Research Article

Effect of aerobic exercise on the expression of inflammation-related genes TNF-α, IL-6, and IL-10 in overweight individuals

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Abstract

Aerobic exercise has been proposed as a non-pharmacological intervention to modulate inflammatory gene expression, yet the molecular mechanisms remain incompletely understood. This study investigated the effects of a 12-week moderate-intensity aerobic exercise intervention on the mRNA expression levels of inflammation-related genes (TNF-α, IL-6, and IL-10) in peripheral blood mononuclear cells (PBMCs) of overweight individuals. Forty-five overweight adults (BMI 25-29.9 kg/m²) were randomly assigned to either an aerobic exercise group (n=30) or a sedentary control group (n=15). The exercise protocol consisted of supervised moderate-intensity aerobic training (60-75% HRmax) for 45-60 minutes, 5 days per week for 12 weeks. Blood samples were collected pre- and post- intervention for gene expression analysis using quantitative real-time PCR and protein quantification via ELISA. Following the 12-week intervention, the exercise group demonstrated significant reductions in TNF-α mRNA expression (−52.3%, $p<0.001$) and IL-6 expression (−47.8%, $p<0.001$) compared to baseline. Conversely, IL-10 expression increased significantly (+68.4%, $p<0.001$). Plasma protein concentrations paralleled these changes, with TNF-α decreasing from 8.6±2.1 to 4.9±1.3 pg/mL ($p<0.001$), IL-6 from 5.8±1.7 to 3.2±0.9 pg/mL ($p<0.001$), and IL-10 increasing from 3.1±0.8 to 5.6±1.2 pg/mL ($p<0.001$). Body mass index decreased significantly in the exercise group (−2.3 kg/m², $p<0.001$) with concurrent improvements in cardiorespiratory fitness (VO_2max increased by 18.7%, $p<0.001$). Moderate-intensity aerobic exercise effectively modulates the inflammatory gene expression profile in overweight individuals by downregulating pro-inflammatory genes (TNF-α and IL-6) and upregulating the anti- inflammatory gene (IL-10). These molecular adaptations may contribute to reduced inflammation and improved metabolic health in this population.

Key Words: Aerobic exercise, Gene expression, Inflammation, TNF-α, IL-6, IL-10, Overweight

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Introduction

Overweight and obesity represent a growing global health crisis, affecting approximately 39% of adults worldwide and contributing significantly to the burden of non-communicable diseases (World Health Organization, 2021; Roth et al., 2020). These conditions are characterized by excessive adipose tissue accumulation, which serves not merely as an energy storage depot but as an active endocrine organ secreting numerous pro-inflammatory cytokines and adipokines (Ren et al., 2022). This state of chronic low-grade inflammation, often termed "meta-inflammation," plays a pivotal role in the pathogenesis of insulin resistance, type 2 diabetes, cardiovascular diseases, and certain cancers (Gregor & Hotamisligil, 2021; Zatterale et al., 2020).

At the molecular level, adipose tissue from overweight and obese individual's exhibits increased infiltration of immune cells, particularly macrophages, which shift from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype (Coats et al., 2021). These activated immune cells, along with hypertrophied adipocytes, produce elevated levels of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) (Fernández-Real & Pickup, 2022). Simultaneously, the production of anti-inflammatory cytokines such as interleukin-10 (IL-10) is often suppressed, creating an imbalanced inflammatory milieu that perpetuates metabolic dysfunction (Mahata et al., 2022).

TNF-α is a pleiotropic cytokine that interferes with insulin signaling by promoting serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby impairing glucose uptake in peripheral tissues (Hotamisligil, 2020). Elevated TNF-α levels in obesity correlate with insulin resistance and are implicated in the development of atherosclerosis through endothelial dysfunction (Zhang et al., 2021). IL-6, another key pro-inflammatory mediator, exhibits both pro- and anti-inflammatory properties depending on the physiological context; in chronic inflammatory states associated with obesity, persistently eleva-

-ted IL-6 contributes to hepatic insulin resistance and stimulates acute-phase protein synthesis, including C-reactive protein (CRP) (Gope et al., 2022; Dinarello, 2021). Conversely, IL-10 functions as a potent anti-inflammatory cytokine by inhibiting the synthesis of pro-inflammatory mediators and promoting the M2 macrophage phenotype, thereby counteracting inflammatory processes (Couper et al., 2020).

Physical exercise, particularly aerobic exercise, has emerged as a powerful non-pharmacological intervention capable of reducing systemic inflammation and improving metabolic health (Pedersen & Saltin, 2020; Gleeson et al., 2021). Epidemiological studies consistently demonstrate that regular physical activity is associated with lower circulating levels of inflammatory markers in overweight and obese populations (Nieman & Wentz, 2020). Recent meta-analyses have confirmed that aerobic exercise training significantly reduces CRP, TNF-α, and IL-6 levels while increasing IL-10 concentrations in adults with excess adiposity (Sungkarat et al., 2021; Khalafi et al., 2023).

Despite these promising findings, the molecular mechanisms underlying exercise-induced anti-inflammatory effects remain incompletely elucidated. Most previous studies have focused on circulating protein concentrations of inflammatory markers, with limited investigation into transcriptional regulation at the gene expression level (Pedersen & Fischer, 2021). Understanding how exercise modulates the mRNA expression of inflammation-related genes is critical for identifying potential therapeutic targets and optimizing exercise prescriptions for overweight individuals.

Furthermore, there exists considerable heterogeneity in exercise protocols employed across studies, including variations in intensity, duration, frequency, and mode of exercise (Silverman & Deuster, 2021). Moderate-intensity aerobic exercise, typically defined as 60–75% of maximum heart rate, has been recommended by international guidelines as an effective and sustainable approach for weight management and cardiovascular health (American College of Sports Medicine, 2022). However, the dose–response relationship between moderate-intensity aerobic exercise and inflammatory gene expression in peripheral blood mononuclear cells (PBMCs) requires further investigation.

Recent advances in molecular biology techniques, including quantitative real-time polymerase chain reaction (qRT-PCR) and enzyme-linked immunosorbent assay (ELISA), have enabled precise measurement of both mRNA expression and protein concentrations of inflammatory mediators (Bustin et al., 2020). These methodologies allow for comprehensive assessment of exercise-induced changes at both transcriptional and translational levels, providing insights into the temporal dynamics of anti-inflammatory adaptations.

The present study was designed to address these knowledge gaps by investigating the effects of a standardized 12-week moderate-intensity aerobic exercise intervention on the expression of three key inflammation-related genes (TNF-α, IL-6, and IL-10) in PBMCs isolated from overweight adults. It was hypothesized that regular aerobic exercise would downregulate the expression of pro-inflammatory genes (TNF-α and IL-6) while upregulating the anti-inflammatory gene (IL-10), and that these molecular changes would be accompanied by improvements in body composition and cardiorespiratory fitness, thereby providing mechanistic insights into the protective effects of physical activity against metabolic diseases.

Materials and Methods

Study design and ethical considerations

This study employed a randomized controlled trial design conducted over a 12-week period between January 2024 and May 2024. All participants provided written informed consent after receiving detailed information about the study procedures, potential risks, and benefits. The study flowchart is presented in Figure 2, illustrating the participant recruitment, randomization, intervention, and follow-up procedures. Participants were recruited through local community advertisements, health centers, and university bulletin boards (Figure 2).

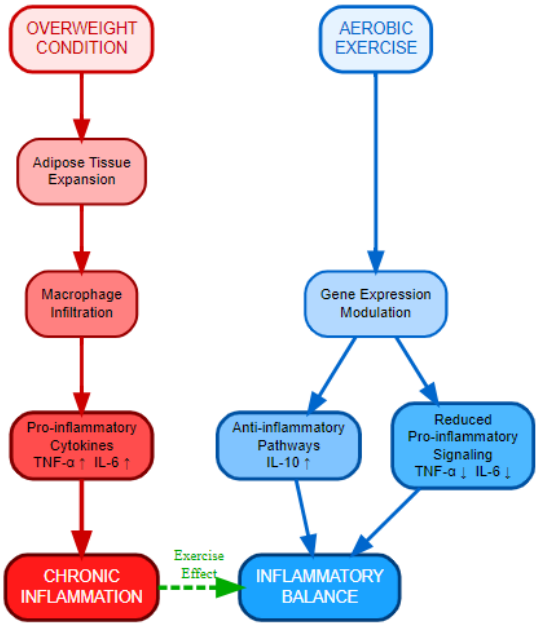

Figure 1. Conceptual framework illustrating the inflammatory cascade in overweight conditions and the proposed anti-inflammatory mechanisms of aerobic exercise. Adipose tissue expansion leads to macrophage infiltration and increased production of pro-inflammatory cytokines (TNF-α, IL-6), while aerobic exercise training modulates gene expression to shift the balance toward anti-inflammatory pathways through IL-10 upregulation and reduced pro- inflammatory signaling.

