



OPEN ACCESS

EDITED BY

Bing Shen,
Macau University of Science and Technology,
Macao SAR, China

REVIEWED BY

João Rafael Valentim-silva,
University of Vassouras, Brazil
Bing Bo,
Henan University, China

*CORRESPONDENCE

Ayoub Saeidi
✉ a.saeidi@uok.ac.ir

RECEIVED 14 January 2025

ACCEPTED 29 October 2025

PUBLISHED 18 November 2025

CITATION

Ataeinosrat A, Abednatanzi H, Hajesfandiari S,
AL Nasser MN, Dara MM, Farzanegi P,
Nahand MS, Almaqhawi A, Karimi N,
Bagherzadeh-Rahmani B, Saeidi A, Laher I
and Zouhal H (2025) Hepatokines modulation
in obesity: which exercise training model is
better in men with obesity?
Front. Endocrinol. 16:1560453.
doi: 10.3389/fendo.2025.1560453

COPYRIGHT

© 2025 Ataeinosrat, Abednatanzi, Hajesfandiari,
AL Nasser, Dara, Farzanegi, Nahand,
Almaqhawi, Karimi, Bagherzadeh-Rahmani,
Saeidi, Laher and Zouhal. This is an open-
access article distributed under the terms of
the [Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction
in other forums is permitted, provided the
original author(s) and the copyright owner(s)
are credited and that the original publication
in this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Hepatokines modulation in obesity: which exercise training model is better in men with obesity?

Ali Ataeinosrat¹, Hossein Abednatanzi²,
Shohreh Hajesfandiari², Maryam N. AL Nasser³,
Marjan Mansouri Dara², Parvin Farzanegi⁴,
Mahnoosh Salari Nahand⁵, Abdullah Almaqhawi⁶,
Niloofar Karimi⁷, Behnam Bagherzadeh-Rahmani⁸,
Ayoub Saeidi^{9*}, Ismail Laher¹⁰ and Hassane Zouhal¹¹

¹Department of Exercise Physiology, University of Tehran, Tehran, Iran, ²Department of Physical Education and Sport Science, Science and Research Branch, Islamic Azad University, Tehran, Iran,

³Department of Biological Sciences, College of Science, King Faisal University, Hofuf, Al-Ahsa, Saudi Arabia, ⁴Department of Physical Education & Sports Sciences, Islamic Azad University, Sari, Iran,

⁵Department of Education Sciences, Farhangian University, Tehran, Iran, ⁶Department of Family and Community Medicine, College of Medicine, King Faisal University, Al Hofuf, Saudi Arabia, ⁷Department of Exercise Physiology, Faculty of Sport Sciences, University of Mazandaran, Mazandaran, Babolsar, Iran, ⁸Department of Exercise Physiology, Faculty of Sports Sciences, Shomal University, Amol, Iran, ⁹Department of Physical Education and Sport Sciences, Faculty of Humanities and Social Sciences, University of Kurdistan, Sanandaj, Kurdistan, Iran, ¹⁰Department of Anesthesiology, Pharmacology and Therapeutics, The University of British Columbia, Vancouver, BC, Canada,

¹¹International Institute of Sport Sciences (212S), Rennes, France,

Objective: Obesity is associated with an exacerbated metabolic condition that is related to impaired secretion of hepatokines. This study aimed to compare the effects of 12 weeks continuous aerobic, Tabata, and high intensity interval training (HIIT) on the levels of fetuin-A, fetuin-B, fibroblast growth factor 21 (FGF-21), plasminogen activator inhibitor-1 (PAI-1), fibrinogen-like protein 1 (FGL1), and selenoprotein P.

Methods: 44 obese males were randomly divided into four groups (n=11): control group (CT), endurance training group (ET), Tabata group (Tabata), and HIIT group (HIIT). Exercise training programs lasted for 12 weeks/three sessions per week. Each session lasted 60 minutes, containing warm-up (10 minutes), main training for each group (40 minutes), and ending with cooling down (10 minutes). Measurements were made 12 and 48 h before the initiation of the main interventional protocols, and then again 48 h after the final session of the training protocol.

Results: Baseline data were similar in all groups ($p>0.05$). There was a significant group-by-time interaction for fetuin B ($p=0.0004$), FGF-21 ($p=0.007$), FGL-1 ($p=0.0139$), weight ($p=0.0110$), BMI ($p=0.009$), %fat ($p<0.0001$) and selenoprotein-1 ($p=0.0052$). There was a main effect of time for fetuin A and PAI-1 ($p<0.0001$). The reductions in fetuin B were greater in HIIT vs. CT (mean diff: -0.13) and Tabata vs. CG (mean diff: -0.14) ($p<0.05$), while decreases in FGF-21 were greater in ET vs. CT (mean diff: -19.1), HIIT vs. CT (mean diff: -26.22) ($p<0.05$), and Tabata vs. CT (mean diff: -22.8). Reductions in FGL-1 were greater

in ET vs. CT (mean diff: -11.5)($p < 0.05$), HIIT vs. CT (mean diff: -8.1), and Tabata vs. CT (mean diff: -11.3)($p < 0.05$).

Conclusion: Performing 12 weeks of physical activity led to decreases in weight, BMI, %fat, fetuin-B, FGF-21, FGL-1, and selenoprotein P, and greater reduction observed in the Tabata and the HIIT groups.

KEYWORDS

exercise, Tabata, HIIT, obesity, hepatokines

1 Introduction

The liver can respond to nutritional excess and deficiency status by regulating glucose and lipid metabolism through lipoprotein synthesis, glycogenolysis, and gluconeogenesis (1). The liver also releases hepatokines (liver secreted proteins) such as fetuin-A, fetuin-B, adiponectin, activinE, follistatin, and angiopoietin-like proteins (ANGPTLs), which can either worsen or improve metabolic conditions (2). Hepatokines can communicate with distant sites such as adipose tissue, skeletal muscle, and the central nervous system (CNS), and dysregulation of hepatokines can disrupt energy homeostasis and cause the metabolic dysfunction (3). In this context, changes in hepatokine levels occur in the obesity and diabetes (4).

Obesity results from positive energy balance (caloric consumption exceeds energy expenditure) over long periods, and is a major risk factor for metabolic syndrome, type 2 diabetes mellitus (T2D), cardiovascular disease, atherosclerosis, dyslipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD), and some types of cancers (5). Alterations in cytokines secreted from the liver (hepatokines), adipose tissues (adipokines) and skeletal muscles (myokines), act in an autocrine, paracrine or endocrine manner (6). Fetuin is a member of the cystatin superfamily protease inhibitors, firstly isolated from bovine serum, and consists of fetuin A and fetuin B, with important roles in various physiological and pathological processes (7). Fetuin-A, also known as α -Heremans-Schmid glycoprotein (AHSG), is predominantly secreted by hepatocytes into the blood circulation (8). The human homolog of fetuin-A is a protein with 349 amino acids and molecular weight between 52–60 kDa (9). In addition to secretion by the liver, lesser amounts of fetuin A secretion are also released by other organs such as the tongue, placenta, and adipose tissues (10, 11). Higher circulating levels of fetuin-A can affect obesity, metabolic syndrome, and insulin resistance/T2D (12), and fetuin A has roles in the development of T2DM, metabolic disorders, NAFLD, cardiovascular diseases (CVD), some types of cancers, and some brain disorders (13).

Fetuin-B is the second member of the fetuin family in the mammals (14), with a 22% homology with fetuin A (10). Fetuin-B is an adipokine/hepatokine that is mostly secreted by the liver and adipose tissue, and its levels increase with impaired insulin action

and during glucose intolerance (15). As is the case with fetuin A, elevation levels of fetuin B also occur in diabetes and metabolic syndrome (16).

Fetuin-A is a novel risk factor for endothelial dysfunction (17), and its levels correlate with changes in interleukin-6 (IL-6), IL-18, tumor necrosis factor α (TNF α), plasminogen activator inhibitor-1 (PAI-1), leptin, and resistin, all of which play roles in the pathophysiology and inflammatory process of diabetic kidney disease (18). Fetuin A increases the expression of pro-inflammatory cytokines including PAI-1 in perivascular fat cells (19). PAI-1, a member of the serine proteinase inhibitors (serpin) superfamily that is secreted by the liver (hepatokine), activates the coagulation system during athero-thrombosis, with important roles in CVDs (20, 21). In addition to the liver, PAI-1 production also occurs in adipocytes, cardiac myocytes, smooth muscle cells, endothelial cells, platelets, and monocytes/macrophages (22). Circulating levels of PAI-1 increase in obesity, T2D, atherosclerosis, thrombosis, and some types of cancer (23).

Fibrinogen-like protein 1 (FGL-1), also known as hepatocyte-derived fibrinogen-related protein-1 (HFREP-1) or heparan sulfate, has mitogenic effects on hepatocytes (24). Adipose tissue can also express FGL-1 as a regulator of lipid metabolism (25). Hepatic expression of FGL-1 increases in the high-fat diet-fed mice with NAFLD, in turn led to activation of ERK1/2 in order to facilitate lipogenesis, ultimately is associated with development of hepatic steatosis (26). Levels of FGL-1 are higher in overweight and obese subjects, and are positively correlated with BMI, waist circumference, degree of obesity, and insulin resistance, suggesting that FGL-1 may link obesity, diabetes and NAFLD (27). In addition, levels of FGL-1 and body fat percentage are positively correlated, and suggesting that FGL-1 as a therapeutic target in obesity (28). Collectively, there is much evidence that hepatokines are dysregulated in metabolic disorders and cardiovascular diseases (29).

