The aim was to verify the effect of non-periodized and linear periodized combined (aerobic more resistance) exercise training on insulin resistance markers in adults with obesity.

Methods

Was conducted a blinded randomized controlled trial with three groups of individuals with obesity (BMI, 30–39.9kg/m²): control group (CG, n=23), non-periodized group (NG, n=23), and linear periodized group (PG, n=23). The NG and PG performed aerobic and resistance exercises in the same session in aerobic-resistance order for 16 weeks. Both intervention groups trained three sessions weekly, with total duration of 60 minutes each. The aerobic training of the NG had duration of 30 min always between 50%–59% of the reserve heart rate (HRres), while resistance part was compost of 6 exercise, performed always in 2×10–12 maximum repetitions (RM). The PG progressed the aerobic and resistance training from 40%–49% to 60%–69% (HRres) and from 2×12–14 to 2×8–10 RM, respectively, along intervention period. The evaluated indicators of insulin resistance included fasting glucose, fasting insulin, and homeostasis model assessment-estimated insulin resistance (HOMA-IR) collected pre and post intervention. The analyses to verify the exercise training effect were performed using generalized estimating equations.

Results

After 16 weeks of training, per protocol analysis (n=39) showed significant reductions in HOMA-IR only in the training groups (NG: Δ=-1.6, PG: Δ=-0.6; p=0.094). Intention-to-treat analysis demonstrated significant reductions in fasting insulin levels (NG: Δ=-1.4, PG: Δ=-1.0; p=0.004) and HOMA-IR (NG: Δ=-5.5, PG: Δ=-3.8; p=0.002).

Conclusion

Periodized and non-periodized combined exercise training reduces similarly insulin resistance markers in adults with obesity.

Trial registration: Brazilian Registry of Clinical Trials, RBR-3c7rt3. Registered 07 February 2019 - https://ensaiosclinicos.gov.br/trial/5970/1

Key Points

* Combined exercise training promotes significant reductions in insulin resistance indicators in obese adults.

* Starting training at low or moderate intensity, promotes similar results in inactive obese.

* Even with low weekly frequency, combined physical exercise improves glycemic metabolism.

* Obese adults have low adherence to treatment with physical exercise.

Background

Obesity is considered a global health problem affecting 13% of the world population[1], with estimates indicating that 18.9% of the Brazilian population has obesity [2]. According to the Central Intelligence Agency of the United States of America, in 2016, 61% of the population of Nauru was considered obese, occupying the first position in the world ranking. The country with the lowest rate was Vietnam, with about 2% of the population in this condition. Excessive accumulation of ectopic fat is associated with metabolic disorders, where adipose tissue hypertrophy increases the secretion of adipokines, which favors insulin resistance [3] and greatly increases the chances of developing type 2 diabetes mellitus(T2DM) [4]. Indeed, the term "diabesity" has been used in view of the close relationship between these diseases. Corroborating this, individuals with obesity tend to have higher insulin resistance values, with a higher incidence of dysglycemia, hypertriglyceridemia, and high blood pressure [5, 6]. Moreover, even individuals with obesity, considered metabolically healthy in the long term, have aggravated insulin resistance status and are more likely to develop other comorbidities, and are more prone to all-cause mortality [7].

Regarding glycemic metabolism in individuals with obesity, an important strategy to prevent the occurrence of T2DM and associated complications is the practice of exercise training, which is an effective and low-cost tool, recommended worldwide [8]. Among the types of training, it has been observed that a combination of aerobic and resistance exercises, called combined training, generates a sum of benefits from both modalities, and is recommended for health promotion and longevity of adults with and without obesity and diabetes [9, 10]. Acutely, a combined training session has superior results in β-cell function, insulin sensitivity, and glucose levels compared to aerobic and resistance training alone [11], also, these benefits can be extended or consonant chronically with such practice [12, 13]

However, changes resulting from training are subject to strategies that aim to modulate training variables such as intensity, volume, recovery interval, and exercise order in programs; thus, periodization is employed for this purpose [14–16]. Although health benefits in the population with obesity are enhanced through the use of periodization, it is observed that when it comes to checking the effects on glycemic metabolism, the articles use the different periodization models in the comparison of aerobic or resistance training in isolation [14, 16]

However, improvements in glycemic metabolism resulting from different combined training models are frequently investigated with T2DM population, and further understanding of the effect of periodic combined training in the population with obesity is required due to the early presentation of significant changes in glucose metabolism, especially insulin resistance, which may collaborate to trigger diabetes mellitus. Moreover, the effects of different periodization possibilities on clinical outcomes in special populations, such as individuals with obesity, are still embryonic. Tracking cases of obesity, which commonly precede multimorbidity, and identifying training strategies that improve or even maintain indicators of glycemic metabolism may provide insights for the treatment and prevention of such chronic diseases.