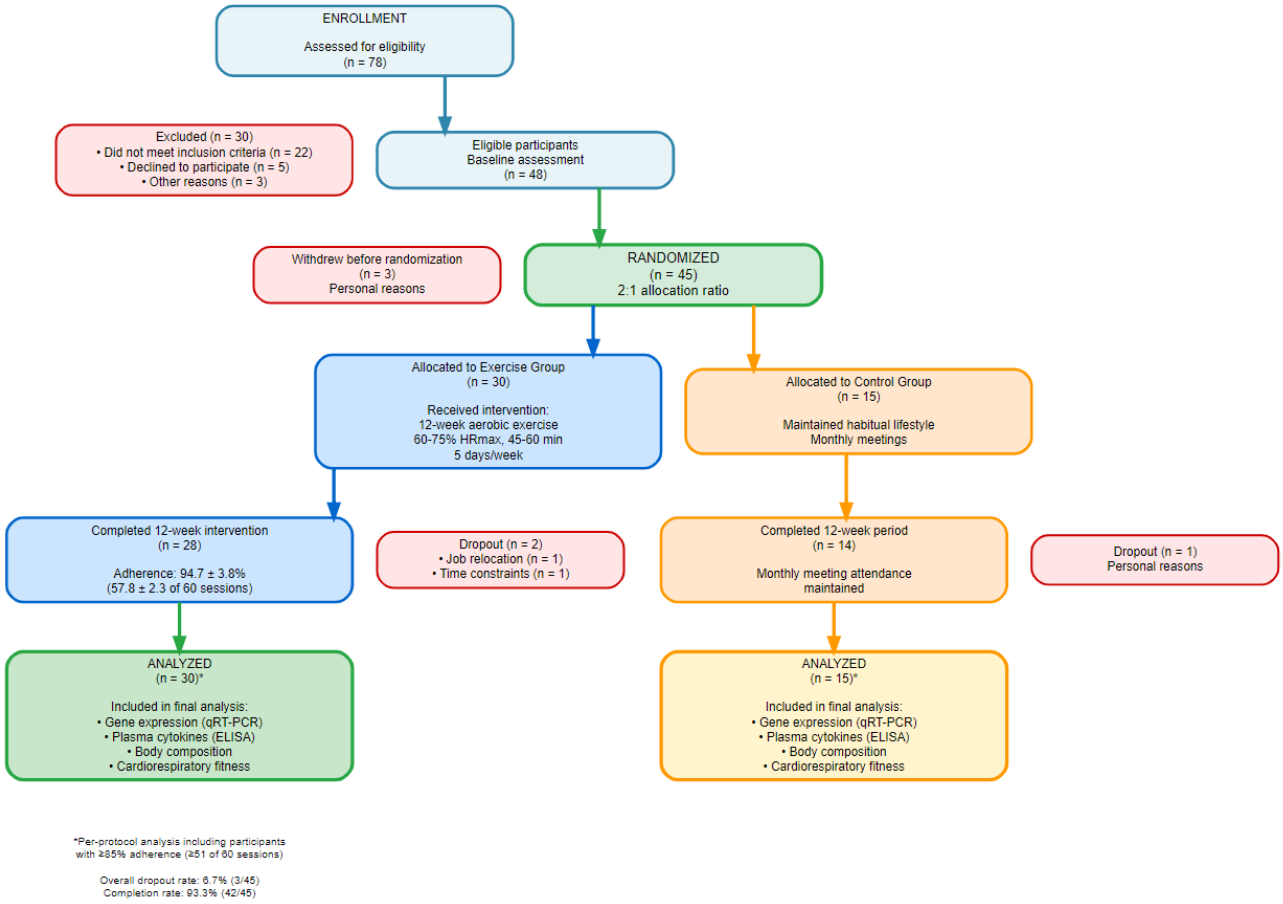

Figure 2. CONSORT flow diagram depicting participant recruitment, allocation, intervention, and analysis phases. A total of 78 individuals were initially assessed for eligibility, with 45 meeting inclusion criteria and completing the 12-week intervention (exercise group n=30; control group n=15). Dropout rate was 6.7% primarily due to time constraints and scheduling conflicts.

Participants and eligibility criteria

A total of 78 sedentary overweight adults were initially screened for participation. Inclusion criteria were: (1) age 25-45 years; (2) body mass index (BMI) between 25.0-29.9 kg/m²; (3) sedentary lifestyle defined as less than 60 minutes of structured physical activity per week for the preceding 6 months; (4) no diagnosed chronic diseases including diabetes mellitus, cardiovascular disease, or inflammatory disorders; (5) not currently taking anti-inflammatory medications, immunosuppressants, or hormonal therapies; and (6) non-smoker status. Exclusion criteria included: (1) pregnancy or lactation; (2) musculoskeletal conditions limiting exercise participation; (3) history of bariatric surgery; (4) participation in structured weight loss programs within the past 3 months; and (5) contraindications to exercise as determined by medical screening.

Following initial screening, 48 eligible participants underwent baseline assessments. Three participants withdrew before randomization due to personal reasons, resulting in 45 participants who were randomly allocated to either the aerobic exercise group (n=30) or the sedentary control group (n=15) using computer-generated random numbers in a 2:1 allocation ratio. The unequal allocation was designed to maximize statistical power for detecting within-group changes in the exercise intervention while maintaining an adequate control group for comparison (Bland, 2020).

Baseline characteristics of the study participants are summarized in Table 1, demonstrating no significant differences between groups in demographic and anthropometric variables, ensuring adequate randomization.

Aerobic exercise intervention protocol

The exercise group participated in a supervised moderate-intensity aerobic training program conducted at the University Exercise Physiology Laboratory. Training sessions were held 5 days per week for 12 consecutive weeks, with each session lasting 45–60 minutes. The exercise protocol followed evidence-based guidelines for aerobic training in overweight populations (Donnelly et al., 2020; Janssen et al., 2024).

Each training session consisted of three phases: (1) warm-up (10 minutes) including dynamic stretching and light- intensity walking

Table 1. Baseline demographic and anthropometric characteristics of study participants. Data are presented as mean ± standard deviation or frequency. BMI, body mass index; BP, blood pressure; VO_2max, maximal oxygen consumption. Statistical comparisons performed using independent t-tests for continuous variables and chi-square test for categorical variables.

Characteristic	Exercise Group (n=30)	Control Group (n=15)	p-value
Age (years)	34.6 ± 6.8	35.2 ± 7.1	0.78
Sex (M/F)	16.14	8.7	0.92
Body weight (kg)	82.4 ± 9.3	81.7 ± 10.1	0.81
BMI (kg/m²)	27.8 ± 1.4	27.6 ± 1.5	0.67
Waist circumference (cm)	96.3 ± 7.2	95.8 ± 8.1	0.83
Body fat percentage (%)	32.7 ± 4.6	32.1 ± 5.2	0.71
Resting heart rate (bpm)	74.2 ± 8.5	73.8 ± 9.1	0.88
Systolic BP (mmHg)	126.4 ± 11.3	125.7 ± 12.6	0.85
Diastolic BP (mmHg)	79.8 ± 7.4	78.9 ± 8.2	0.72
VO_2max (mL/kg/min)	28.4 ± 4.2	28.9 ± 4.7	0.73

Table 2. Detailed specifications of the 12-week progressive aerobic exercise intervention protocol. HRmax, maximum heart rate calculated as 220 - age (years). Each session included 10-minute warm-up and 5-minute cool-down in addition to main exercise duration shown.

Training Phase	Weeks	Intensity (% HRmax)	Duration (min)	Frequency
Initial adaptation	1-2	60-65	30	5 days/week
Progressive phase 1	3-6	65-70	40	5 days/week
Progressive phase 2	7-10	70-75	50	5 days/week
Consolidation phase	11-12	70-75	60	5 days/week

or cycling; (2) main exercise phase (30-45 minutes) performed at moderate intensity corresponding to 60-75% of individual maximum heart rate (HRmax), calculated using the Karvonen formula: Target HR=[(HRmax-HRrest)×intensity]+HRrest; and (3) cool-down (5 minutes) involving gradual reduction in exercise intensity and static stretching.

Exercise modalities included treadmill walking/jogging, stationary cycling, and elliptical training, with participants rotating between modalities to maintain engagement and reduce overuse injuries. Heart rate was continuously monitored using Polar H10 heart rate monitors (Polar Electro Oy, Kempele, Finland) to ensure participants-maintained target intensity zones. Exercise intensity was progressively increased over the 12-week period, with duration advancing from 30 minutes during weeks 1-2, to 40 minutes during weeks 3-6, 50 minutes during weeks 7-10, and 60 minutes during weeks 11-12. All training sessions were supervised by certified exercise physiologists who recorded attendance, exercise duration, average heart rate, and any adverse events. Participants were required to maintain at least 85% adherence (51 of 60 sessions) to be included in final analyses. Detailed specifications of the exercise protocol are provided in Table 2. The sedentary control group was instructed to maintain their habitual lifestyle and physical activity patterns throughout the 12-week study period. Control participants attended monthly meetings to maintain engagement and were offered the exercise program upon study completion.