Different types of exercise training are used to manage overweight and obesity in adults (30), but their effects can be different. Moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) produce similar improvements in weight loss and cardiovascular risk factors, while HIIT has additional benefits in cardiorespiratory fitness (31), and is considered a time-efficient weight management

exercise (32). Tabata is one of the most popular forms of shorter HIIT workouts (33), and reduces body fat in healthy sedentary subjects (34). The effects of different types of exercise training, especially Tabata training, on the levels of hepatokines as a possible mechanism for mediating the benefits of exercise in overweight and obese subjects are unclear. We compared the effects of 12 weeks MICT, Tabata, and high intensity interval training (HIIT) on levels of fetuin-A, fetuin-B, FGF-21, PAI-1, FGL-1, and selenoprotein P in obese men. Therefore, this study was designed to show which exercise training model has the greatest effect on levels of fetuin-A, fetuin-B, FGF-21, PAI-1, FGL-1, and selenoprotein P in obese men.

2 Material and methods

2.1 Participants

Subjects in this study were males aged 21 to 35 years with obesity. The decision to enroll only male participants was intentional to minimize biological variability related to sex-specific factors, including menstrual-cycle-related hormonal fluctuations, contraceptive use, menopausal status, and age-related comorbidities or medications that could confound hepatokine and metabolic responses. This approach aimed to improve internal validity for detecting exercise-induced changes, though we acknowledge that it limits generalizability to women and older adults. A total of 117 volunteers were recruited through social media and in-person outreach. Participants received documentation outlining the study's aims and methods, and they were asked to complete health and physical activity questionnaires, as well as provide written consent. The inclusion criteria (I) Body mass index (BMI) $> 30 \text{ kg/m}^2$; (II) Waist-to-Height Ratio (WHtR) > 0.5 ; (III) non-consumption of alcohol and smoking; (IV) no regular intense physical activities or exercise during the last six months; (V) no chronic diseases; (VI) no consumption of any medications or supplements; and (VII) no somatic injuries. Subjects were excluded if they were unable to continue in the study, did not attend training sessions for two or three consecutive days, or if they were injured or fell ill during the study period. All study participants were examined by a cardiologist, resulting in a final sample size of 44 individuals with a mean age of 27.32 ± 3.20 years, height of $177.47 \pm 2.97 \text{ cm}$, weight of $101.03 \pm 3.09 \text{ kg}$, and BMI of $32.08 \pm 1.04 \text{ kg/m}^2$. No participants were withdrawn from the study as a result of musculoskeletal injuries. Subjects were randomly divided into four groups of 11 participants each: a control group ($n=11$), Tabata training group ($n=11$), a HIIT group ($n=11$), and a continuous aerobic training group ($n=11$), by adaptive randomization method. Eligibility was assessed and 44 participants were randomized to four arms ($n=11$ per arm) using covariate-adaptive minimization with a random component to balance on age and BMI. Strata were defined as age (21–28 vs 29–35 years) and BMI (30–32.9 vs 33–38). The minimization procedure was executed by an independent statistician using R (version 4.1.3) to generate a computer-based sequence with a

predefined imbalance-minimizing probability. Allocation concealment was ensured via centralized, web-based randomization; the enrolling investigators had no access to upcoming allocations. Study participants were free to leave the study whenever they wished (Figure 1). The study was approved by the National Research and Ethics Committee of Islamic Azad University (Ethics code: IR.IAU.AMOL.REC.1402.070).

Overall, 117 volunteers were assessed for eligibility. Of these, 44 met the predefined inclusion criteria and were randomized into four groups ($n = 11$ per group); the remaining 73 individuals were either ineligible ($n = 28$) or declined participation ($n = 45$). Reasons for ineligibility at screening ($n = 28$) were as follows: failure to meet anthropometric criteria (BMI/WHtR) ($n = 10$), recent regular structured exercise ($n = 6$), medical contraindications (cardiovascular/hepatic/renal disease or diabetes) ($n = 4$), abnormal screening laboratory results ($n = 2$), current use of excluded medications or supplements ($n = 3$), and logistical issues ($n = 3$). A CONSORT flow diagram summarizing recruitment, screening, allocation, follow-up, and analysis is provided in Figure 1. All participants underwent baseline medical and cardiology screening prior to enrollment. Exercise sessions were supervised by trained personnel and intensity was continuously monitored using Polar Team 2 chest-belt heart-rate monitors. Supervisors recorded attendance and any symptoms or adverse events at each session; these were entered into an adverse-event log and reviewed by the principal investigator. No serious adverse events or study withdrawals attributable to injury were observed.

2.2 Training protocols

Training programs occurred over 12 weeks, with three sessions per week. Each session lasted 60 minutes, comprising a 10-minute warm-up, 40 minutes of main training for each group, and a 10-minute cool-down period (35) (Figure 2).

2.2.1 Tabata training

Participants in this group completed eight training sets, each lasting 4 minutes, with 1 minute of rest between sets. Each set included eight repetitions of the exercise, featuring 20 seconds of intense work (85–95% HRmax) followed by 10 seconds of rest (45–55% HRmax) (35).

Each training set included the following exercises: 1) lower limb muscles (squats and jumps); 2) back muscles (back extensions); 3) rectus abdominal muscles (crunches); 4) chest muscles (push-ups); 5) arm muscles (triceps dips); 6) oblique abdominal muscles (side crunches); 7) shoulder girdle muscles (military press with a medicine ball); and 8) trapezius muscles (chin-ups) (36). The final 10 minutes of each session consisted of light stretching. The intensity of each session was monitored by measuring heart rates using Polar Team 2 monitors (Kempele, Finland).

2.2.2 High-intensity interval training

Participants in this group completed eight training sets lasting 4 minutes, with 1 minute of rest between each set. Each set consisted

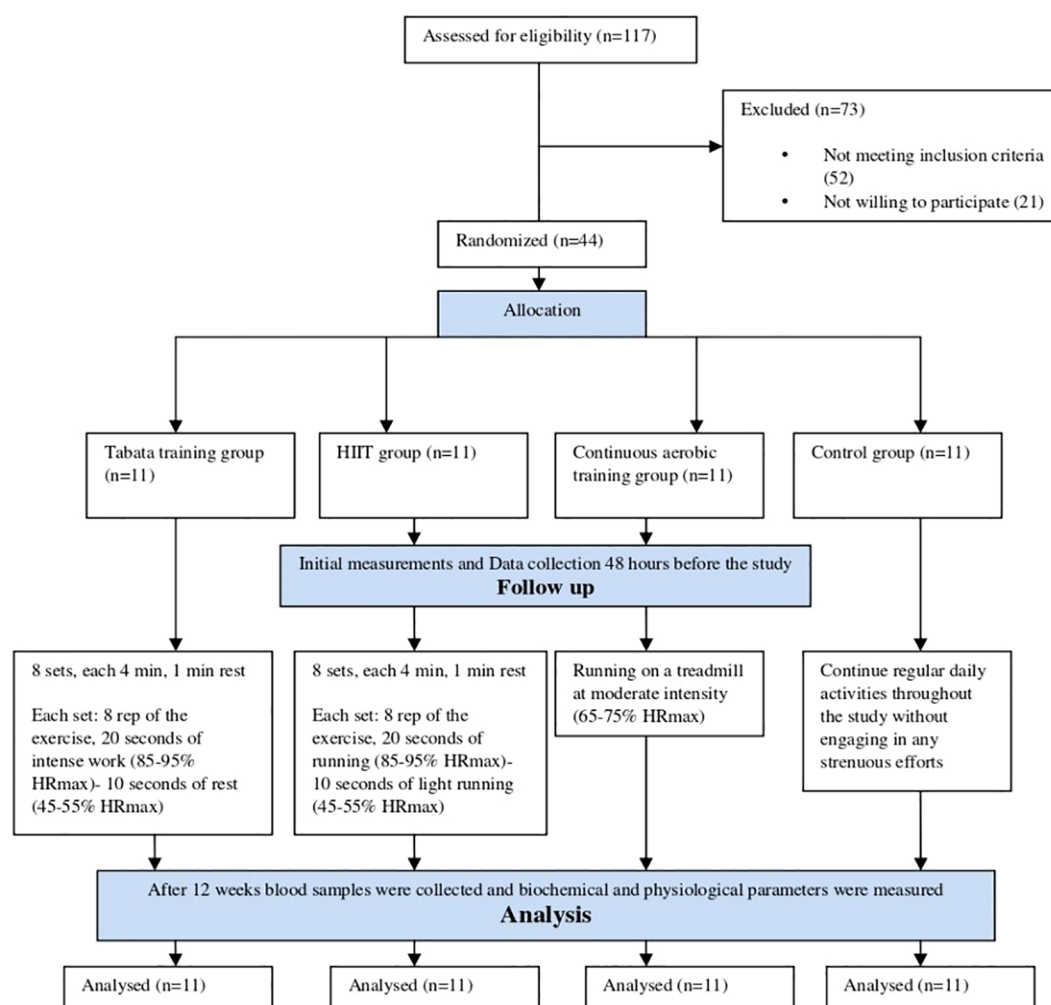


FIGURE 1
CONSORT flow diagram.

of eight repetitions of running, with 20 seconds of intense work (85–95% HRmax) followed by 10 seconds of light running (45–55% HRmax).

2.2.3 Continuous aerobic training

Exercise protocols consisted of running on a treadmill at moderate intensity (65–75% HRmax). The intensity of the training was monitored by changes in heart rate using Polar Team 2 monitors (Kempele, Finland).

2.2.4 Control group

Participants in the control group were monitored for 12 weeks, during which they continued their normal daily activities without engaging in any strenuous efforts.