T o fill the gap and create a study with a pioneer designer, we aimed to verify the effect of non-periodized and linear periodized combined exercise training on insulin resistance markers in adults with obesity. We

hypothesized that both forms of training would benefit insulin resistance markers but that training combined with linear periodization would be superior to non-periodized training.

Methods

2.1 Study design

This study was a blind randomized controlled trial that included three groups of individuals with obesity, conducted in parallel over 16 weeks. The present study is part of a larger project, entitled “Effects of different protocols of adult health training on obese people, which was approved by the Ethics Committee and Research on Human Beings of the institution of origin (protocol 2.448.674) and registered in the Brazilian Registry of Clinical Trials (RBR-3c7rt3). The methodological details of the larger project of this study are described in its protocol [17].

2.2 Participants

The initial disclosure of the study was made in electronic and printed media. Interested volunteers contacted the researchers via an online form to be filled in order to verify their eligibility. Following were the eligibility criteria: age between 20 and 50 years, obesity grade I and II in terms of body mass index (BMI) (30–34.9 kg/m² and 35–39.9 kg/m², respectively), and no physical exercise with a weekly frequency of more than twice a week in the past 3 months. In addition, participants could not present with any cardiometabolic disease and/or use continuous medications, as well as not using medications to control and/or treat obesity, nor having performed any surgical procedure aimed at weight reduction. Those who met all the criteria and consented to participate were included in the study and provided written informed consent.

2.3 Randomization

All participants underwent a series of evaluations before being randomly allocated to three groups: control group (CG), non-periodized training group (NG), and linear periodization group (PG). Randomization was stratified by sex, age, and BMI, collected at baseline, with a ratio of 1:1:1 by the program www.randomizer.com. This process was conducted by independent researchers who were not involved in the evaluations or the intervention process. The allocation list was only unveiled to trainers on the start date of the intervention.

2.4 Interventions

The NG and PG participated in 16 weeks of combined training (including aerobic and strength exercises in the same session). Aerobic training was performed continuously through walking and/or running, with intensities prescribed by percent reserve heart rate ranges (%HRres). Strength training was performed in multiple sets, using six exercises, all performed with weight training equipment, with prescription for maximal repetition ranges and the increase in load (kilograms) was indicated whenever the participants sustained the expected series in the upper repetition range for two consecutive sessions.

. The established weekly frequency was three times, with an average duration of 60 minutes; the first 5 minutes for warm-up, 30 minutes for aerobic training, 20 minutes for strength training, and the final 5 minutes for stretching. The first week was used as training familiarization for both groups. Afterward, the PG participated in training with increasing linear periodization, which was divided into three mesocycles, while the NG remained at moderate intensity throughout the study. In the end, the training volume of both groups was equivalent. The CG did not receive any intervention and the participants were instructed to maintain routine activities. Figure 1 shows the prescribed intensities according to the groups at different times of the study. Additional methodological details can be found in the study protocol [17].

2.5 Assessment for sample characterization and exercise prescription

Participants completed an online questionnaire on the Question Pro Platform, containing sociodemographic information. For the body composition evaluation, a tetrapolar bioelectrical impedance In Body 720 (Ottoboni, Rio de Janeiro, Brazil) was used and manipulated by experienced evaluators who followed the recommended protocol to use the equipment. To prescribe physical training, the maximum and resting heart rates were used to calculate the ideal training zone; these were obtained using Polar® portable heart rate monitors, model S810i. The maximum heart rate was measured by exercise test until voluntary treadmill exhaustion (ImbramedMillenium Super ATL, Porto Alegre, Brazil), according to the protocol previously validated by Jones and Doust [18], with a 1% success rate for reproducing race conditions outdoors. The resting heart rate was recorded with the participant lying down with a heart rate monitor strap positioned. Three notes were taken over 5 minutes (minutes 3, 4, and 5), and the average was recorded as a reference value. Strength heart rate reassessments were performed at the end of each mesocycle to adjust the intensity.