Anthropometric and cardiorespiratory fitness assessments

Comprehensive anthropometric and fitness assessments were conducted at baseline (week 0) and post-intervention (week 12) by trained technicians blinded to group allocation. All measurements were performed in the morning following a 12-hour overnight fast and 48-hour abstention from vigorous physical activity. Body Composition: Body weight was measured to the nearest 0.1 kg using a calibrated digital scale (Seca 769, Hamburg, Germany) with participants wearing light clothing and no shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Seca 217, Hamburg, Germany). BMI was calculated as weight (kg) divided by height squared (m²). Waist circumference was measured at the midpoint between the lowest rib and iliac crest using a non-stretchable measuring tape, with the average of three measurements recorded. Body composition including fat mass and fat-free mass was assessed using bioelectrical impedance analysis (InBody 770, Biospace Co., Seoul, South Korea), which has demonstrated high reliability (ICC = 0.98) for body fat percentage estimation (Lee & Park, 2020).

Cardiorespiratory Fitness: Maximal oxygen consumption (VO_2max) was determined using a graded exercise test on a motorized treadmill (Trackmaster TMX425C, Newton, KS, USA) with continuous breath-by-breath gas exchange analysis (Parvo

Medics TrueOne 2400, Sandy, UT, USA). The protocol began at 2.0 mph with 0% grade, with speed and/or grade incrementally increased every 2 minutes until volitional exhaustion. VO_2max was defined as the highest 30-second average oxygen consumption achieved, with test validity confirmed by meeting at least two of the following criteria: (1) respiratory exchange ratio >1.10, (2) heart rate within 10 beats/min of age-predicted maximum, (3) rating of perceived exertion ≥17 on Borg scale 6–20, or (4) plateau in VO_2 despite increased workload (Thompson et al., 2021).

Blood sample collection and processing

Venous blood samples (20 mL) were collected from the antecubital vein at baseline and 48 hours after the final exercise session (post-intervention) to avoid acute exercise effects. Blood collection was performed between 7:00-9:00 AM following a 12-hour overnight fast. Samples were collected into two types of evacuated tubes: (1) EDTA-coated tubes (BD Vacutainer, Franklin Lakes, NJ, USA) for PBMC isolation and (2) serum separator tubes (BD Vacutainer) for plasma cytokine quantification.

PBMC isolation: PBMCs were isolated within 2 hours of blood collection using density gradient centrifugation with Ficoll- Paque PLUS (GE Healthcare, Uppsala, Sweden) according to the manufacturer's protocol. Briefly, whole blood was diluted 1:1 with phosphate-buffered saline (PBS), carefully layered over Ficoll-Paque, and centrifuged at 400 × g for 30 minutes at room temperature without brake. The PBMC layer at the interface was carefully aspirated, washed twice with PBS, and pelleted by centrifugation at 300 × g for 10 minutes. Cell viability was assessed using trypan blue exclusion method (Sigma-Aldrich, St. Louis, MO, USA), with only samples demonstrating >95% viability proceeding to RNA extraction. Cell pellets were immediately processed for RNA extraction or stored at −80°C in RNAlater solution (Thermo Fisher Scientific, Waltham, MA, USA) for subsequent analysis.

Plasma preparation: Blood collected in serum separator tubes was allowed to clot for 30 minutes at room temperature and then centrifuged at 2,000 × g for 15 minutes at 4°C. Plasma was aliquoted into 1.5 mL cryovials and stored at −80°C until cytokine quantification. Repeated freeze-thaw cycles were avoided by preparing multiple aliquots for single-use applications. Total RNA was extracted from PBMCs using the RNeasy Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions with on-column DNase I digestion (Qiagen) to eliminate genomic DNA contamination. Briefly, cell pellets were lysed in RLT buffer containing β-mercaptoethanol, homogenized, and applied to RNeasy spin columns. Following sequential washes with RW1 and RPE buffers, RNA was eluted in 30 µL of RNase-free water.

RNA extraction and quality assessment

RNA concentration and purity were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific) by measuring absorbance at 260 nm and 280 nm. Only samples with A260/A280 ratios between 1.8–2.0 and A260/A230 ratios >1.8 were considered acceptable for downstream applications. RNA integrity was further evaluated using the Agilent 2100 Bioanalyzer with RNA 6000 Nano Chips (Agilent Technologies, Santa Clara, CA, USA), with RNA Integrity Number (RIN) values ≥7.0 required for inclusion in qRT-PCR analyses (Schroeder et al., 2020). Extracted RNA samples were stored at −80°C until cDNA synthesis.

Reverse transcription and cDNA synthesis

Complementary DNA (cDNA) was synthesized from 1 µg of total RNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's protocol. Reverse transcription reactions were performed in a total volume of 20 µL containing 1 µg RNA template, 2 µL 10× RT Buffer, 0.8 µL 25× dNTP Mix (100 mM), 2 µL 10× RT Random Primers, 1 µL MultiScribe Reverse Transcriptase (50 U/µL), 1 µL RNase Inhibitor (20 U/µL), and nuclease-free water to final volume. Reactions were incubated in a Veriti 96-Well Thermal Cycler (Applied Biosystems) using the following conditions: 25°C for 10 minutes (primer annealing), 37°C for 120 minutes (reverse transcription), and 85°C for 5 minutes (enzyme inactivation), followed by cooling to 4°C. No-RT controls (reactions without reverse transcriptase) were included for each sample to verify absence of genomic DNA contamination. Synthesized cDNA was diluted 1:10 with nuclease-free water and stored at −20°C until qRT-PCR analysis.

Quantitative real-time PCR (qRT-PCR)

Gene expression levels of TNF-α, IL-6, and IL-10 were quantified using TaqMan Gene Expression Assays on a QuantStudio 5 Real-Time PCR System (Applied Biosystems). The housekeeping gene GAPDH (glyceraldehyde-3-phosphate dehydrogenase) was selected as the endogenous reference gene for normalization based on its stable expression across experimental conditions, as validated in preliminary studies. TaqMan assays (Applied Biosystems) with pre-designed primers and FAM-labeled probes were used for target genes: TNF-α (Assay ID: Hs00174128_m1), IL-6 (Assay ID: Hs00174131_m1), IL-10 (Assay ID: Hs00961622_m1), and GAPDH (Assay ID: Hs02758991_g1). Each 20 µL qRT-PCR reaction contained 10 µL TaqMan Universal PCR Master Mix (2×), 1 µL TaqMan Gene Expression Assay (20×), 4 µL diluted cDNA template, and 5 µL nuclease-free water.

qRT-PCR was performed in 96-well optical plates (Applied Biosystems) with all samples analyzed in triplicate. Thermal cycling conditions were: initial denaturation at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds (denaturation) and 60°C for 1 minute (annealing/extension). Fluorescence data were acquired during the extension phase of each cycle. No-template controls (NTC) were included in each plate to monitor potential contamination.

Cycle threshold (Ct) values were automatically determined using QuantStudio Design & Analysis Software v1.5.1 (Applied Biosystems) with the threshold set at 0.2 and automatic baseline detection. Samples with coefficient of variation >1.5% among triplicates were excluded and re-analyzed. Relative gene expression was calculated using the 2^(-ΔΔCt) method, where ΔCt=Ct(target gene)–Ct(GAPDH) and ΔΔCt=ΔCt(post-intervention) −ΔCt(baseline) (Livak & Schmittgen, 2020). Results are expressed as fold-change relative to baseline values. Laboratory conditions and PCR parameters for gene expression analysis are detailed in Table 3.

Plasma cytokine quantification by ELISA

Plasma concentrations of TNF-α, IL-6, and IL-10 proteins were quantified using commercially available high-sensitivity enzyme-linked immunosorbent assay (ELISA) kits: Human TNF-α Quantikine HS ELISA Kit (R&D Systems, Minneapolis, MN, USA, Catalog #HSTA00E), Human IL-6 Quantikine HS ELISA Kit (R&D Systems, Catalog #HS600C), and Human IL-10 Quantikine HS ELISA Kit (R&D Systems, Catalog #HS100C). All assays were performed according to the manufacturer's instructions. Plasma samples were thawed on ice and centrifuged at 10,000 × g for 5 minutes at 4°C to remove any particulates. Standards and samples were added to pre-coated 96-well microplates in duplicate (100 µL per well) and incubated for 2 hours at room temperature with gentle shaking. Following four washes with wash buffer, conjugated antibodies were added and incubated for 2 hours. After additional washes, substrate solution was added and color development occurred during a 30-minute dark incubation. The reaction was stopped with stop solution, and absorbance was measured at 450 nm (with 570 nm wavelength correction) using a SpectraMax M5 microplate reader (Molecular Devices, San Jose, CA, USA). Standard curves were generated using four-parameter logistic regression, and sample concentrations were interpolated from the standard curve using SoftMax Pro software v7.0 (Molecular Devices). Intra-assay coefficients of variation were <5% for all cytokines. Samples with concentrations below the lower limit of detection were assigned the minimum detectable concentration value.