2.2.5 Adherence and heart–rate monitoring

Participants completed a 12-week supervised program (3 sessions per week; 36 scheduled sessions per participant). Session attendance was recorded by the session facilitator and reasons for any absences were documented; the vast majority of participants

attended the scheduled sessions with only sporadic absences, and no participant was withdrawn due to musculoskeletal injury. Per-group attendance was CT 97%, ET 95%, Tabata 99%, HIIT 96%.

Exercise intensity and training volume were prescribed relative to each participant's maximal heart rate (HRmax). Heart rate was continuously recorded during all supervised sessions using Polar Team 2 chest-belt monitors (Polar Electro, Kempele, Finland). HRmax was estimated at baseline using the conventional formula ($\text{HRmax} = 220 - \text{age}$). Session HR data were expressed as %HRmax and used to ensure adherence to the intended intensity. The average session intensity across the three training groups was calculated by averaging %HRmax values recorded during each session across all participants within each group. Additionally, individual session data were analyzed to ensure compliance with the prescribed intensity range (65–75% HRmax) throughout the intervention period. All attendance logs and HR recordings were stored securely for further analysis.

Throughout the 12-week intervention, adverse events and symptoms were documented at each supervised session by trained facilitators. These logs were reviewed weekly by the principal investigator to ensure participant safety and adherence to the

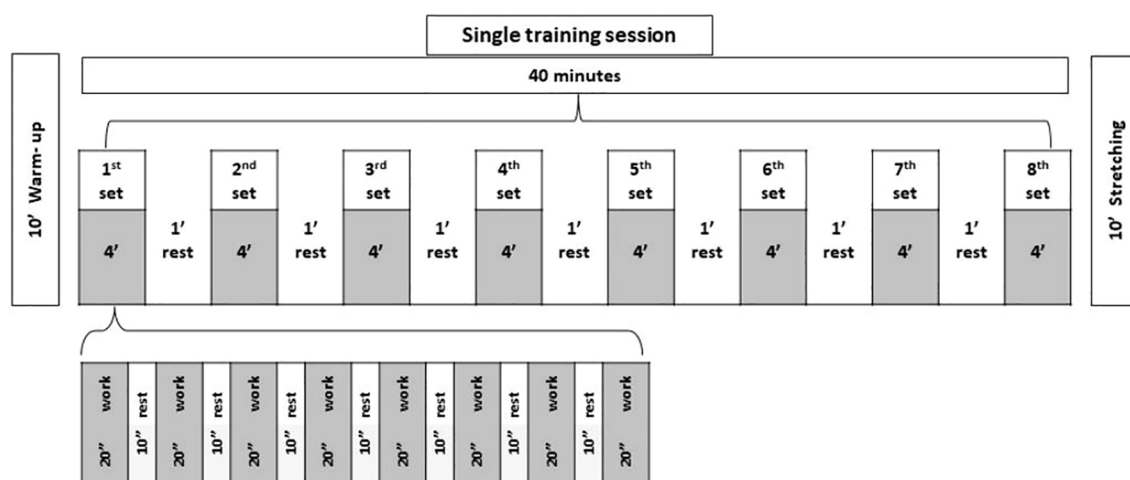


FIGURE 2
Scheme of the training sessions.

protocol. While serious adverse events were not observed during the study, the lack of independent adjudication of adverse events remains a limitation.

2.3 Anthropometry and body composition measurements

Body weight and height were measured using a calibrated scale (Seca, Germany) and a stadiometer (Seca, Germany), respectively. These measurements were then used to calculate body mass index (BMI, kg/m²).

2.4 Nutrient intake and dietary analysis

Three-day food records (two weekdays and one weekend day) were obtained before and after the study to assess changes in habitual dietary intake over time. Each food item was individually entered into Diet Analysis Plus version 10 (Cengage, Boston, MA, USA), allowing for the calculation of total energy consumption and the amount of energy derived from proteins, fats, and carbohydrates (Table 1).

2.5 Blood analysis

Due to the nature of the supervised exercise interventions, participants and session facilitators were not blinded to group allocation. Outcome assessors performing anthropometry, body composition measurements, and laboratory analyses were blinded to group assignment; biological samples and records were coded to preserve blinding. Measurement procedures were standardized and equipment calibrated, and assessors followed pre-specified protocols to minimize detection bias. In addition, several primary outcomes were objectively measured (e.g., continuously recorded heart rate), further reducing the potential for measurement bias. While participant blinding was not feasible, this limitation has been acknowledged as a potential source of bias, and steps were taken to mitigate its impact through rigorous standardization and objective outcome measurements. The first blood samples were collected 48 hours before the start of the exercise protocols and the second samples were collected 48 hours after 12 weeks of training programs. Blood samples were drawn from the right brachial vein and after an overnight fast. Samples were collected in tubes containing EDTA and centrifuged at 3000 rpm for 10 min to separate plasma which was stored at -70°C until subsequent analysis. Blood samples were drawn between 8–

TABLE 1 Mean ($\pm$ SD) values of nutritional intake in the four study groups.

	Control		Continuous aerobic		HIIT		Tabata	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Energy (kcal/d)	2249 $\pm$ 58	2258 $\pm$ 77	2269 $\pm$ 93	2198 $\pm$ 143	2261 $\pm$ 127	2199 $\pm$ 149	2267 $\pm$ 164	2195 $\pm$ 179
Carbohydrates (g/d)	279 $\pm$ 11.9	283 $\pm$ 18.7	281.4 $\pm$ 25.1	271 $\pm$ 36.7	279 $\pm$ 37.6	258 $\pm$ 26.2	290 $\pm$ 30.6	272 $\pm$ 21.1
Fats (g/d)	82.1 $\pm$ 9.7	83 $\pm$ 7.6	84.4 $\pm$ 10.8	76 $\pm$ 12.3	81.8 $\pm$ 13.9	73.2 $\pm$ 14.5	80.7 $\pm$ 11.83	71.6 $\pm$ 14.5
Proteins (g/d)	104 $\pm$ 10.1	106 $\pm$ 11.4	102 $\pm$ 13.6	95 $\pm$ 10.7	103 $\pm$ 14.7	94 $\pm$ 16.3	105 $\pm$ 13.9	88 $\pm$ 17.1

HIIT, High intensity interval training.

TABLE 2 Characteristics of experimental and control subjects in men with obesity.

Groups	Age (years)	Height (Cm)	Weight (Kg)	BMI (Kg/m ²)	BFP (%)
Continuous aerobic	27.5 ± 6.2	178.25 ± 3.18	101.55 ± 4.15	31.95 ± 1.00	35.24 ± 3.19
Tabata	26.4 ± 5.4	176.62 ± 2.58	100.92 ± 2.58	32.37 ± 1.26	35.20 ± 2.34
High intensity interval	28.1 ± 4.8	176.36 ± 3.18	100.91 ± 2.53	32.46 ± 1.17	34.37 ± 2.78
Control	27.3 ± 5.1	178.67 ± 2.60	100.73 ± 3.23	31.54 ± 0.41	34.10 ± 2.78
P-Value	0.897	0.173	0.936	0.149	0.705

BFP, body fat percent; BMI, body mass index.

10 am. Plasma markers were measured using ELISA kits having the following characteristics:

Fetuin A human elisakit(R&D Systems Quantikine, Minneapolis, Minnesota, USA). Catalogue No: #DFTA00. Intra-CV = 4.3%, inter-CV = 7.3%.

FetuinBhumanelisakit(Biovendor, Karasek, Czech Republic). Catalogue No: #RD191172200R. Intra-CV = 3.7%, inter-CV = 5.2%.

PAI-1 human elisakit(Trinity Biotech USA, St. Louis, MO). Catalogue No: # 210221. Intra-CV = 2.9%, inter-CV = 3.3%.

FGL1 human elisakit(Cusabio, Wuhan, China). Catalogue No: CSB-EL008653HU. Intra-CV <8%, inter-CV <10%.

FGF-21 human elisakit(Biovendor, Czech Republic). Catalogue No: RD191108200R. Intra-CV = 2.0%, inter-CV = 3.3%.

Selenoprotein P human ELISA kit (USCN Life Science, Wuhan, China) with an intraassay coefficient of variation of 6.7% and an interassay coefficient of variation of 4.7%.

2.6 Statistical analysis

The sample size justification was based on prior interval-exercise research using G*Power 3.1.9.2. Prior studies indicated a meaningful reduction in fetuin-A with an effect size (ES) of ~0.45. Using an F-test for repeated-measures ANOVA with within-between interaction ($\alpha = 0.05$, power = 0.95), a minimum total sample of 28 participants ($n = 7$ per group) was required; to allow for potential disruptions related to COVID-19 and limited prior data on the studied hepatokines, the per-group sample was increased to 11 ($N = 44$) to preserve statistical power. All variables were inspected for normality using the Shapiro-Wilk test prior to inferential analyses. There were no missing values at any time point. Baseline characteristics are presented as mean $\pm$ SD. For longitudinal comparisons, a two $\times$ four repeated-measures ANOVA (time: pre vs. post $\times$ group: CT vs. ET vs. HIIT vs. Tabata) was used to evaluate main effects and time $\times$ group interactions. Sphericity was assessed with Mauchly's test and, when violated, Greenhouse-Geisser corrections were applied to the degrees of freedom. When a significant time $\times$ group interaction was detected, between-group post-hoc comparisons were conducted using Sidak correction for multiple testing. Effect sizes are reported consistently throughout the

manuscript: partial eta-squared (η^2) is presented for omnibus ANOVA main effects and interactions, and standardized mean differences are reported for pairwise/post-hoc comparisons as Cohen's d (with Hedges' g provided where small-sample bias may affect estimates). Ninety-five percent confidence intervals (95% CI) for pairwise effect sizes and mean differences are provided in the Results and Tables. Conventional interpretation thresholds are stated in Methods (η^2 : small ≈ 0.01 , medium ≈ 0.06 , large ≥ 0.14 ; Cohen's d : small ≈ 0.2 , medium ≈ 0.5 , large ≥ 0.8). All tests were two-tailed and a significance threshold of $p < 0.05$ was used. Analyses and effect-size calculations were performed using GraphPad Prism v8.4.3 and verified with supplementary computations.