2.6 Outcome assessments

Outcomes were obtained by venipuncture, where 20ml samples were collected in dry bottles with separating gel and another in parallel with anticoagulant (EDTA). Collections took place between 7 am and 9 am, and the participants fasted for 12 hours before collection. Post-treatment collections were made between 48 and 72 hours after the last exercise session. Blood samples were processed and centrifuged to obtain plasma and serum, before storing in a -80ºC bio freezer. The evaluated indicators of insulin resistance were fasting glucose, fasting insulin, and insulin resistance (HOMA-IR). An enzymatic-colorimetric kit (Trinder) was used according to the manufacturer's recommendations for the determination of fasting glucose values. The serum insulin concentration values in mU/L were measured by chemiluminescence immunoassay using the ADVIA CentaurXP ™ Automated Chemiluminescence System. Both analyses were performed at the Clinical Analysis Laboratory of the University Hospital of the Federal University of Santa Catarina. Insulin resistance was estimated using the insulin resistance homeostasis model (HOMA-IR) using the formula: HOMA-IR = [fasting glucose (mmol/L) * fasting insulin (uU/ml)] / 22.5.

2.7 Statistical analysis

The sociodemographic variables, sex (male or female), marital status (with and without a partner), ethnicity (white or brown), and schooling (high school and college) were used to characterize the sample. Continuous

variables were expressed as mean and standard deviation, and categorical variables were expressed as relative frequency and percentage. Data distribution was verified using the Shapiro-Wilk test. Differences between the groups at baseline were tested by one-way analysis of variance for independent samples (one-way ANOVA) and Chi-square test.

Outcomes were analyzed by per protocol analysis in those who participated until the end of the study and had complete post-evaluation data. Outcomes were also analyzed by intention-to-treat analysis, in which all randomized participants were included, and the missing values were imputed by regression predictive factors by the maximum likelihood estimator given by generalized estimating equations (GEE). Intra and intergroup analyses were also performed by GEE with the adoption of the Bonferroni post-hoc test. Data are expressed as mean and standard error. The level of significance adopted for the interaction was $p<0.10$, while for the isolated effect of time and/or group was $p<0.05$. All analyses were performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA). The intra-group effect sizes (ES) were calculated by Cohen's d-test [19]; for this, the value of dividing the mean difference between each intragroup assessment was considered by grouping the standard deviation between the same assessment period. According to Cohen (1988), it was agreed that d values are considered small if ($0.20 \leq d < 0.50$), medium if ($0.50 \leq d < 0.80$), and large if ($d \geq 0.80$)[19].

For fasting glucose and insulin data the results of the individual responses (Δ=post intervention data – pre-intervention data) of the participants analyzed per protocol are presented.

Results

More than 500 volunteers applied for the study; however, after the initial evaluation processes, 69 participants remained and were randomized into three equal groups (NG, PG, and CG). After sixteen weeks of training, part of the sample was lost for reasons such as unavailability, work or study, and even health problems (Figure 2).

A total of 39 people completed all phases of the trial and were included in the per-protocol analyses. The frequency of sessions was 64% and 61% for NG and PG, respectively, with no differences in aerobic ($p= 0.350$) and strength training volume ($p= 0.987$). The overall average weekly frequency was 2.0 sessions in the first mesocycle, while in the third mesocycle it was 1.6, with no significant differences between training groups. However, the intensity proposed during the sessions was met by 90% of the participants. There were no adverse events during the exercises during the study.

Table 1 shows the baseline comparison of the sociodemographic characteristics and nutritional status of adults with obesity participating in the study. The study sample had a mean BMI of 33.3kg/m² (±3.13kg/m²) and an age of 36 years (±6 years). Most of the participants were women, who lived with a partner, white ethnic, and had completed high school.

Table 2 shows the insulin resistance indicators with analysis per protocol and intention-to-treat. In the per protocol analysis, HOMA-IR was reduced in the training groups (NG- pre: 4.1±0.9; post: 2.5±0.4; PG- pre: 3.3±0.3; post: 2.7±0.4; $p=0.094$) with medium effect size. The intention-to-treat analysis, despite not

showing any significant difference, demonstrated that the fasting insulin (CG=0.17; NG=0.74; PG=0.52) and HOMA-IR (CG=0.12; NG=0.84; PG=0.60) decreased in all groups with medium and high effect size for training groups.