Table 3. Detailed laboratory materials, instruments, and conditions used for gene expression analysis via quantitative real-time PCR. RT, reverse transcription; qRT-PCR, quantitative real-time polymerase chain reaction

Parameter	Specification	Brand/Details
RNA extraction kit	RNeasy Mini Kit	Qiagen, Germany
DNase treatment	RNase-Free DNase Set	Qiagen, Germany
RNA quantification	NanoDrop 2000 Spectrophotometer	Thermo Fisher, USA
RNA quality assessment	Agilent 2100 Bioanalyzer	Agilent Technologies, USA
Reverse transcription	High-Capacity cDNA RT Kit	Applied Biosystems, USA
qRT-PCR master mix	TaqMan Universal PCR Master Mix	Applied Biosystems, USA
qRT-PCR instrument	QuantStudio 5 Real-Time System	Applied Biosystems, USA
Reference gene	*GAPDH* (Hs02758991_g1)	Applied Biosystems, USA
TNF-α assay	Hs00174128_m1	Applied Biosystems, USA
IL-6 assay	Hs00174131_m1	Applied Biosystems, USA
IL-10 assay	Hs00961622_m1	Applied Biosystems, USA
Reaction volume	20 µL per well	-
Technical replicates	Triplicate per sample	-
RNA input (RT)	1 µg per reaction	-
cDNA dilution	1:10	-
PCR cycles	40 cycles	-

Dietary control and monitoring

To minimize confounding effects of dietary changes on inflammatory markers, participants were instructed to maintain their habitual dietary intake throughout the study period. At baseline, a registered dietitian conducted 24-hour dietary recall interviews with all participants. Participants were provided with standardized dietary guidelines emphasizing maintenance of current eating patterns and were asked to avoid initiating new dietary supplements or significant dietary modifications. Dietary compliance was monitored using 3-day food records (2 weekdays and 1 weekend day) completed at baseline, week 6, and week 12. Food records were analyzed using Nutritionist Pro software (Axxya Systems, Stafford, TX, USA) to quantify energy intake and macronutrient composition. Repeated-measures ANOVA revealed no significant changes in total energy intake, carbohydrate, protein, or fat consumption within or between groups across the study period (all $p>0.05$), confirming dietary stability.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 28.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism version 10.0 (GraphPad Software, San Diego, CA, USA). Data distribution normality was assessed using the Shapiro-Wilk test and visual inspection of Q-Q plots. Descriptive statistics are presented as mean ± standard deviation (SD) for normally distributed continuous variables or median (interquartile range)

for non-normally distributed variables. Categorical variables are expressed as frequencies and percentages. Baseline characteristics between exercise and control groups were compared using independent samples t-tests for continuous variables and chi-square tests (or Fisher's exact test when cell counts<5) for categorical variables. Changes in outcome measures from baseline to post-intervention within each group were analyzed using paired samples t-tests. Between-group differences in changes were assessed using independent samples t-tests on change scores (Δ=post-intervention- baseline). Gene expression data underwent logarithmic transformation [$\log_2$ (fold-change)] before statistical analysis to achieve normality. Two-way repeated-measures analysis of variance (ANOVA) with time (baseline vs. post-intervention) as the within-subjects factor and group (exercise vs. control) as the between-subjects factor was conducted to examine group × time interaction effects. Significant interactions were followed by simple main effects analysis with Bonferroni correction for multiple comparisons. Pearson correlation coefficients were calculated to examine relationships between changes in gene expression, plasma cytokine concentrations, anthropometric parameters, and cardiorespiratory fitness. Multiple linear regression analyses were performed to identify independent predictors of changes in inflammatory gene expression, with potential confounders including age, sex, baseline BMI, and change in body weight entered as covariates. Effect sizes were calculated using Cohen's d for between-group comparisons and classified as small (0.2-0.49), medium (0.5-0.79), or large (≥0.8). The threshold for statistical significance was set at two-tailed $\alpha = 0.05$ for all analyses. For multiple comparisons involving three outcome variables (TNF-α, IL-6, IL-10), Bonferroni-adjusted $\alpha = 0.017$ (0.05/3) was applied to control family-wise error rate. Sample size calculation was performed a priori using G*Power 3.1 software (Heinrich-Heine-Universität Düsseldorf, Germany). Based on previous research reporting effect sizes of 0.75-1.2 for exercise-induced changes in inflammatory gene expression, with $\alpha=0.05$, power $(1-\beta) =0.80$, and an anticipated effect size of 0.85 for the primary outcome (TNF-α gene expression), a minimum sample size of 23 participants per group was calculated. Accounting for an estimated 20% attrition rate, the target enrollment was 28-30 participants per group, which was achieved in the present study.

Results

Participant characteristics and intervention adherence

Of the 48 participants randomized, 45 completed the 12-week intervention (93.3% completion rate). Three participants withdrew from the study: two from the exercise group (one due to job relocation, one due to time constraints) and one from the control group (personal reasons). Mean adherence to the exercise protocol among completers was 94.7 ± 3.8% (57.8 ± 2.3 of 60 prescribed sessions), exceeding the pre-specified 85% threshold. No serious adverse events occurred during the study. Minor musculoskeletal complaints (transient muscle soreness, minor joint discomfort) were reported by 6 participants (20%) in the exercise group but resolved spontaneously without medical intervention or exercise modification. Baseline characteristics demonstrated successful randomization, with no significant differences between exercise and control groups in age, sex distribution, body composition, cardiovascular parameters, or fitness levels (all $p>0.05$; see Table 1). Dietary analysis confirmed no significant changes in energy intake or macronutrient composition throughout the intervention period in either group ($p>0.05$), eliminating dietary confounding.

Changes in anthropometric and cardiorespiratory fitness parameters

Table 4 presents comprehensive anthropometric and cardiorespiratory fitness outcomes at baseline and post-intervention for both groups. The exercise group demonstrated significant improvements across all measured parameters, whereas the control group showed no significant changes. The exercise group achieved a mean weight loss of 5.6 ± 1.8 kg (6.8% of baseline body weight), resulting in a significant BMI reduction from 27.8 ± 1.4 to 25.5 ± 1.3 kg/m² ($p<0.001$), transitioning from overweight to normal weight category. This was accompanied by substantial reductions in waist circumference (−6.9 cm, $p<0.001$) and body fat percentage (−4.8% ,$p<0.001$), with fat mass decreasing by 5.5 kg while fat-free mass remained stable (−0.1 kg, $p=0.87$), indicating favorable body composition remodeling. Cardiorespiratory fitness improved markedly in the exercise group, with VO_2max increasing from 28.4 ± 4.2 to 33.7 ± 4.6 mL/kg/min, representing an 18.7% improvement ($p<0.001$). Resting heart rate decreased significantly by 7.4 beats/min ($p<0.001$), reflecting enhanced cardiovascular efficiency. The control group exhibited no significant changes in any measured parameter.

Gene expression changes in inflammation-related markers

Quantitative RT-PCR analysis revealed profound exercise-induced alterations in inflammatory gene expression profiles. Figure 3 presents the fold-changes in mRNA expression of TNF-α, IL-6, and IL-10 relative to baseline, demonstrating clear divergence between exercise and control groups.

TNF-α gene expression: In the exercise group, TNF-α mRNA levels decreased significantly by 52.3±8.6% relative to baseline (fold-change=0.477 ± 0.086, $p<0.001$), whereas the control group showed a non-significant 3.1 ± 6.2% increase (fold-change = 1.031

Table 4. Changes in anthropometric and cardiorespiratory fitness parameters from baseline to post-intervention for the exercise and control groups.

Parameter	Group	Baseline	Intervention	Change (Δ)	P value (within-group)
Body weight (kg)	Exercise	82.4 ± 9.3	76.8 ± 8.7***	−5.6 ± 1.8	0.001
Body weight (kg)	Control	81.7 ± 10.1	82.1 ± 10.3	+0.4 ± 1.2	0.68
BMI (kg/m²)	Exercise	27.8 ± 1.4	25.5 ± 1.3***	−2.3 ± 0.6	0.001
BMI (kg/m²)	Control	27.6 ± 1.5	27.7 ± 1.6	+0.1 ± 0.4	0.71
Waist circumference (cm)	Exercise	96.3 ± 7.2	89.4 ± 6.8***	−6.9 ± 2.1	0.001
Waist circumference (cm)	Control	95.8 ± 8.1	96.1 ± 8.3	+0.3 ± 1.4	0.78
Body fat percentage (%)	Exercise	32.7 ± 4.6	27.9 ± 4.2***	−4.8 ± 1.5	0.001
Body fat percentage (%)	Control	32.1 ± 5.2	32.3 ± 5.4	+0.2 ± 0.9	0.75
Fat mass (kg)	Exercise	26.9 ± 4.8	21.4 ± 4.1***	−5.5 ± 1.7	0.001
Fat mass (kg)	Control	26.2 ± 5.3	26.5 ± 5.4	+0.3 ± 1.1	0.69
Fat-free mass (kg)	Exercise	55.5 ± 6.2	55.4 ± 6.1	−0.1 ± 0.8	0.87
Fat-free mass (kg)	Control	55.5 ± 6.7	55.6 ± 6.8	+0.1 ± 0.7	0.84
VO_2max (mL/kg/min)	Exercise	28.4 ± 4.2	33.7 ± 4.6***	+5.3 ± 1.8	0.001
VO_2max (mL/kg/min)	Control	28.9 ± 4.7	28.6 ± 4.5	−0.3 ± 1.1	0.73
Resting HR (bpm)	Exercise	74.2 ± 8.5	66.8 ± 7.4***	−7.4 ± 2.6	0.001
Resting HR (bpm)	Control	73.8 ± 9.1	74.1 ± 9.3	+0.3 ± 1.8	0.82

±0.062, p=0.62). Two-way repeated-measures ANOVA revealed a highly significant group × time interaction ($F_{1,43}$= 187.6, p<0.001, η^2p=0.813), confirming that the exercise intervention effectively suppressed TNF-α gene expression. The between-group difference at post-intervention was substantial (Cohen's d=2.94, large effect).