3 Results

3.1 Participant characteristics

All variables met the assumptions for parametric testing: distributions were approximately normal (Shapiro-Wilk test, $p > 0.05$ for all variables) and variances were homogeneous across groups (Levene's test, $p > 0.05$). One hundred and twelve participants were assessed for eligibility. Twenty-eight did not meet the inclusion criteria, while 36 were not interested in participating after the first interview. One participant from each group withdrew from the study for reasons of a lack of time, not interested in the study, COVID-19, or musculoskeletal injury. There were no significant between-group differences in all baseline characteristics. The characteristics of the subjects in the experimental and control groups are shown in (Table 2). Participants' age, height, weight, BMI and body fat percent did not differ at baseline.

3.1.3 Body composition and dietary monitoring

Analysis of the 3-day dietary records showed no significant between-group or pre-to-post changes in total energy intake or macronutrient composition during the intervention (all $p > 0.05$) (Table 1).

As indicated in Table 3, there was a significant group $\times$ time interaction on weight [$F = 4.22$, $p = 0.011$], with significant decreases observed in the Tabata and high-intensity interval groups. Additionally, significant changes were noted in the exercise group, which exhibited a significant effect of time [$F = 16.44$, $p = 0.001$] and a significant effect of group [$F = 4.05$, $p =$

0.013]. The weight-related effect size for between-group effects was large (partial $\eta^2 = 0.233$). The weight variable in the training groups showed a significant decrease compared to the control group ($p = 0.017$, 95% CI: 0.362 to 5.237, and $p = 0.043$, 95% CI: 0.054 to 4.92 for weight in the Tabata and high-intensity interval training groups, respectively). Furthermore, there was no significant difference between the continuous aerobic and control groups ($p = 0.338$, 95% CI: 0.776 to 4.10).

There was a significant group $\times$ time interaction on BMI [$F = 4.38$, $p = 0.009$], with notable decreases observed in both the Tabata and high-intensity interval groups. Additionally, significant changes were seen in the exercise group, showing a significant effect of time [$F = 16.18$, $p = 0.001$], but not a significant effect of group [$F = 0.357$, $p = 0.784$]. The BMI-related effect size for between-group effects was small (partial $\eta^2 = 0.026$). As a result, there were no statistically significant differences between the continuous aerobic, Tabata, high-intensity interval, and control groups ($p = 0.962$, 95% CI -0.884 to 1.621; $p = 1.00$, 95% CI -1.10 to 1.39; and $p = 1.00$, 95% CI -1.31 to 1.19, respectively; [Table 3](#)).

Our results revealed a statistically significant difference in the group $\times$ time interaction for body fat percentage [$F = 14.15$, $p = 0.001$]. Significant decreases were observed in the continuous aerobic, Tabata, and high-intensity interval groups, with a significant effect of time [$F = 20.65$, $p = 0.001$] and a significant effect of group [$F = 4.97$, $p = 0.005$]. Additionally, the effect sizes for between-group comparisons related to body fat percentage were large (partial $\eta^2 = 0.272$). The results of the *post hoc* test indicated that body fat percentage in the Tabata and high-intensity interval groups was significantly reduced compared to the control group ($p = 0.006$, 95% CI: 0.70 to 5.67 and $p = 0.036$, 95% CI: 0.112 to 5.08, respectively; [Table 3](#)). Furthermore, there was no significant difference between the continuous aerobic and control groups ($p = 0.613$, 95% CI: -1.155 to 3.817).

3.2 Biochemical markers

There was not a significant group $\times$ time interaction on Fetuin A [$F = 2.50$, $p = 0.072$]. Additionally, significant changes were seen in the exercise group, showing a significant effect of time [$F = 5.40$, $p = 0.025$], but not a significant effect of group [$F = 1.28$, $p = 0.291$]. The Fetuin A -related effect size for group $\times$ time interaction effects were large (partial $\eta^2 = 0.158$). As a result, there were no statistically significant differences between the continuous aerobic, HIIT, Tabata compared to the control group ($p = 0.717$, 95% CI -0.51 to 1.88; $p = 1.00$, 95% CI -0.66 to 1.72; and $p = 0.486$, 95% CI -0.424 to 1.96, respectively).

Our results revealed a statistically significant difference in the group $\times$ time interaction for Fetuin B [$F = 7.44$, $p = 0.001$]. Significant decreases were observed in the Tabata and HIIT groups, with a significant effect of time [$F = 11.83$, $p = 0.001$] and a significant effect of group [$F = 4.00$, $p = 0.014$]. Additionally, the effect sizes for group $\times$ time interaction were large (partial $\eta^2 = 0.358$). The results of the *post hoc* test indicated that Fetuin B in the Tabata and HIIT groups was significantly decrease compared to the control group ($p = 0.042$, 95% CI: 0.003 to 0.266 and $p = 0.020$, 95%

CI: 0.016 to 0.279, respectively). Furthermore, there was no significant difference between the continuous aerobic and control groups ($p = 0.188$, 95% CI: -0.026 to 0.237).

Our results revealed a statistically significant difference in the group $\times$ time interaction for FGL1 [$F = 4.00$, $p = 0.014$]. Significant decreases were observed in the continuous aerobic, Tabata and HIIT groups, with a significant effect of time [$F = 14.59$, $p = 0.001$] and a significant effect of group [$F = 8.97$, $p = 0.001$]. Additionally, the effect sizes for group $\times$ time interaction were large (partial $\eta^2 = 0.231$). The results of the *post hoc* test indicated that FGL1 in the continuous aerobic, HIIT and Tabata groups was significantly decrease compared to the control group ($p = 0.001$, 95% CI: 4.46 to 18.62; $p = 0.017$, 95% CI: 1.04 to 15.20 and $p = 0.001$, 95% CI: 4.27 to 18.43, respectively).

Our results revealed a statistically significant difference in the group $\times$ time interaction for FGF21 [$F = 4.65$, $p = 0.007$]. Significant decreases were observed in the Tabata and HIIT groups, with a significant effect of time [$F = 8.32$, $p = 0.006$] and a significant effect of group [$F = 10.51$, $p = 0.001$]. Additionally, the effect sizes for group $\times$ time interaction were large (partial $\eta^2 = 0.259$). The results of the *post hoc* test indicated that FGF21 in the continuous aerobic, HIIT and Tabata groups was significantly decrease compared to the control group ($p = 0.003$, 95% CI: 4.94 to 33.34; $p = 0.001$, 95% CI: 12.02 to 40.42 and $p = 0.001$, 95% CI: 8.65 to 37.05, respectively).

Our results revealed a statistically significant difference in the group $\times$ time interaction for Sel1 [$F = 4.93$, $p = 0.005$]. Significant decreases were observed in the Tabata and HIIT groups, with a significant effect of time [$F = 20.35$, $p = 0.001$] and a significant effect of group [$F = 7.44$, $p = 0.001$]. Additionally, the effect sizes for group $\times$ time interaction were large (partial $\eta^2 = 0.270$). The results of the *post hoc* test indicated that Sel1 in the HIIT and Tabata groups was significantly decrease compared to the control group ($p = 0.002$, 95% CI: 34.38 to 206.12 and $p = 0.001$, 95% CI: 45.80 to 217.54, respectively). Furthermore, there was no significant difference between the continuous aerobic and control groups ($p = 0.110$, 95% CI: -9.74 to 161.99).

There was not a significant group $\times$ time interaction on PAI [$F = 2.57$, $p = 0.067$]. Additionally, significant changes were seen in the exercise group, showing a significant effect of time [$F = 8.28$, $p = 0.006$], but not a significant effect of group [$F = 2.26$, $p = 0.096$]. The PAI-related effect size for group $\times$ time interaction effects were large (partial $\eta^2 = 0.162$). As a result, there were no statistically significant differences between the continuous aerobic, HIIT, Tabata, and control groups ($p = 1.00$, 95% CI -3.82 to 8.64; $p = 0.203$, 95% CI -1.29 to 11.17 and $p = 0.188$, 95% CI -1.22 to 11.24, respectively).

4 Discussion

Our study indicates that 12-weeks of different types of exercise training (including HIIT, MICT, Tabata) decreased levels of cardiometabolic risk factors and circulating levels of fetuin-A, fetuin-B, FGF-21, PAI-1, FGL-1, and selenoprotein P in obese

TABLE 3 Changes in body composition and the levels of biochemical markers in the research groups.