Figures 3 and 4 show the individual response data to fasting glucose and insulin according to the groups, respectively. This descriptive information allows the visualization of positive results predominantly in the groups that participated in the training, even without statistical significance.

Table 1. Characteristics of study participants (n=69).

Variables	**CG (23)**	**NG (23)**	**PG (23)**	**p-value**
	(±sd)	**(±sd)**	**(±sd)**	
Age (years)	34.2 (±7.6)	34.2 (±6.7)	35.6 (±7.4)	0.740
BMI (kg/m²)	33.2 (±2.4)	33.7 (±3.0)	33.5 (±3.1)	0.129
	n (%)	**n (%)**	**n (%)**	
Sex				1.000
Female	14 (60.9)	14 (60.9)	14 (60.9)	
Marital status				0.442
With a partner	17 (73.9)	14 (60.9)	13 (56.5)	
Skin color				0.910
White	19 (82.6)	19 (82.6)	18 (78.3)	
Educational level				0.914
High-school	18 (78.3)	18 (79.7)	18 (78.3)	

Note: n = absolute frequency; % = relative frequency.

X = average; ± dp = standard deviation.

CG: control group; NG: non-periodized group; PG: periodized group.

BMI = body mass index.

Table 2. Blood glucose, insulin and insulin resistance for control group (CG), non-periodized group (NG) and periodized group (PG) before and after 16 weeks of intervention.

Group	Pré-Intervention (±se)	Post-Intervention (±se)	Mean difference	Cohen d	P-value group	P-value time	P-value Group * time
Per protocol (n=39)							
Blood glucose (mg/dL)							
CG(n=14)	95.0 (±1.0)	101.0 (±4.0)	6.0	0.58	0.584	0.788	0.102
NG(n=11)	97.1 (±2.7)	91.9 (±3.6)	-5.2	0.54			
PG(n=14)	97.0 (±3.4)	94.7 (±3.2)	-2.3	0.20			
Insulin (mU/L)							
CG(n=14)	15.3 (±2.1)	16.1 (±2.1)	0.8	0.11	0.438	0.072	0.141
NG(n=11)	16.8 (±3.4)	10.8 (±1.6)	-6.0	0.75			
PG(n=14)	13.8 (±1.2)	11.6 (±1.5)	-2.2	0.46			
HOMA-IR							
CG(n=14)	3.6 (±0.5)	4.0 (±0.9)	0.4	0.15	0.441	0.130	0.094
NG(n=11)	4.1 (±0.9)	2.5 (±0.4)*	-1.6	0.76			
PG(n=14)	3.3 (±0.3)	2.7 (±0.4)*	-0.6	0.49			
By intention to treat (n=69)							
Blood glucose (mg/dL)							
CG(n=23)	99.8 (±4.1)	99.6 (±3.4)	-0.2	0.01	0.426	0.124	0.614
NG(n=23)	96.2 (±1.8)	92.4 (±3.1)	-3.8	0.31			
PG(n=23)	97.5 (±2.1)	94.3 (±3.1)	-3.2	0.25			
Insulin(mU/L)							
CG(n=23)	16.8 (±2.1)	15.2 (±1.8)	-1.6	0.17	0.536	0.002	0.430
NG(n=23)	16.4 (±1.8)	10.9 (±1.3)	-5.5	0.74			
PG(n=23)	16.0 (±1.4)	12.2 (±1.7)	-3.8	0.52			
HOMA-IR							
CG(n=23)	4.1 (±0.5)	3.8 (±0.5)	-0.3	0.12	0.405	0.004	0.447
NG(n=23)	3.9 (±0.4)	2.5 (±0.3)	-1.4	0.84			

PG(n=23)	3.9 (±0.3)	2.9 (±0.4)	-1.0	0.60

Note: X = average; ±se = standard error;

CG: control group; NG: non-periodized group; PG: periodized group;

Generalized estimated equation (GEE); Bonferroni post-hoc test. * Significant difference intra groups ($p < 0.05$).

Discussion

In the current study, the aim was to determine the effect of 16 weeks of combined training with linear periodization and without periodization on insulin resistance indicators in adults with obesity. The markers investigated included blood glucose, insulin, and HOMA-IR. Clinical and statistical improvements were observed for insulin and insulin resistance outcomes for both training groups, refuting the initial hypothesis of superiority to the PG. The interpretation of this finding can be added to the result of another study published previously, using the same participants, where similar effects were reported in the increase in maximum strength of upper and lower limbs for both training groups, and the body composition remained unchanged [20]. It is possible that the muscular hypertrophy acquired with training causes endocrine modulations, mainly related to the increase in insulin sensitivity and the control of leptin, regardless of the change in body composition [21].