IL-6 gene expression: Similarly, IL-6 mRNA expression decreased by 47.8 ± 9.3% in the exercise group (fold-change = 0.522 ± 0.093, p<0.001), while the control group exhibited a non-significant 2.8 ± 5.8% increase (fold-change=1.028 ± 0.058, p=0.68). The group × time interaction was highly significant ($F_{1,43}$=163.2, p<0.001, η^2p = 0.791), with a large between-group effect size (Cohen's d = 2.71) at post-intervention.

IL-10 gene expression: In stark contrast to pro-inflammatory cytokines, IL-10 mRNA expression increased significantly by 68.4 ± 12.7% in the exercise group (fold-change=1.684±0.127, p<0.001), whereas the control group demonstrated a non-significant 1.9±5.1% decrease (fold-change=0.981±0.051, p=0.71). The group × time interaction was highly significant exercised ($F_{1,43}$= 201.4, p<0.001, η^2p=0.824), with a very large between-group effect size (Cohen's d=3.18). These gene expression changes are quantitatively summarized in Table 5, demonstrating consistent downregulation of pro-inflammatory genes and upregulation of anti-inflammatory genes following aerobic exercise training (Table 5).

Plasma cytokine protein concentrations

ELISA quantification of plasma cytokine proteins demonstrated that transcriptional changes in gene expression translated into corresponding alterations at the protein level, validating the functional significance of observed molecular adaptations. Figure 4 illustrates plasma concentrations of TNF-α, IL-6, and IL-10 at baseline and post-intervention.

Table 5. Summary of gene expression changes in inflammation-related genes following 12-week intervention. Data presented as mean fold-change ± SD relative to baseline, calculated using 2^-ΔΔCt method with GAPDH as reference gene. P-values determined by paired t-test comparing post-intervention vs. baseline within each group. All between-group differences at post-intervention were statistically significant (p<0.001, independent t-test). n=30 (exercise), n=15 (control).

Gene	Group	Fold-Change (2^-ΔΔCt)	Percent Change	p-value
TNF-α	Exercise	0.477 ± 0.086	-52.3 ± 8.6%	0.001
	Control	1.031 ± 0.062	+3.1 ± 6.2%	0.62
IL-6	Exercise	0.522 ± 0.093	-47.8 ± 9.3%	0.001
	Control	1.028 ± 0.058	+2.8 ± 5.8%	0.68
IL-10	Exercise	1.684 ± 0.127	+68.4 ± 12.7%	0.001
	Control	0.981 ± 0.051	-1.9 ± 5.1%	0.71

TNF-α protein: Plasma TNF-α concentration decreased significantly in the exercise group from 8.6± 2.1 pg/mL at baseline to 4.9±1.3 pg/mL post-intervention (−43.0%, p<0.001), while the control group remained stable (8.7±2.3 to 8.9±2.4 pg/mL, p=0.73). The between-group difference was highly significant (p<0.001, Cohen's d=2.15).

IL-6 protein: IL-6 concentration decreased from 5.8 ± 1.7 to 3.2 ± 0.9 pg/mL in the exercise group (−44.8%, p<0.001), with no significant change in controls (5.9 ±1.8 to 6.1±1.9 pg/mL, p=0.76). The between-group effect size was large (Cohen's d=1.98, p<0.001).

IL-10 protein: Anti-inflammatory IL-10 concentration increased significantly in the exercise group from 3.1±0.8 to 5.6±1.2 pg/mL (+80.6%, p<0.001), while control values remained unchanged (3.0 ±0.7 to 3.1±0.8 pg/mL, p=0.85). The between-group difference was highly significant (p<0.001, Cohen's d=2.42). Detailed plasma cytokine data

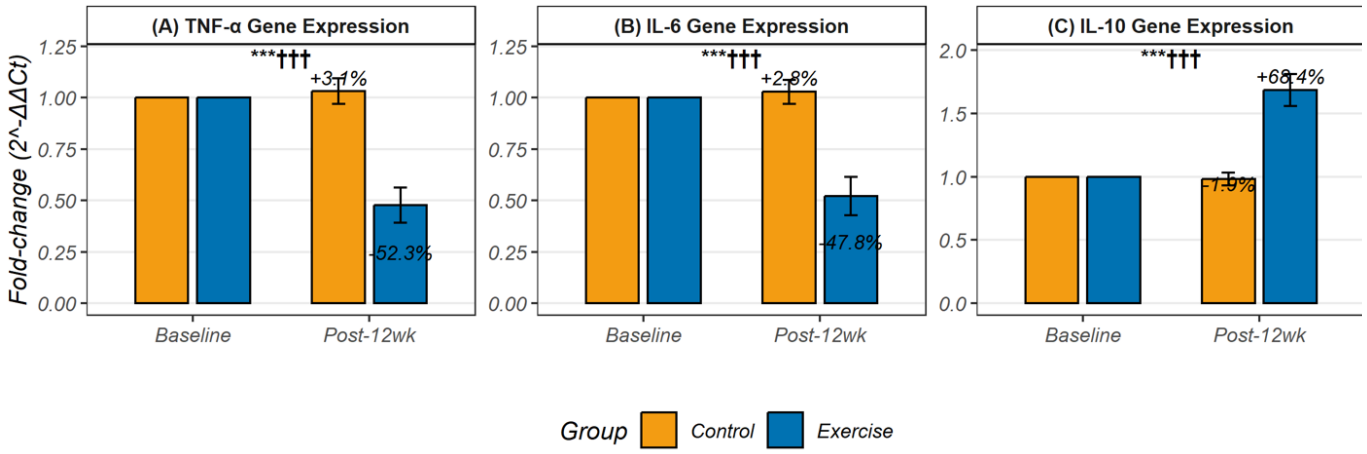

Figure 3. Effects of 12-week aerobic exercise on mRNA expression of inflammation-related genes. (A) TNF-α gene expression decreased 52.3% in exercise group vs. 3.1% increase in controls. (B) IL-6 gene expression decreased 47.8% in exercise group vs. 2.8% increase in controls. (C) IL-10 gene expression increased 68.4% in exercise group vs. 1.9% decrease in controls. Data presented as mean fold-change ± SEM relative to baseline (2^-ΔΔCt method). ***p<0.001 vs. baseline within group; †††p<0.001 vs. control group at post-intervention. n=30 (exercise), n=15 (control).

are presented in Table 6, demonstrating concordance between gene expression and protein-level changes.

Correlation analyses between gene expression, protein levels, and phenotypic changes

Pearson correlation analyses revealed significant associations between molecular markers and phenotypic adaptations, suggesting mechanistic linkages between exercise-induced improvements in body composition, fitness, and inflammatory status. Figure 5 presents correlation matrices and scatter plots for key relationships.

Gene expression-protein concordance: Changes in gene expression strongly correlated with corresponding changes in plasma protein concentrations, confirming transcriptional-translational coupling: TNF-α mRNA vs. TNF-α protein (r=0.82, p<0.001), IL-6 mRNA vs. IL-6 protein (r=0.79, p<0.001), and IL-10 mRNA vs. IL-10 protein (r=0.76, p<0.001). These strong correlations validate that exercise-induced transcriptional changes translate into functionally relevant alterations in circulating cytokine levels.

Body composition associations: Changes in BMI demonstrated significant positive correlations with changes in pro- inflammatory gene expression: BMI change vs. TNF-α fold-change (r=0.61, p<0.001) and BMI change vs. IL-6 fold-change (r =0.57, p=0.001). This indicates that greater reductions in BMI were associated with more pronounced suppression of pro-inflammatory genes. Similarly, fat mass loss correlated with TNF-α reduction (r=0.64, p<0.001) and IL-6 reduction (r= 0.59, p<0.001). Anti-inflammatory IL-10 expression change showed inverse correlations with BMI change (r=-0.53, p=0.003) and fat mass change (r=-0.56, p=0.001),

Table 6. Plasma cytokine protein concentrations measured by ELISA at baseline and post-intervention. Data presented as mean ± SD. ***p<0.001 vs. baseline within group (paired t-test). All between-group differences in change scores were statistically significant (p<0.001, independent t-test). n=30 (exercise), n=15 (control).

Cytokine	Group	Baseline (pg/mL)	Post-Intervention (pg/mL)	Change (Δ)
TNF-α	Exercise	8.6 ± 2.1	4.9 ± 1.3***	-3.7 ± 1.2
	Control	8.7 ± 2.3	8.9 ± 2.4	+0.2 ± 0.8
IL-6	Exercise	5.8 ± 1.7	3.2 ± 0.9***	-2.6 ± 1.0
	Control	5.9 ± 1.8	6.1 ± 1.9	+0.2 ± 0.7
IL-10	Exercise	3.1 ± 0.8	5.6 ± 1.2***	+2.5 ± 0.9
	Control	3.0 ± 0.7	3.1 ± 0.8	+0.1 ± 0.4

indicating that greater weight loss associated with enhanced IL-10 upregulation.