Stages								
Variables and groups	Pre-test M ± SD ^a	12 th week M ± SD ^a	Percentage of changes	P-value ^b	Time p-value	Group p-value	Time × group p-value	Partial eta squared
Weight (kg)								
Continuous aerobic	101.55 ± 4.15	97.95 ± 2.45	-3.67	0.052	0.001	0.013	0.011	0.233
High intensity interval	100.91 ± 2.53	96.93 ± 3.44	-4.10	0.006				
Tabata	100.92 ± 2.58	96.30 ± 2.31	-4.79	0.001				
Control	100.73 ± 3.23	102.09 ± 3.06	1.33	0.403				
BMI (kg/m2)								
Continuous aerobic	31.95 ± 1.00	30.85 ± 1.36	-3.56	0.054	0.001	0.784	0.009	0.026
High intensity interval	32.46 ± 1.17	31.20 ± 1.91	-4.03	0.006				
Tabata	32.37 ± 1.26	30.88 ± 1.06	-4.82	0.001				
Control	31.54 ± 0.41	32.00 ± 1.45	1.43	0.374				
BFP (%)								
Continuous aerobic	35.24 ± 3.19	32.96 ± 3.02	-6.91	0.036	0.001	0.005	0.001	0.272
High intensity interval	34.37 ± 2.78	31.29 ± 2.34	-9.84	0.018				
Tabata	35.20 ± 2.34	29.29 ± 1.81	-20.17	0.001				
Control	34.10 ± 2.78	36.76 ± 3.33	7.23	0.025				
Fetuin A(pg/ml)								
Continuous aerobic	4.79 ± 1.56	4.24 ± 1.67	-12.97	0.518	0.025	0.291	0.072	0.158
High intensity interval	5.40 ± 1.11	3.95 ± 1.62	-36.70	0.02				
Tabata	5.29 ± 1.45	3.57 ± 1.28	-48.17	0.014				
Control	4.89 ± 1.82	5.51 ± 1.29	11.25	0.385				
Fetuin B (pg/ml)								
Continuous aerobic	0.46 ± 0.14	0.37 ± 0.12	-24.32	0.169	0.001	0.014	0.001	0.358
High intensity interval	0.47 ± 0.14	0.30 ± 0.12	-56.66	0.007				
Tabata	0.46 ± 0.12	0.28 ± 0.15	-64.28	0.001				
Control	0.47 ± 0.12	0.57 ± 0.13	17.54	0.04				
FGL1(ng/ml)								
Continuous aerobic	47.11 ± 10.22	36.34 ± 7.54	-29.63	0.013	0.001	0.001	0.014	0.231
High intensity interval	51.17 ± 9.30	39.13 ± 7.20	-30.76	0.02				
Tabata	50.71 ± 11.31	33.12 ± 12.77	-53.10	0.008				
Control	51.06 ± 8.09	55.48 ± 10.81	7.96	0.426				
FGF21 (pg/ml)								
Continuous aerobic	193.54 ± 18.18	185.47 ± 12.92	-4.35	0.274	0.006	0.001	0.007	0.259
High intensity interval	195.09 ± 23.78	169.76 ± 14.23	-14.92	0.018				
Tabata	203.77 ± 21.16	167.80 ± 15.24	-21.43	0.004				
Control	202.36 ± 31.29	214.94 ± 18.90	5.85	0.353				

(Continued)

TABLE 3 Continued

Stages								
Variables and groups	Pre-test M ± SD ^a	12 th week M ± SD ^a	Percentage of changes	P-value ^b	Time p-value	Group p-value	Time x group p-value	Partial eta squared
Sel1 (ng/ml)								
Continuous aerobic	798.94 ± 126.51	711.31 ± 103.06	-12.31	0.094	0.001	0.001	0.005	0.270
High intensity interval	778.67 ± 85.17	643.32 ± 73.78	-21.03	0.007				
Tabata	797.33 ± 109.26	601.81 ± 101.96	-32.48	0.001				
Control	816.20 ± 131.98	846.30 ± 60.05	3.55	0.549				
PAI (ng/ml)								
Continuous aerobic	26.75 ± 7.77	23.05 ± 4.42	-16.05	0.226	0.006	0.096	0.067	0.162
High intensity interval	25.46 ± 10.29	19.29 ± 4.45	-31.98	0.116				
Tabata	26.64 ± 9.95	17.96 ± 4.76	-48.32	0.011				
Control	26.28 ± 7.28	28.34 ± 4.65	7.26	0.327				

^aValues are expressed as mean ± standard deviation.
^bWithin-group P-value.
^cSignificant at P < 0.05.
Values are presented as mean ± standard deviation. BFP, Body fat percent; BMI, Body mass index; Sell, selenium; FGF-21, fibroblast growth factor 21; PAI-1, plasminogen activator inhibitor-1; FGL-1, fibrinogen-like protein 1 FGL1; CT, Control group; HIIT, High intensity interval training group; ET, Endurance training group.

men. There were additional improvements in hepatokine levels in the HIIT and Tabata training groups compared to the MICT group. The liver is a central regulator of whole-body energy homeostasis, with hepatokines considered as an promising targets for the treatment of development of metabolic disorders (37). Exercise training modulates the levels of different organokines, including adipokines, myokines and hepatokines (38) and exercise induced changes in hepatokine levels have been suggested to ameliorate metabolic disorders such as obesity or T2D (39). We confirmed that the benefits of various type of exercise training are mediated by changes in hepatokine levels.

4.1 Fetuins

Our findings indicate reductions in fetuin A and fetuin B levels with HIIT, MICT and Tabata training. There are limited reported on the effects of exercise on fetuin levels (particularly fetuin B), but down regulation of both fetuin A and fetuin B with aerobic and resistance training have been reported (40). Studies report that exercise decreases (41), increases (42) and or causes no changes (43) of fetuin A levels. Fetuin A is a chemo-attractant secretory protein that stimulates the macrophage secretion by the liver and adipose tissue, and activated macrophage in turn cause increase the expression of pro-inflammatory cytokines (such as TNF-α and IL-6) which can impair glucose metabolism and result in obesity related disorders (44). Moreover, fetuin A is an important risk factor for insulin resistance related to Akt and phosphatidylinositide 3-kinase (PI3K) signaling pathways (19). In addition, fetuinA enhances insulin

resistance by decreasing the expression of glucose transporter-4 (GLUT-4) proteins by activating toll-like receptor 4 (TLR-4) in skeletal muscles (45). Glucose and lipid metabolism is also affected by fetuin B, and significantly higher circulating levels of fetuin B occur inT2D patients (46). Furthermore, fetuin B induces a pro inflammatory response in adipocytes, and could mediate peripheral insulin resistance (45), which could lead to NAFLD (47). Activation of AMP-activated protein kinase (AMPK), a central energy sensor upregulated during exercise, enhances insulin receptor sensitivity and fatty acid oxidation, contributing to the downregulation of fetuin-A and selenoprotein P—both associated with impaired insulin signaling (48).

Targeting fetuinsis of interest because of their many adverse effects, as shown by enhanced insulin sensitivity, resistance to a high-fat diet and aging induced weight gain infetuin-A-knockout mice (49, 50). Our study demonstrates that exercise reduces fetuin A and fetuin B levels. Possible mechanisms for the lowering of fetuin A levels by exercise include: decreases in intrahepatic fat content by reduction of sterol regulatory element-binding protein (SREBP)-1cand enhanced peroxisome proliferator-activated receptor γ (PPAR-γ) expression; decreased hepatic glucolipotoxicity by reactive oxygen species (ROS); inhibition of pro-inflammatory mediators; and activation of Akt and Akt substrate of 160 kDa (AS160) phosphorylation, which in turn reduce insulin resistance (51). Exercise attenuates hepatic expression of fetuin A by high levels of free fatty acids (FFAs) by stimulation of NF-κB signaling (56), and reduces hyperglycemia increases hepatic expression by activating the ERK-1 and ERK-2 (61). Our results demonstrate that exercise reduces both glucose

and fetuin A levels. Levels of fetuin-B levels in patients with metabolic syndrome are by improvements in insulin sensitivity, with a positive correlation between fetuin B and oxidative stress (16). Therefore, fetuin B reduction by exercise can be partly mediated by exercise induced reductions of oxidative stress (52).

4.2 Plasminogen activator inhibitor-1

PAI-1 inhibits PA (tissue-type plasminogen activator) and uPA (urinary-type plasminogen activator), and is a key regulator of fibrinolysis and cell migration (53). PAI-1 has endocrine functions, including in obesity. A positive energy balance increases the expression of PAI-1 in adipocytes, where it increases differentiation of adipocytes, causes adipocyte hypertrophy, and obesity. PAI-1 stimulates inflammatory pathways (including increasing the production of TNF- α) and decreases the expression of PPAR- γ , and promoting insulin resistance and obesity (23, 54).

Our findings indicate that different exercise training modalities can decrease PAI-1 levels. Several mechanisms have been proposed for the reductions in PAI-1 by exercise, including by increased endothelial integrity of vascular endothelium, and stimulating the release on of nitric oxide (NO), which suppresses PAI-1 production by vascular smooth muscle cells and platelets (55). Also, Exercise stimulates PPARs, particularly PPAR- α and PPAR- γ , which regulate genes involved in lipid metabolism and hepatic fat clearance, leading to suppressed expression of lipotoxic hepatokines such as fetuin-B and PAI-1 (54).

Our findings agree with those of Ahmad et al (56) who reported that eight weeks HIIT and MICT reduced PAI-1 levels women with T2D women, but with no difference between the HIIT and MICT groups likely because exercise of adaptation of skeletal muscles to the effects of PAI, including the gene expression and post-translational modifications (56). Exercise increases tPA protein levels and decreases PAI-1 levels in trained skeletal muscles, and thus increases local fibrinolytic status and blood flow to active muscles (57). However, in contrast to our findings, Ahmad et al. (58) reported that HIIT did not reduce PAI-1 levels more than the effects of MICT, probably due to the shorter duration of exercise (eight weeks) used by Ahmad et al. (58). A study by Bodary et al. (58) reported no changes in PAI-1 levels in overweight and obese subjects after 10 weeks moderate aerobic training (walking with 65 percent of reserve heart rate), and concluded that reductions in PAI-1 require decreases in adipose tissue and changes in metabolic variables (58). Our study indicate PAI-1 reductions simultaneous with decreases in adipose tissue, suggesting that exercise reduces PAI-1 levels by loss of adipose tissue (59, 60).