Our findings corroborate those of Bonfante et al., (2017) that 24 weeks of combined training with linear periodization in men with obesity resulted in improvements in the aforementioned indicators[12]. These improvements in insulin markers in obese population are important because are against of obesity physipopatology, that is characterized by a state of low-grade systemic inflammation[22] due to increased secretion of inflammatory cytokines, such as TNF-α and IL-6. In addition, it increases the secretion of leptin, resistin, and inhibitor-1 of plasminogen activation, which causes insulin resistance [23]. Physical exercise, in turn, reduces the inflammatory condition, decreasing the secretion of leptin and TNF-α, which is a metabolic cascade of changes in other adipokines, it reduces the secretion and cytokines of the insulin antagonist and subsequently improves insulin resistance. Reductions in the indicators of such resistance are important and affect the improvement of this mechanism, which, in the long run, interferes with the appearance of the metabolic syndrome and DM2 [23].

Regarding fasting blood glucose, no significant changes were detected in our study, regardless of the group or analysis. Despite this, when analyzing only the participants who completed the training, it is possible to notice a greater amount of positive responses in this variable. This finding can be partially explained because the serum values are already normal at baseline, according to the reference values established by the Brazilian Diabetes Society (2018) [24], and this minimizes the scope for improvement. However, these participants, who were already in a state of metabolic abnormality, were able to keep their glycemic levels within normal limits due to increased insulin secretion. This fact is relevant in this scenario, since physiological changes, such as increased pro-inflammatory cytokines and free circulating fatty acids, as well as reduced insulin sensitivity, increase the need for insulin secretion to maintain glycemic homeostasis. Over time, and with the worsening of the disease, hyperglycemia will establish itself due to the saturation of

insulin production, as well as by resistance mechanisms [9]. In addition, the evidence points to the importance of training volume and intensity for significant results of blood glucose [25,26], which were not highin the present study.

In the per protocol analysis, HOMA-IR showed significant reductions over time only in the combined training groups. However, in the intention-to-treat analysis, in addition to HOMA-IR, fasting insulin also indicated reductions over time, with effect sizes of moderate magnitude for the intervention groups. Ahmadizad et al. (2014) and Inoue et al. (2015) investigated in their respective studies the effect of different forms of periodization on insulin resistance indicators and found no differences [14,27]. Strohacker et al. (2015) understood that it is premature to conclude that periodized training is superior to non-periodized training in terms of improving health indicators in non-athletes [28]. However, they stated the need for more research to understand the effectiveness of periodization and the feasibility of implementing flexible methods. To date, an insufficient number of studies have investigated this topic.

Inoue et al. (2015) built interdisciplinary therapy models that included periodized combined training (linear versus undulating) and realized that both ways were effective in improving the lipid profile and insulin sensitivity in adults with obesity [27]. Still, with this population, and with similar comparisons, Foschini et al. (2010) demonstrated a reduction in insulin and HOMA-IR concentrations only in the group that used daily undulating periodization [29]. An important detail is that the participants in this study [29] and ours were not previously trained, which enlarges and/or limits the zone of training regardless of the periodization model. However, such findings reinforce the relevance of structured physical exercise in modulating these metabolic variables regardless of the form of periodization. For inactive and/or unfamiliar people with physical exercise, the type of periodization does not seem to interfere with the effects of glucose metabolism in the first months of training. Thus, gaps in the body of evidence on the superiority of training with different forms of periodization are indicated for health outcomes of special populations. Clinically, the results of periodization are relevant, as they suggest significant reductions in insulin resistance indicators in a population at metabolic risk. In general, these positive effects can be effective in the prevention and treatment of obesity, as well as DM2 and other diseases, by promoting adjustments in adipocytokines and other metabolic markers [30].