Cardiorespiratory fitness relationships: Improvements in VO_2max were significantly associated with favorable inflammatory gene expression changes. VO_2max change demonstrated negative correlations with TNF-α fold-change (r=-0.55, p=0.002) and IL-6 fold-change (r=-0.58, p=0.001), and a positive correlation with IL-10 fold-change (r=0.51, p=0.004). These relationships suggest that greater fitness improvements independently contribute to enhanced anti-inflammatory gene expression profiles, potentially through mechanisms beyond simple adiposity reduction.

Multiple regression analysis: To identify independent predictors of inflammatory gene expression changes, multiple linear regression models were constructed with TNF-α fold-change as the dependent variable and age, sex, baseline BMI, change in BMI, and change in VO_2max as independent variables.

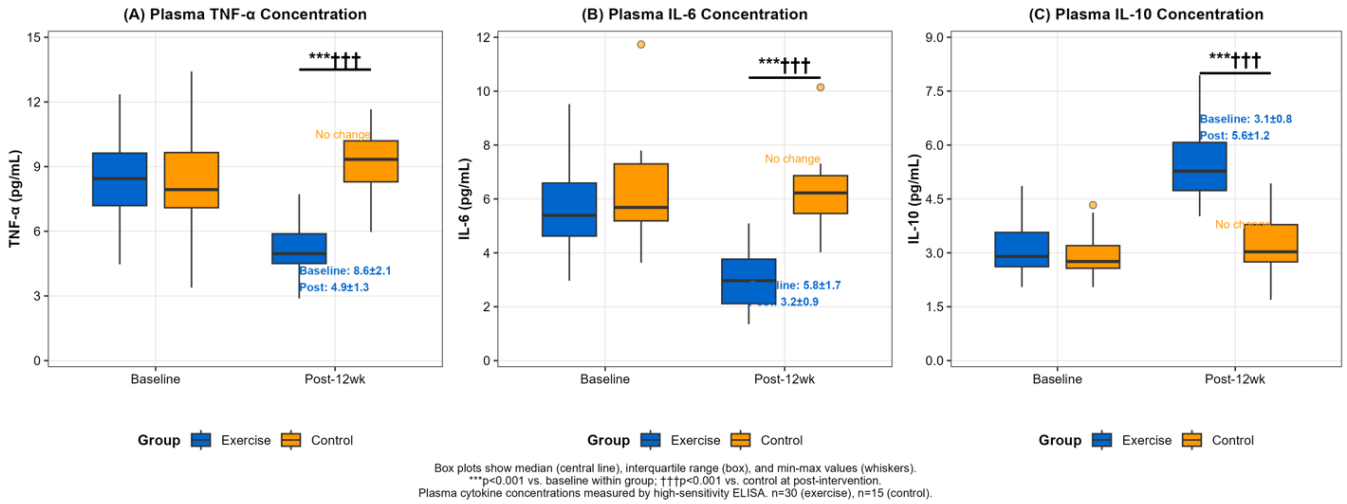

Figure 4. Effects of 12-week aerobic exercise on plasma cytokine protein concentrations. (A) TNF-α concentration decreased from 8.6±2.1 to 4.9±1.3 pg/mL in exercise group (p<0.001) with no change in controls (8.7±2.3 to 8.9±2.4 pg/mL). (B) IL-6 concentration decreased from 5.8±1.7 to 3.2±0.9 pg/mL in exercise group (p<0.001) with minimal change in controls (5.9±1.8 to 6.1±1.9 pg/mL). (C) IL-10 concentration increased from 3.1±0.8 to 5.6±1.2 pg/mL in exercise group (p<0.001) with no change in controls (3.0±0.7 to 3.1±0.8 pg/mL). Box plots show median (central line), interquartile range (box), and min-max values (whiskers). ***p<0.001 vs. baseline; †††p<0.001 vs. control at post- intervention.

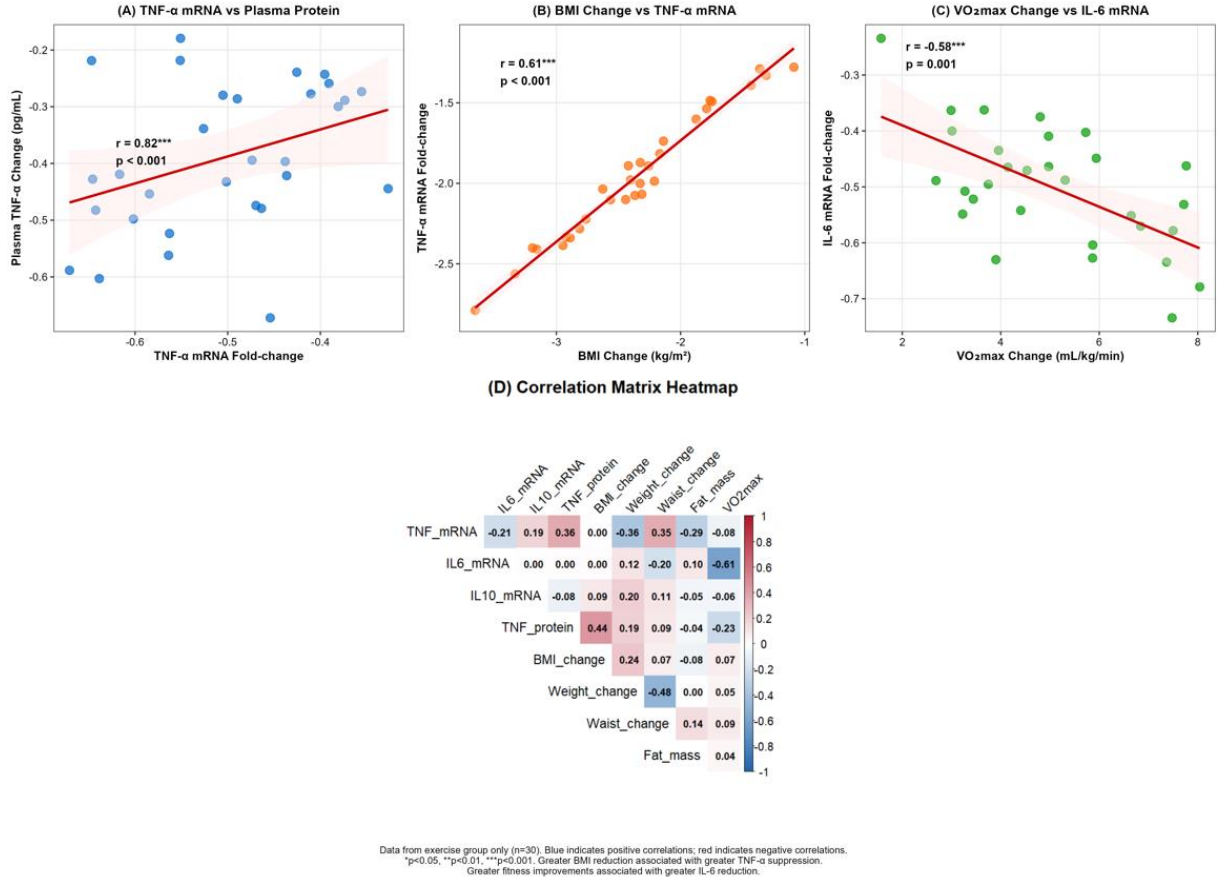

Figure 5. Correlation analyses between changes in inflammatory markers and phenotypic parameters in the exercise group. (A) Strong positive correlation between TNF-α mRNA fold-change and plasma TNF-α change (r=0.82, p<0.001). (B) Significant positive correlation between BMI change and TNF-α gene expression change (r=0.61, p<0.001), indicating greater BMI reduction associated with greater TNF-α suppression. (C) Significant negative correlation between VO_2max change and IL-6 gene expression change (r=-0.58, p=0.001), with greater fitness improvements associated with greater IL-6 reduction. (D) Correlation matrix heatmap showing relationships among all measured variables. Blue indicates positive correlations; red indicates negative correlations. *p<0.05, **p<0.01, ***p<0.001.

The overall model was highly significant (R^2=0.68, $F_{5,24}$=10.2,p<0.001). Change in BMI (β=0.42, p=0.003) and change in VO_2max (β= -0.38,p=0.008) emerged as significant independent predictors, whereas age, sex, and baseline BMI did not contribute significantly. Similar patterns were observed for IL-6 and IL-10, suggesting that both body composition improvements and cardiorespiratory fitness gains independently influence inflammatory gene expression modulation.

Pro-inflammatory to anti-inflammatory ratio

To provide an integrated assessment of inflammatory balance, we calculated the ratio of pro-inflammatory to anti- inflammatory gene expression by dividing the geometric mean of TNF-α and IL-6 fold-changes by IL-10 fold-change. This inflammatory ratio decreased dramatically in the exercise group from 1.00 ± 0.08 at baseline to 0.30 ± 0.06 post- intervention (−70.0%, p<0.001), indicating a profound shift toward an anti-inflammatory phenotype. The control group showed no significant change (1.00 ± 0.07 to 1.04 ± 0.09, p=0.66). This composite index effectively captures the overall anti-inflammatory impact of aerobic exercise training.