4.3 Fibrinogen-like protein 1

Our study also indicates that exercise reduced FGL-1 levels. FGL-1 is a novel hepatokine mainly expressed in the liver under normal physiological conditions, but whose levels are increased by

high fat conditions and lead to lipid accumulation and inflammation, which in turn trigger the development of NAFLD, diabetes, and obesity (61). ERK1/2 is activated by FGL-1 to induce lipogenesis, and increased ERK1/2 phosphorylation stimulates C/EBP β . FGL1 facilitates adipogenesis by ERK1/2-C/EBP β -dependent pathway, and targeting FGL-1 could be a novel therapeutic strategy in obesity and its related disorders (28). For example, FGL-1 plays an important role in insulin resistance and T2D by ERK1/2-dependent mechanisms, and FGL-1 up regulation could increase ERK1/2 activity, inhibit insulin signaling and lead to insulin resistance (62). There is a positive correlation between FGL-1 and obesity markers (31), and FGL-1 levels are reduced by laparoscopic sleeve gastrectomy (LSG) for weight loss (63), supporting our findings that exercise reduces decrease in the FGL-1 levels and also decreases body weight and adiposity. Decreases in FGL-1 levels by exercise training maybe intensity dependent, as demonstrated by Jokar et al. (64) where moderate and high intensity circuit resistance training, but not low intensity training, decreased FGL-1 levels likely related to loss of adipose tissue by exercise training (64). Although we observed adipose tissue loss after exercise training, we did not measure the FGL-1 expression in the adipose tissue.

4.4 Fibroblast growth factor 21

The adipo-hepatokine FGF-21 is a major energy regulator that affects ROS levels, endoplasmic reticulum stress and other cellular processes, and has favorable effects on body weight control and triglyceride or cholesterol levels (65). Despite the positive effects of FGF-21 on metabolism, up-regulation of FGF-21 and its correlation with BMI has been reported in obesity, leading to the suggestion FGF-21 resistance condition may occur in obesity (66). Since FGF-21 levels are correlated with adipose tissue mass, plasma glucose and insulin levels (insulin resistance) (67). However, exercise training may not always change FGF-21 levels, as exercise can sensitize FGF-21 actions without its concentrations (68). Although FGF-21 has beneficial actions, levels are paradoxically elevated in obesity and metabolic disease, often reflecting compensatory up-regulation and “FGF-21 resistance” (66). Therefore, reductions in plasma FGF-21 after chronic exercise may indicate improved metabolic health with reduced compensatory secretion (and improved FGF-21 sensitivity), rather than loss of benefit (67). Alternatively, lower FGF-21 could reflect reduced production independent of sensitivity (67). In our study FGF-21 declined alongside reductions in adiposity and cardiometabolic markers, favoring reduced compensation; however, without receptor/signaling, insulin-sensitivity or hepatic-fat measures, causal inference is limited.

4.5 Selenoprotein P

Selenoprotein P (SeP) is another protein secreted by the liver (69), and is transported to peripheral tissues (70). Levels of SeP are increased in overweight and obese people, indicating SeP secretion from adipose tissue (32). Therefore, decrease in adipose tissue by

exercise may lower SeP release as shown in our study. SeP causes insulin resistance in hepatocytes and myocytes by several mechanisms, including suppressing auto-phosphorylation of insulin receptor, AKT pathways responding to insulin, decreasing insulin-induced cellular glucose uptake, suppressing the hepatic AMPK signaling pathways, and by disrupting insulin production by pancreatic beta cells (71, 72). Insulin resistance and liver function are closely linked to the physiological role of SeP, a hepatokine primarily synthesized in the liver (24, 26). SeP functions as a selenium transport protein, but it also plays a critical role in metabolic regulation. Elevated levels of SeP have been associated with impaired insulin signaling and glucose homeostasis, contributing to systemic insulin resistance (70, 71). In insulin-resistant states, such as type 2 diabetes and NAFLD, hepatic overproduction of SeP exacerbates metabolic dysfunction by inhibiting insulin action in peripheral tissues (24, 73). Furthermore, insulin normally suppresses SeP expression; however, in insulin-resistant conditions, this regulatory mechanism is impaired, creating a feedback loop that promotes further metabolic derangement (26, 32). Therefore, understanding the interplay between SeP, insulin resistance, and liver function provides key insights into the pathophysiology of metabolic disorders and highlights SeP as a potential biomarker and therapeutic target (72, 73).

Tabata training and short-term HIIT formats are popular forms of interval training, and can be used to increase aerobic and anaerobic fitness, reduce fat and even improve blood pressure, insulin sensitivity and glucose regulation in a relatively short time (33). Furthermore, even short term (four weeks) Tabata training reduces body fat percentage in obese subjects (74). Our findings indicate that HIIT and Tabata training appeared more effective than MICT in improving glycemic control and hepatokine profiles in obese adults.

5 Conclusion

Performing 12 weeks of Tabata and HIIT training decreased weight, BMI, fat percentage, fetuin-B, FGF-21, FGL-1, and selenoprotein P, levels, and it seems the benefits of Tabata and HIIT were more than MICT. The lack of significant changes in the control group over time can be attributed to their sedentary behavior and absence of metabolic stimulation. These hepatokines are sensitive to physiological stressors such as exercise, which modulate their expression through improvements in insulin sensitivity, inflammation, and liver metabolism. In contrast, the training group showed alterations in several of these markers, highlighting the role of physical activity in regulating hepatokine secretion.

6 Limitations

This study is subject to several methodological limitations. First, we used a predictive equation ($HR_{max} = 220 - \text{age}$) to estimate

HR_{max} ; this approach may over- or under-estimate true HR_{max} and thus introduce error into % HR_{max} calculations and exercise intensity classification. The relatively small sample size may have reduced statistical power and limits external validity. To minimize biological variability related to sex- and age-specific factors, we intentionally enrolled only male participants within a narrow age range (21–35 years): this choice aimed to reduce variability from menstrual-cycle-related hormonal fluctuations, contraceptive use, menopausal status, and age-related comorbidities or medications that could confound hepatokine and metabolic responses. While restricting the sample improved internal validity for detecting exercise-induced changes, it limits generalizability to women and older adults. Dietary intake was not standardized during the 12-week intervention, although three-day food records (two weekdays and one weekend day) were collected at baseline and post-intervention to assess changes in habitual dietary intake over time. These records were analyzed using Diet Analysis Plus version 10 (Cengage, Boston, MA, USA) to calculate total energy consumption and macronutrient distribution (proteins, fats, and carbohydrates). However, self-reported short-term records may not fully capture habitual intake, and residual confounding from uncontrolled dietary changes cannot be excluded. Glucose and insulin concentrations were not measured; therefore, references to glucose–insulin signaling as a potential mediator are hypothetical and were discussed only to provide mechanistic context based on prior literature. Future studies should include women (with appropriate cycle-phase or contraceptive stratification), older adults, more comprehensive metabolic and molecular profiling, controlled dietary conditions or repeated dietary monitoring, and formal safety surveillance to evaluate sex- and age-specific responses and underlying mechanisms. An important limitation is the lack of mechanistic biomarker assessment. Although we discuss pathways such as insulin signaling, AMPK activation, GLUT-4 translocation and oxidative stress, these mechanisms were not measured here and therefore remain speculative. Future studies should include direct measures of glucose homeostasis and insulin sensitivity (e.g., fasting glucose/insulin, HOMA-IR, OGTT or hyperinsulinemic-euglycemic clamp), hepatic fat quantification (e.g., MRI-PDFF), molecular markers of insulin/AMPK signaling and GLUT-4 (muscle or peripheral cells), and oxidative-stress/inflammatory biomarkers, with sampling at baseline, acute post-exercise and post-intervention time points to better define causal pathways. While adverse events were regularly documented and reviewed by the principal investigator, the lack of independent adjudication for safety monitoring represents a methodological limitation. Future studies should consider implementing independent safety committees to enhance the rigor of adverse event reporting and adjudication.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by National Research and Ethics Committee of Islamic Azad University (Ethics code: IR.IAU.AMOL.REC.1402.070). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ALA: Data curation, Formal Analysis, Methodology, Writing – original draft. HA: Formal Analysis, Software, Writing – review & editing. SH: Data curation, Methodology, Software, Writing – review & editing. MN: Data curation, Formal Analysis, Methodology, Writing – original draft. MD: Data curation, Methodology, Software, Writing – review & editing. PF: Data curation, Methodology, Software, Writing – review & editing. MS: Data curation, Formal Analysis, Methodology, Writing – original draft. AbA: Data curation, Methodology, Software, Writing – review & editing. NK: Formal Analysis, Software, Writing – review & editing. BB-R: Data curation, Methodology, Software, Writing – review & editing. AS: Conceptualization, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. IL: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Writing – review & editing. HZ: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