The strengths of this blind randomized clinical trial were the control of the aerobic training variables, the maintenance of the relative intensity in the NG, and the gradual increase of intensity in the PG over the mesocycles, both adjusted by the resting heart rate and considered a control method of low-cost. The progression of intensity and similarity in the training volume, is another strength, as it allows to verify the effects of different forms of periodization in the combined training program in an equal way. However, limitations, such as the low frequency of participants in the training program and sample loss, are also recognized due to the lack of data on the outcome variables of this study, which can lead to a low sampling power for statistically significant findings. Besides, the lack of control of food intake is an important consideration, and the lack of glycated hemoglobin may be another limitation. Also, it is plausible to consider the biological individuality of the participants, their respective routines, and other factors that could not be measured here as determinants in the changes, whether they were highlighted or not. Other studies

should investigate such outcomes in other age groups, with a higher percentage of adherence to training sessions and other forms of prescription, which can influence the results that will be found.

Conclusion

Thus, in 16 weeks, periodized combined training improve similarly to non-periodized combined training the insulin levels and HOMA-IR decreased but glucose levels did not change in adults with obesity. The training used, which has practical applicability, even with low adherence, provided a reduction in important risk factors for triggering other comorbidities in a population already considered at risk. For future studies, greater attention is recommended to these health indicators in adults with obesity not yet diagnosed with other comorbidities. In addition, we recommended the implementation of adherence strategies to enhance the results of this study, as well as further exploration of other training methods.

Abbreviations

T2DM: type 2 diabetes mellitus

BMI: body mass index

CG: control group

NG: non-periodized training group

PG: linear periodization group

%HRres: reserve heart rate ranges

GEE: Generalized estimated equation

Declarations

Ethics approval and consent to participate

Ethics Committee and Research on Human Beings at Federal University of Santa Catarina, protocol 2.448.674;

Brazilian Registry of Clinical Trials number RBR-3c7rt3

Consent for publication - Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ARS contributed to literature review, data collection, data analysis and interpretation and writing of the manuscript. LSL and RSD contributed to data analysis and interpretation and writing of the manuscript. CRC and GFDD contributed research concept and study design and draft of manuscript. All authors read and approved the final manuscript.

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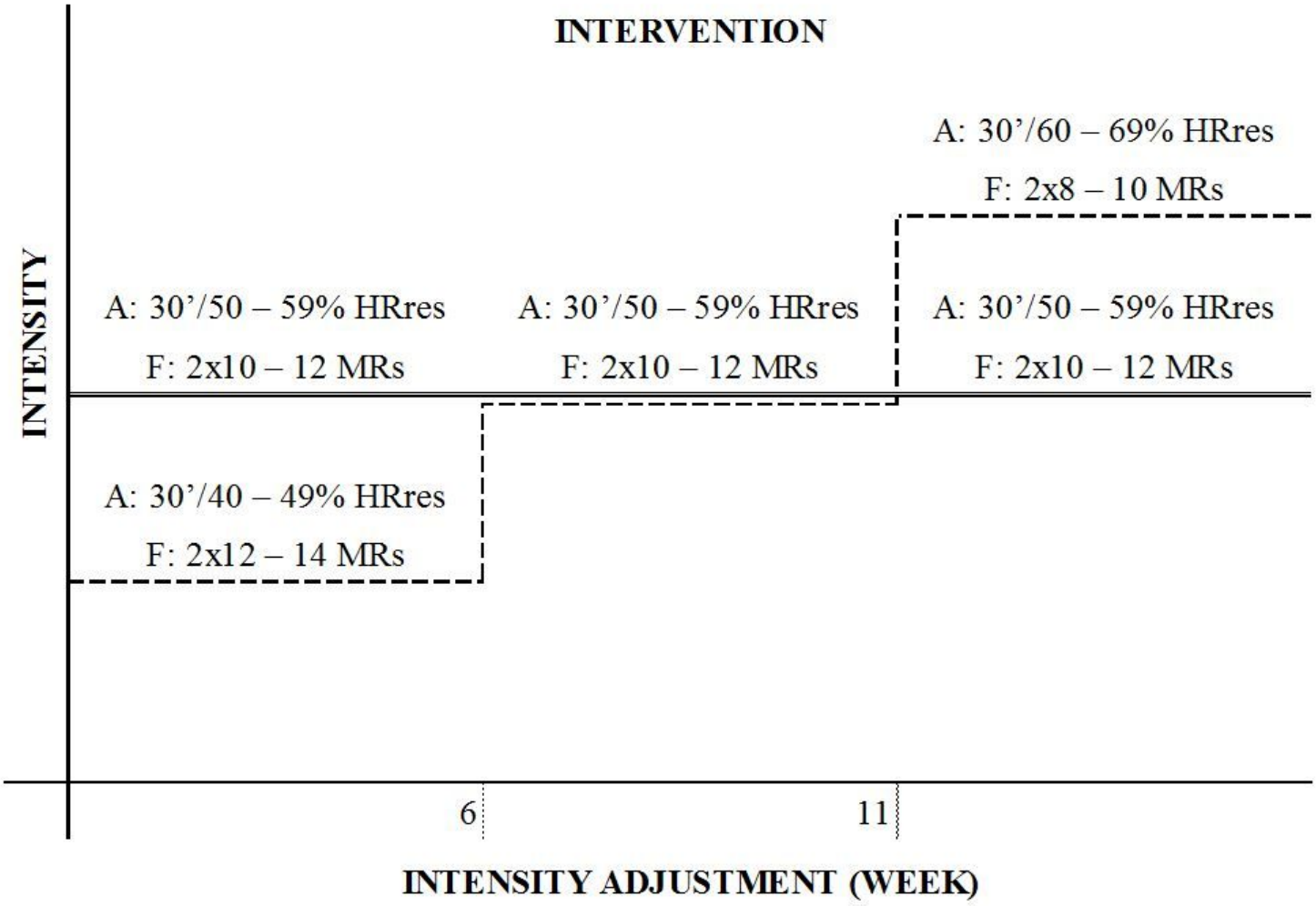
Figures