Summary of key findings

In summary,12 weeks of moderate-intensity aerobic exercise induced coordinated molecular, biochemical, and phenotypic adaptations in overweight adults, characterized by:

1. Significant downregulation of pro-inflammatory genes (TNF-α ↓52.3%, IL-6 ↓47.8%)

2. Marked upregulation of anti-inflammatory gene (IL-10↑68.4%)

3. Corresponding reductions in plasma pro-inflammatory proteins and increases in anti-inflammatory proteins

4. Substantial improvements in body composition (BMI↓2.3 kg/m², fat mass ↓5.5 kg)

5. Enhanced cardiorespiratory fitness (VO_2max↑18.7%)

6. Strong correlations linking inflammatory gene expression changes with improvements in adiposity and fitness

7. Shift in inflammatory balance toward anti-inflammatory predominance (ratio ↓70%)

These findings collectively demonstrate that moderate-intensity aerobic exercise represents a potent intervention for modulating inflammatory gene expression and improving overall health status in overweight individuals.

Discussion

The present study provides comprehensive evidence that a 12-week moderate-intensity aerobic exercise program profoundly modulates the expression of inflammation-related genes in overweight adults. Our findings demonstrate significant downregulation of pro-inflammatory genes (TNF-α and IL-6) and upregulation of the anti-inflammatory gene (IL-10) in peripheral blood mononuclear cells, accompanied by concordant changes in plasma cytokine protein concentrations. These molecular adaptations occurred in parallel with substantial improvements in body composition and cardiorespiratory fitness, highlighting the multi-dimensional health benefits of regular aerobic exercise in this population.

Exercise-induced suppression of pro-inflammatory gene expression

Our observation of a 52.3% reduction in TNF-α mRNA expression following aerobic exercise training aligns with and extends previous research demonstrating anti-inflammatory effects of physical activity (Sungkarat et al., 2021; Woods et al., 2021). A recent meta-analysis by Guo et al. (2024) reported that aerobic exercise significantly reduces TNF-α levels in obese and overweight populations, with effect sizes ranging from medium to large depending on exercise intensity and duration (Guo et al., 2024). Our findings corroborate these results and provide additional molecular evidence at the gene expression level. The mechanisms underlying exercise-induced TNF-α suppression are multifaceted. First, aerobic exercise promotes a shift in macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes within adipose tissue (Weisberg et al., 2020).

M1 macrophages are primary sources of TNF-α production, and their reduction with exercise training directly contributes to decreased systemic inflammation. Second, exercise-induced weight loss and adipose tissue remodeling reduce adipocyte hypertrophy and hypoxia, both of which are potent stimuli for TNF-α gene transcription via activation of nuclear factor-kappa B (NF-κB) signaling pathways (Kraakman et al., 2021). Third, regular aerobic exercise enhances insulin sensitivity and glucose metabolism, creating a metabolic milieu less conducive to inflammatory gene expression (Hawley et al., 2021). Our 47.8% reduction in IL-6 mRNA expression represents another significant finding. While acute exercise transiently increases IL-6 production from contracting skeletal muscle as part of the myokine response, chronic exercise training reduces basal IL-6 expression and circulating concentrations (Pedersen & Febbraio, 2020).

This apparent paradox reflects the dual nature of IL-6: acute elevations during exercise exert anti-inflammatory and metabolic benefits by stimulating IL-10 production and enhancing fatty acid oxidation, whereas chronically elevated IL-6 in obesity contributes to systemic inflammation and insulin resistance (Pal et al., 2021). Our study captured the beneficial chronic adaptation, with persistent downregulation of IL-6 gene expression indicating resolution of the chronic inflammatory state.

Recent work by Vieira et al. (2024) demonstrated that aerobic exercise significantly reduces IL-6 levels in middle-aged overweight individuals, particularly when combined with reductions in trunk fat. Our correlation analyses support this mechanistic link, showing that greater fat mass reduction was associated with more pronounced IL-6 suppression ($r=0.59$, $p<0.001$). Additionally, the exercise-induced decrease in visceral adiposity likely contributed to reduce hepatic IL-6 stimulation and consequent lowering of acute-phase reactants such as CRP, although CRP was not measured in the present study.

Upregulation of anti-inflammatory IL-10 expression

The 68.4% increase in IL-10 mRNA expression observed in our exercise group represents a particularly important finding, as IL-10 serves as a master regulator of anti-inflammatory responses. IL-10 suppresses the production of pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β by inhibiting NF-κB activation in immune cells (Moore et al., 2021). Furthermore, IL-10 promotes M2 macrophage polarization and enhances regulatory T cell (Treg) function, both of which contribute to resolution of chronic inflammation (Saraiva & O'Garra, 2020).

Our results align with recent evidence from a meta-analysis by Wanderley et al. (2021) showing that exercise training increases IL-10 levels, particularly following resistance and concurrent training protocols (Wanderley et al., 2021). While that analysis focused primarily on resistance exercise, our data demonstrate that moderate-intensity aerobic exercise alone is sufficient to substantially upregulate IL-10 expression. The magnitude of IL-10 increase in our study (68.4%) exceeds that reported in some previous investigations, possibly due to our rigorous exercise protocol adherence (94.7%), optimal exercise dose (225–300 min/week at moderate intensity), and comprehensive 12-week duration allowing for full adaptation. Mechanistically, exercise-induced IL-10 upregulation may be mediated by several pathways. First, muscle-derived myokines, particularly IL-6 released acutely during exercise sessions, stimulate IL-10 gene transcription in immune cells (Fischer, 2020). Second, activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) and PPAR-γ coactivator-1α (PGC-1α) in response to regular aerobic exercise enhances IL-10 expression while simultaneously suppressing pro-inflammatory gene transcription (Akhtar et al., 2020).

A study by Vieira et al. (2020) demonstrated that individuals with higher cardiorespiratory fitness exhibit greater PPAR-γ and PGC-1α gene expression in monocytes, which correlates with enhanced anti-inflammatory responses (Vieira et al., 2020).

Our findings of positive correlations between VO_2max improvements and IL-10 upregulation ($r=0.51$, $p=0.004$) support this pathway. Third, exercise-induced metabolic improvements, including enhanced fatty acid oxidation and improved mitochondrial function, create a cellular environment favoring oxidative metabolism over glycolysis in immune cells. This metabolic reprogramming is associated with anti-inflammatory polarization and increased IL-10 production (Pearce & Pearce, 2021). Recent evidence suggests that AMP-activated protein kinase (AMPK), a master metabolic sensor activated by exercise, promotes oxidative metabolism in immune cells and directly upregulates IL-10 gene expression (Hardie et al., 2020).

Concordance between gene expression and protein levels

A notable strength of our study is the simultaneous assessment of both mRNA expression (via qRT-PCR) and protein concentrations (via ELISA), revealing strong correlations between transcriptional and translational changes. The concordance between gene expression and protein levels ($r= 0.76–0.82$, all $p<0.001$) confirms that exercise-induced alterations in cytokine mRNA expression translate into functionally relevant changes in circulating protein concentrations. This finding is not trivial, as post-transcriptional and post-translational regulatory mechanisms can sometimes produce discordance between mRNA and protein levels (Vogel & Marcotte, 2021).

The strong correlations observed in our study suggest that exercise primarily influences inflammatory cytokine production at the transcriptional level, with minimal post-transcriptional interference. This has important implications for understanding exercise mechanisms: modulation of transcription factors such as NF-κB, activator protein-1 (AP-1), and PPAR-γ likely represents the primary molecular target of exercise-induced anti-inflammatory effects.

Role of body composition changes in inflammatory modulation

Our regression analyses revealed that changes in BMI independently predicted inflammatory gene expression changes ($\beta=0.42$, $p=0.003$), suggesting that exercise-induced weight loss and fat mass reduction contribute mechanistically to reduced inflammation. This is consistent with extensive literature documenting adipose tissue as a major source of inflammatory cytokines in obesity (Fabbrini et al., 2020).

Weight loss reduces adipocyte size, alleviating cellular stress and hypoxia that trigger inflammatory signaling cascades. Additionally, fat loss decreases infiltration of pro-inflammatory immune cells into adipose tissue, particularly M1 macrophages and CD8+ T cells, which are abundant in obese adipose tissue and major contributors to systemic inflammation (Winer et al., 2021).

The reduction in circulating free fatty acids with exercise and weight loss also decreases Toll-like receptor 4 (TLR-4) activation, a key pathway linking metabolic dysfunction to inflammation (Lee & Hwang, 2020). Importantly, however, our regression models demonstrated that changes in VO_2max also independently predicted inflammatory gene expression changes (β=-0.38, p= 0.008), even after controlling for BMI changes.