References

- Rui L. Energy metabolism in the liver. *Compr Physiol.* (2014) 4:177. doi: 10.1002/cphy.c130024
- de Oliveira dos Santos AR, de Oliveira Zanuso B, Miola VF, Barbalho SM, Santos Bueno PC, Flato UA, et al. Adipokines, myokines, and hepatokines: crosstalk and metabolic repercussions. *Int J Mol Sci.* (2021) 22:2639. doi: 10.3390/ijms22052639
- Jensen-Cody SO, Potthoff MJ. Hepatokines and metabolism: Deciphering communication from the liver. *Mol Metab.* (2020) 44:101138. doi: 10.1016/j.molmet.2020.101138
- Misu H. Identification of hepatokines involved in pathology of type 2 diabetes and obesity. *Endocrine J.* (2019) 66:659–62. doi: 10.1507/endocrj.EJ19-0255
- Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. *Circulation.* (2012) 126:126–32. doi: 10.1161/CIRCULATIONAHA.111.087213
- Oh KJ, Lee DS, Kim WK, Han BS, Lee SC, Bae KH. Metabolic adaptation in obesity and type II diabetes: myokines, adipokines and hepatokines. *Int J Mol Sci.* (2016) 18:8. doi: 10.3390/ijms18010008
- Sardana O, Goyal R, Bedi O. Molecular and pathobiological involvement of fetuin-A in the pathogenesis of NAFLD. *Inflammopharmacology.* (2021) 29:1061–74. doi: 10.1007/s10787-021-00837-4
- Schäfer C, Heiss A, Schwarz A, Westenfeld R, Ketteler M, Floege J, et al. The serum protein α 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. *J Clin Invest.* (2003) 112:357–66. doi: 10.1172/JCI17202
- Icer MA, Yıldıran H. Effects of fetuin-A with diverse functions and multiple mechanisms on human health. *Clin Biochem.* (2021) 88:1–0. doi: 10.1016/j.clinbiochem.2020.11.004
- Denecke B, Gräber S, Schäfer C, Heiss A, Wöltje M, Jahnen-Dechent W. Tissue distribution and activity testing suggest a similar but not identical function of fetuin-B and fetuin-A. *Biochem J.* (2003) 376:135–45. doi: 10.1042/BJ20030676
- Chatterjee P, Seal S, Mukherjee S, Kundu R, Mukherjee S, Ray S, et al. Adipocyte fetuin-A contributes to macrophage migration into adipose tissue and polarization of macrophages. *J Biol Chem.* (2013) 288:28324–30. doi: 10.1074/jbc.C113.495473
- Roshanzamir F, Miraghajani M, Rouhani MH, Mansourian M, Ghiasvand R, Safavi SM. The association between circulating fetuin-A levels and type 2 diabetes mellitus risk: systematic review and meta-analysis of observational studies. *J endocrinological Invest.* (2018) 41:33–47. doi: 10.1007/s40618-017-0697-8
- Chekol Abebe E, Tilahun Muche Z, Behaile T/Mariam A, Mengie Ayele T, Mekonnen Agidew M, Teshome Azezew M, et al. The structure, biosynthesis, and biological roles of fetuin-A: A review. *Front Cell Dev Biol.* (2022) 10:945287. doi: 10.3389/fcell.2022.945287
- Olivier E, Soury E, Ruminy P, Husson A, Parmentier F, Daveau M, et al. Fetuin-B, a second member of the fetuin family in mammals. *Biochem J.* (2000) 350:589–97. doi: 10.1042/bj3500589
- Kralisch S, Hoffmann A, Lössner U, Kratzsch J, Blüher M, Stummvoll M, et al. Regulation of the novel adipokines/hepatokines fetuin A and fetuin B in gestational diabetes mellitus. *Metabolism.* (2017) 68:88–94. doi: 10.1016/j.metabol.2016.11.017

Acknowledgments

The authors wish to thank all the participants of research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