: linear periodized training group;
═══: non-periodized training group;
A: aerobic training;
F: resistance training;
HRres: reserve heart rate;
MRs= maximal repetition;
x: series.

Figure 1

Structure of the training protocols performed by the periodized combined training group (PG) and the non-periodized training group (NG).

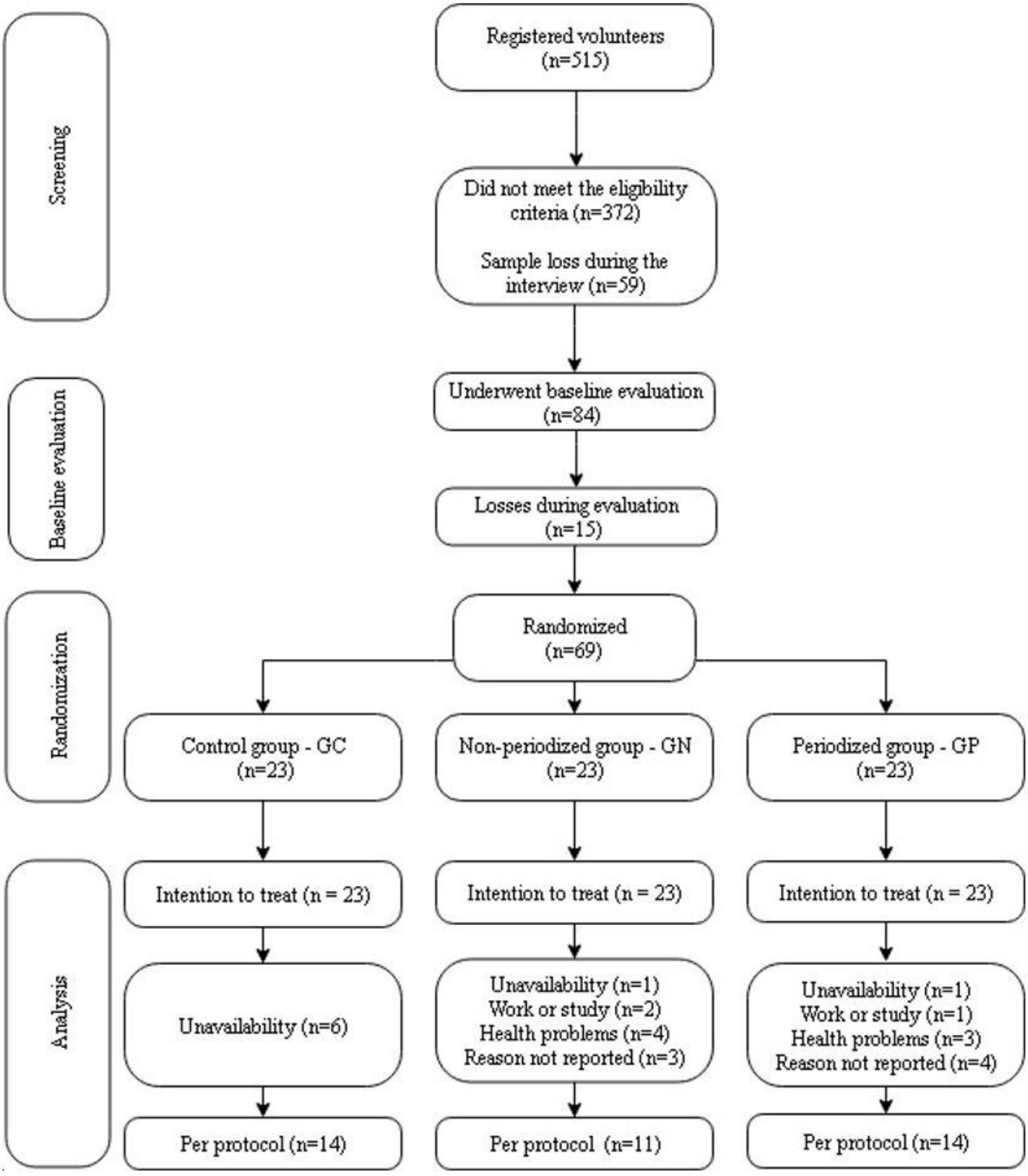


Figure 2

Study Flowchart.

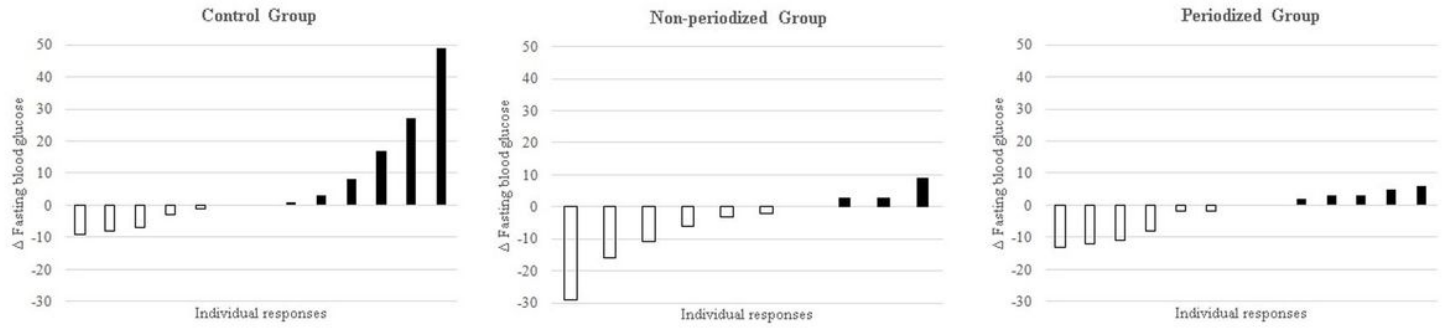


Figure 3

Individual responses of fasting blood glucose according to the groups.

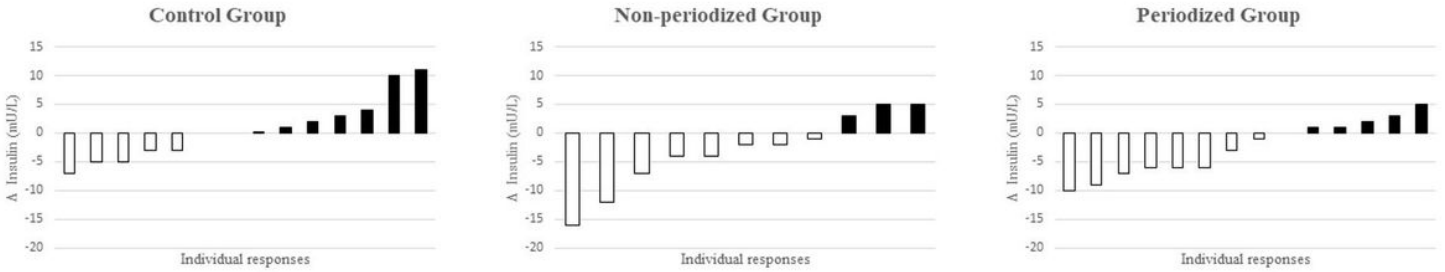


Figure 4

Individual responses of insulin according to the groups.