16. Xue S, Han H, Rui S, Yang M, Huang Y, Zhan B, et al. Serum fetuin-B levels are elevated in women with metabolic syndrome and associated with increased oxidative stress. *Oxid Med Cell longevity*. (2021) 2021:6657658. doi: 10.1155/2021/6657658
17. Hussein N, Mahmoud O, Zahran M, Rafaat MA. Serum Fetuin-A in chronic renal disease patients: contribution to endothelial dysfunction and hemostatic alteration. *J Am Sci*. (2010) 6:1098–5. doi: 10.1159/000120209
18. Nawaz SS, Joy SS, Al Farsi Y, George TP, Siddiqui K. Potential role of serum fetuin-A in relation with pro-inflammatory, chemokine and adhesion molecules in diabetic kidney disease: A case-control study. *Mol Biol Rep*. (2019) 46:1239–46. doi: 10.1007/s11033-019-04592
19. Siegel-Axel DI, Ullrich S, Stefan N, Rittig K, Gerst F, Klingler C, et al. Fetuin-A influences vascular cell growth and production of proinflammatory and angiogenic proteins by human perivascular fat cells. *Diabetologia*. (2014) 57:1057–66. doi: 10.1007/s00125-014-3177-0
20. Yoo HJ, Choi KM. Hepatokines as a link between obesity and cardiovascular diseases. *Diabetes Metab J*. (2015) 39:10–5. doi: 10.4093/dmj.2015.39.1.10
21. Altalhi R, Pechlivani N, Ajjan RA. PAI-1 in diabetes: pathophysiology and role as a therapeutic target. *Int J Mol Sci*. (2021) 22:3170. doi: 10.3390/ijms22063170
22. Gils A, Declercq PJ. The structural basis for the pathophysiological relevance of PAI-1 in cardiovascular diseases and the development of potential PAI-1 inhibitors. *Thromb haemostasis*. (2004) 91:425–37. doi: 10.1160/TH03-12-0764
23. Batiha GE, Al-Kuraishy HM, Al-Maiyah TJ, Al-Buhadily AK, Saad HM, Al-Gareeb AI, et al. Plasminogen activator inhibitor 1 and gestational diabetes: the causal relationship. *Diabetol Metab syndrome*. (2022) 14:127. doi: 10.1186/s13098-022-00900-2
24. Hara H, Yoshimura H, Uchida S, Toyoda Y, Aoki M, Sakai Y, et al. Molecular cloning and functional expression analysis of a cDNA for human heparosin, a liver-specific protein with hepatocyte mitogenic activity. *Biochim Biophys Acta (BBA)-Gene Structure Expression*. (2001) 1520:45–53. doi: 10.1016/s0167-4781(01)00249-4
25. Demchev V, Malana G, Vangala D, Stoll J, Desai A, Kang HW, et al. Targeted deletion of fibrinogen like protein 1 reveals a novel role in energy substrate utilization. *PLoS One*. (2013) 8:e58084. doi: 10.1371/journal.pone.0058084
26. Wu HT, Lu FH, Ou HY, Su YC, Hung HC, Wu JS, et al. The role of heparosin in the development of non-alcoholic fatty liver disease. *J Hepatology*. (2013) 59:1065–72. doi: 10.1016/j.jhep.2013.06.004
27. Huang RL, Li CH, Du YF, Cheng KP, Lin CH, Hu CY, et al. Discovery of a role of the novel hepatokine, heparosin, in obesity. *Biofactors*. (2020) 46:100–5. doi: 10.1002/biof.1574
28. Wu HT, Chen SC, Fan KC, Kuo CH, Lin SY, Wang SH, et al. Targeting fibrinogen-like protein 1 is a novel therapeutic strategy to combat obesity. *FASEB J*. (2020) 34:579228. doi: 10.3389/fimmu.2020.579228
29. Jung TW, Yoo HJ, Choi KM. Implication of hepatokines in metabolic disorders and cardiovascular diseases. *BBA clinical*. (2016) 5:108–13. doi: 10.1016/j.bbacli.2016.03.002
30. Oppert JM, Bellicha A, van Baak MA, Battista F, Beaulieu K, Blundell JE, et al. Exercise training in the management of overweight and obesity in adults: Synthesis of the evidence and recommendations from the European Association for the Study of Obesity Physical Activity Working Group. *Obes Rev*. (2021) 22:e13273. doi: 10.1111/obr.13273
31. D'Amuri A, Sanz JM, Capatti E, Di Vece F, Vaccari F, Lazzar S, et al. Effectiveness of high-intensity interval training for weight loss in adults with obesity: A randomised controlled non-inferiority trial. *BMJ Open Sport Exercise Med*. (2021) 7:e001021. doi: 10.1136/bmjsem-2020-001021
32. Weweg M, Van Den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. *Obes Rev*. (2017) 18:635–46. doi: 10.1111/obr.12532
33. Olson M. TABATA: it's a HIIT! *ACSM'S Health Fitness J*. (2014) 18:17–24. doi: 10.1249/FIT.0000000000000065
34. Ljubojević A, Gerdijan N, Pavlović R, Šebić L. Effect of Tabata training program on body fat reduction in healthy inactive women. *Pedagogy Phys Culture Sports*. (2023) 27:198–207. doi: 10.15561/26649837.2023.0303
35. Feito Y, Brown C, Olmos A. A content analysis of the high-intensity functional training literature: A look at the past and directions for the future. *Hum Movement*. (2019) 20:1–15. doi: 10.5114/hm.2019.81020
36. Murawska-Cialowicz E, Wolanski P, Zuwała-Jagiello J, Feito Y, Petr M, Kokstajn J, et al. Effect of HIIT with Tabata protocol on serum irisin, physical performance, and body composition in men. *Int J Environ Res Public Health*. (2020) 17:3589. doi: 10.3390/ijerph17103589
37. Iroz A, Couty JP, Postic C. Hepatokines: unlocking the multi-organ network in metabolic diseases. *Diabetologia*. (2015) 58:1699–703. doi: 10.1007/s00125-015-3634-4
38. Gonzalez-Gil AM, Elizondo-Montemayor L. The role of exercise in the interplay between myokines, hepatokines, osteokines, adipokines, and modulation of inflammation for energy substrate redistribution and fat mass loss: a review. *Nutrients*. (2020) 12:1899. doi: 10.3390/nu12061899
39. Weigert C, Hoene M, Plomgaard P. Hepatokines—a novel group of exercise factors. *Pflügers Archiv-European J Physiol*. (2019) 471:383–96. doi: 10.1007/s00424-018-2216-y
40. Keihanian A, Arazi H, Kargarfard M. Effects of aerobic versus resistance training on serum fetuin-A, fetuin-B, and fibroblast growth factor-21 levels in male diabetic patients. *Physiol Int*. (2019) 106:70–80. doi: 10.1556/2060.106.2019.01
41. Zhang LY, Liu T, Teng YQ, Yao XY, Zhao TT, Lin LY, et al. Effect of a 12-week aerobic exercise training on serum fetuin-A and adipocytokine levels in type 2 diabetes. *Exp Clin Endocrinol Diabetes*. (2018) 126:487–92. doi: 10.1055/s-0043-115904
42. Blumenthal JB, Gitterman A, Ryan AS, Prior SJ. Effects of exercise training and weight loss on plasma fetuin-A levels and insulin sensitivity in overweight older men. *J Diabetes Res*. (2017) 2017:1492581. doi: 10.1155/2017/1492581
43. Schultes B, Frick J, Ernst B, Stefan N, Fritzsche A. The effect of 6-weeks of aerobic exercise training on serum fetuin-A levels in non-diabetic obese women. *Exp Clin Endocrinol diabetes*. (2010) 118:754–6. doi: 10.1055/s-0030-1253418
44. Trepanowski JF, Mey J, Varady KA. Fetuin-A: a novel link between obesity and related complications. *Int J Obes*. (2015) 39:734–41. doi: 10.1038/ijo.2014.203
45. Soelstijjo SA, Pranoto A, Tjokroprawiro A. The effect of fetuin-a and palmitate on the translocation of glucose transporter-4 through the activation of toll-like receptor 4 in skeletal muscle cells. *J Global Pharma Technology*. (2020) 12:413–20.
46. Qu H, Qiu Y, Wang Y, Liao Y, Zheng Y, Zheng H. Plasma fetuin-B concentrations are associated with insulin resistance and first-phase glucose-stimulated insulin secretion in individuals with different degrees of glucose tolerance. *Diabetes Metab*. (2018) 44:488–92. doi: 10.1016/j.diabet.2018.02.003
47. Li Z, Lin M, Liu C, Wang D, Shi X, Chen Z, et al. Fetuin-B links nonalcoholic fatty liver disease to type 2 diabetes via inducing insulin resistance: association and path analyses. *Cytokine*. (2018) 108:145–50. doi: 10.1016/j.cyt.2018.03.023
48. Misu H, Takamura T, Takayama H, Hayashi M, Matsuzawa-Nagata N, Kurita S, et al. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. *Cell Metab*. (2010) 12:483–95. doi: 10.1016/j.cmet.2010.09.015
49. Mathews ST, Singh GP, Ranalletta M, Cintron VJ, Qiang X, Goustin AS, et al. Improved insulin sensitivity and resistance to weight gain in mice null for the Ahsg gene. *Diabetes*. (2002) 51:2450–8. doi: 10.2337/diabetes.51.8.2450
50. Mathews ST, Rakhade S, Zhou X, Parker GC, Coscina DV, Grunberger G. Fetuin-null mice are protected against obesity and insulin resistance associated with aging. *Biochem Biophys Res Commun*. (2006) 350:437–43. doi: 10.1016/j.bbrc.2006.09.071
51. Ramirez-Vélez R, García-Hermoso A, Hackney AC, Izquierdo M. Effects of exercise training on Fetuin-a in obese, type 2 diabetes and cardiovascular disease in adults and elderly: a systematic review and Meta-analysis. *Lipids Health disease*. (2019) 18:1–1. doi: 10.1186/s12944-019-0962-2
52. Gomez-Cabrera MC, Domenech E, Viña J. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. *Free Radical Biol Med*. (2008) 44:126–31. doi: 10.1016/j.freeradbiomed.2007.02.001
53. Badran M, Gozal D. PAI-1: a major player in the vascular dysfunction in obstructive sleep apnea? *Int J Mol Sci*. (2022) 23:5516. doi: 10.3390/ijms23105516
54. Correia ML, Haynes WG. A role for plasminogen activator inhibitor-1 in obesity: from pie to PAI? *Arteriosclerosis thrombosis Vasc Biol*. (2006) 26:2183–5. doi: 10.1161/01.ATV.0000244018.24120.70
55. Elsayed MM, Rabiee A, Elrefay GE, Elsis HF. Effect of aerobic exercise with diet on sex hormones and selected coagulation biomarkers in obese postmenopausal women: a randomized clinical trial. *Eur Rev Med Pharmacol Sci*. (2022) 26. doi: 10.26355/eurrev_202201_27886
56. Ahmad A, Ali F, Ali H. Effect of high-intensity interval training versus moderate-intensity continuous training on plasminogen activator inhibitor-1 in Type 2 diabetic women. *Adv Rehabil*. (2022) 36. doi: 10.3390/ijerph16091533
57. Hittel DS, Kraus WE, Hoffman EP. Skeletal muscle dictates the fibrinolytic state after exercise training in overweight men with characteristics of metabolic syndrome. *J Physiol*. (2003) 548:401–10. doi: 10.1113/jphysiol.2002.036616
58. Bodary PF, Yasuda N, Watson DD, Brown AS, Davis JM, Pate RR. Effects of short-term exercise training on plasminogen activator inhibitor (PAI-1). *Med Sci sports exercise*. (2003) 35:1853–8. doi: 10.1249/01.MSS.0000093751.82616.F0
59. Mertens I, Gaal LV. Obesity, haemostasis and the fibrinolytic system. *Obes Rev*. (2002) 3:85–101. doi: 10.1046/j.1467-789x.2002.00056.x
60. Juhan-Vague I, Alessi MC, Mavri A, Morange PE. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. *J Thromb Haemostasis*. (2003) 1:1575–9. doi: 10.1046/j.1538-7836.2003.00279.x
61. Liu XH, Qi LW, Alolga RN, Liu Q. Implication of the hepatokine, fibrinogen-like protein 1 in liver diseases, metabolic disorders and cancer: The need to harness its full potential. *Int J Biol Sci*. (2022) 18:292. doi: 10.7150/ijbs.66834
62. Wu HT, Ou HY, Hung HC, Su YC, Lu FH, Wu JS, et al. A novel hepatokine, HFREPI, plays a crucial role in the development of insulin resistance and type 2 diabetes. *Diabetologia*. (2016) 59:1732–42. doi: 10.1007/s00125-016-3991-7
63. Dilimulati D, Du L, Huang X, Jayachandran M, Cai M, Zhang Y, et al. Serum fibrinogen-like protein 1 levels in obese patients before and after laparoscopic sleeve gastrectomy: a six-month longitudinal study. *Diabetes Metab Syndrome Obesity: Targets Ther*. (2022) 1:2511–20. doi: 10.2147/DMSO.S374011
64. Jokar SE, Peeri M, Azarbayjani MA. The effect of high, low and moderate intensity circuit resistance training on the levels of hepatocyte-derived fibrinogen-

related protein 1 (HFREP1) and lipid profile in obese postmenopausal women. *J Basic Res Med Sci.* (2022) 9.

65. Mukhuty A, Mondal SA, Mukhopadhyay S. Hepatokines and adipokines in metabolic syndrome. *Ann Natl Acad Med Sci (India).* (2023) 59:004–12. doi: 10.1055/s-0042-1760087

66. van Baak MA, Vink RG, Roumans NJ, Cheng CC, Adams AC, Mariman EC. Adipose tissue contribution to plasma fibroblast growth factor 21 and fibroblast activation protein in obesity. *Int J Obes.* (2020) 44:544–7. doi: 10.1038/s41366-019-0433-x

67. Ni B, Farrar JS, Vaitkus JA, Celi FS. Metabolic effects of FGF-21: thermoregulation and beyond. *Front Endocrinology.* (2015) 6:148. doi: 10.3389/fendo.2015.00148

68. Motahari Rad M, Bijeh N, Attarzadeh Hosseini SR, Raouf Saeb A. The effect of two concurrent exercise modalities on serum concentrations of FGF21, irisin, follistatin, and myostatin in men with type 2 diabetes mellitus. *Arch Physiol Biochem.* (2023) 129:424–33. doi: 10.1080/13813455.2020.1829649

69. Burk RF, Hill KE. Selenoprotein P: an extracellular protein with unique physical characteristics and a role in selenium homeostasis. *Annu Rev Nutr.* (2005) 25:215–35. doi: 10.1146/annurev.nutr.24.012003.132120

70. Hariharan S, Dharmaraj S. Selenium and selenoproteins: It's role in regulation of inflammation. *Inflammopharmacology.* (2020) 28:667–95. doi: 10.1007/s10787-020-00690-x

71. El-Kafrawy NA, Azza EB, Abdelsattar S, Zewain SK. Serum selenoprotein P in lean and obese Egyptian individuals and its relation to insulin resistance. *Alexandria J Med.* (2021) 57:61–9. doi: 10.1080/20905068.2021.1876288

72. Tsutsumi R, Saito Y. Selenoprotein P; P for plasma, prognosis, prophylaxis, and more. *Biol Pharm Bulletin.* (2020) 43:366–74. doi: 10.1248/bpb.b19-00837

73. Oo SM, Htut MT, Htun YW, Mon AA, Kyaw MP. Lower plasma selenoprotein P levels in regularly exercising young adults. *J ASEAN Fed Endocrine Societies.* (2022) 38:6. doi: 10.15605/jafes.037.S4

74. Maesaroh S, Purwoto SP, Novendri D. Effects of tabata body weight training on body fat percentage in obese women. *Jurnal Maempo: Jurnal Pendidikan Jasmani Kesehatan dan Rekreasi.* (2022) 12:118–27. doi: 10.35194/jm.v12i1.2327