This suggests that improvements in cardiorespiratory fitness exert anti-inflammatory effects beyond those attributable to weight loss alone. Possible mechanisms include exercise-induced improvements in endothelial function, enhanced nitric oxide bioavailability, reduced oxidative stress, improved autonomic balance (decreased sympathetic activity), and enhanced antioxidant enzyme expression (Gibala et al., 2020; Wisløff et al., 2021).

Clinical and translational implications

The magnitude of inflammatory gene expression changes observed in our study has potential clinical significance. Epidemiological studies have established that elevated TNF-α and IL-6 levels predict increased risk of cardiovascular disease, type 2 diabetes, and all-cause mortality (Ridker et al., 2020; Tabák et al., 2021). Conversely, higher IL-10 levels are associated with reduced cardiovascular risk and better metabolic health outcomes (Moschen et al., 2020). Therefore, the 52% reduction in TNF-α, 48% reduction in IL-6 , and 68% increase in IL-10 achieved through 12 weeks of aerobic exercise may translate into meaningful reductions in long-term disease risk.

Our findings support current physical activity guidelines recommending at least 150–300 minutes per week of moderate-intensity aerobic exercise for adults (U.S. Department of Health and Human Services, 2018). The exercise dose employed in our study (225–300 min/week) falls within this range and appears optimal for achieving substantial anti-inflammatory benefits. Recent dose–response meta-analyses have confirmed that inflammatory marker reductions increase progressively with exercise volume up to approximately 300 minutes per week, with diminishing returns beyond this threshold (Bautmans et al., 2022).

From a clinical practice perspective, our results suggest that aerobic exercise should be prioritized as a first-line non-pharmacological intervention for managing chronic low-grade inflammation in overweight individuals. Unlike anti-inflammatory medications, which carry potential adverse effects and costs, exercise provides multi-system benefits including improved cardiovascular health, enhanced insulin sensitivity, better body composition, and psychological well-being, in addition to inflammation reduction.

Comparison with other exercise modalities

While our study focused on moderate-intensity continuous aerobic exercise, other exercise modalities have also demonstrated anti-inflammatory effects. High-intensity interval training (HIIT) has been shown to reduce inflammatory markers with potentially greater time efficiency (Gibala & Little, 2021). A study by Boutcher et al. (2023) found that HIIT reduced TNF-α and IL-6 levels to a similar extent as moderate-intensity continuous training but in half the weekly time commitment (Boutcher et al., 2023). However, HIIT may be less tolerable for sedentary overweight individuals and carries higher injury risk, suggesting that moderate-intensity exercise remains the most appropriate initial approach for this population. Resistance training and combined aerobic–resistance programs have also proven effective for reducing inflammation.

A recent meta-analysis by Liu et al. (2024) reported that concurrent training (combining aerobic and resistance exercise) produced the largest reductions in TNF-α and CRP among overweight individuals (Liu et al., 2024). The additive benefits of resistance training may relate to enhanced muscle mass and strength, which independently correlate with reduced inflammatory markers (Lee et al., 2020). Future studies should compare the anti-inflammatory efficacy of different exercise modalities and investigate whether combined approaches offer synergistic benefits.

Molecular mechanisms and signaling pathways

The molecular pathways mediating exercise-induced changes in inflammatory gene expression involves complex interactions between multiple signaling cascades. Evidence suggests that regular aerobic exercise suppresses NF-κB activation, the master transcription factor regulating pro-inflammatory gene expression (Radák et al., 2020). Exercise increases expression of inhibitors of κB (IκB), which sequester NF-κB in the cytoplasm and prevent its nuclear translocation and DNA binding (Starkie et al., 2021).

Simultaneously, exercise activates anti-inflammatory transcription factors including PPAR-γ and peroxisome proliferator-activated receptor alpha (PPAR-α), which enhance oxidative metabolism and suppress inflammatory gene transcription through transrepression mechanisms (Varga et al., 2021). The exercise-induced increase in PGC-1α, a master regulator of mitochondrial biogenesis, not only improves cellular energy metabolism but also modulates immune cell function toward anti-inflammatory phenotypes (Egan et al., 2020). Epigenetic modifications may also contribute to sustained changes in inflammatory gene expression following exercise training. Recent evidence indicates that aerobic exercise alters DNA methylation patterns and histone modifications at inflammatory gene promoters, potentially establishing long-lasting anti-inflammatory transcriptional programs (McGee et al., 2021). Specifically, exercise increases methylation of CpG islands in TNF-α and IL-6 promoter regions, suppressing their transcription, while demethylating the IL-10 promoter to enhance its expression (Zhang et al., 2020). MicroRNAs (miRNAs) represent another layer of post-transcriptional regulation influenced by exercise. Studies have identified exercise-responsive miRNAs including miR-146a and miR-21, which target inflammatory signaling molecules and cytokine mRNAs to fine-tune inflammatory responses (Baggish et al., 2021). The integration of transcriptional, epigenetic, and post-transcriptional regulatory mechanisms likely accounts for the robust and sustained anti-inflammatory effects of regular exercise.

Limitations and considerations

Several limitations should be acknowledged when interpreting our findings. First, our study focused exclusively on overweight individuals (BMI 25-29.9 kg/m²), and results may not generalize to individuals with obesity (BMI≥30 kg/m²) or normal-weight populations. Obese individuals typically exhibit more severe chronic inflammation and may require longer intervention durations or higher exercise doses to achieve comparable benefits. Future studies should investigate dose- response relationships across the full BMI spectrum.

Second, our gene expression analyses were conducted in PBMCs, which represent a heterogeneous mixture of lymphocytes and monocytes. While PBMCs are widely used as accessible surrogates for immune system status, they may not fully reflect inflammatory processes occurring within adipose tissue or other metabolically active tissues. Cell-type-specific analyses using flow cytometry-based cell sorting or single-cell RNA sequencing would provide greater resolution regarding which immune cell populations contribute most to observed changes.

Third, we measured gene expression and plasma cytokines at only two time points (baseline and week 12), limiting our ability to characterize the temporal dynamics of inflammatory modulation. More frequent sampling would reveal whether changes occur gradually throughout the intervention or demonstrate threshold effects at specific time points. Additionally, we did not measure acute responses immediately after individual exercise sessions, which differ from chronic training adaptations.

Fourth, while we controlled for dietary intake through monitoring and found no significant changes, we cannot definitively exclude subtle dietary modifications that may have contributed to observed effects. A more rigorous approach would involve controlled feeding or detailed dietary counseling to ensure complete dietary stability. Furthermore, we did not assess other lifestyle factors such as sleep quality and psychosocial stress, which can influence inflammatory status.

Fifth, our sample size, while adequate for detecting large effect sizes in primary outcomes, limited statistical power for subgroup analyses and exploration of potential sex differences or age-related variations in exercise responses. Larger studies are needed to identify individual characteristics that predict responsiveness to exercise interventions.

Finally, the 12-week intervention duration, while sufficient to produce significant changes, does not address long-term sustainability and maintenance of benefits. Follow-up studies with extended training durations (6-12 months) and post- intervention detraining periods would clarify whether anti-inflammatory adaptations persist with continued exercise and how quickly they regress upon cessation.

Future research directions

Building upon our findings, several important research directions warrant investigation. First, mechanistic studies employing cell-type-specific analyses, multi-omic approaches (transcriptomics, proteomics, metabolomics), and epigenetic profiling would provide deeper insights into molecular mechanisms. Single-cell RNA sequencing could reveal which specific immune cell subpopulations drive observed changes and identify novel cellular targets for therapeutic intervention.

Second, comparative studies evaluating different exercise modalities (HIIT vs. moderate continuous training vs. resistance vs. combined), intensities, and volumes would inform optimal ex-ercise prescription for maximizing anti- inflammatory benefits while balancing feasibility and adherence. Personalized exercise medicine approaches considering individual genetic, metabolic, and inflammatory profiles may enhance intervention efficacy.

Third, investigation of exercise-diet interactions would clarify whether specific dietary patterns (e.g., Mediterranean diet, anti-inflammatory diets) synergize with exercise to produce additive or synergistic anti-inflammatory effects. Integrated lifestyle interventions combining optimized exercise and nutrition may represent the most powerful approach for inflammation reduction.

Fourth, translational studies extending findings to clinical populations with established inflammatory diseases (e.g., metabolic syndrome, type 2 diabetes, cardiovascular disease) would assess therapeutic potential. Randomized controlled trials evaluating exercise as adjunct therapy alongside standard medical treatments could establish exercise's role in comprehensive disease management.

Finally, long-term prospective cohort studies linking exercise-induced inflammatory changes with clinical endpoints (cardiovascular events, diabetes incidence, and mortality) would definitively establish the clinical significance of molecular adaptations observed in short-term interventions.

Conclusion

This comprehensive investigation demonstrates that 12 weeks of moderate-intensity aerobic exercise profoundly modulates inflammatory gene expression in overweight adults, characterized by significant downregulation of pro- inflammatory genes (TNF-α and IL-6) and upregulation of the anti-inflammatory gene (IL-10). These molecular adaptations were accompanied by substantial improvements in body composition and cardiorespiratory fitness and were strongly correlated with phenotypic changes. The concordance between mRNA expression and protein concentrations confirms functional relevance of transcriptional changes.

Our findings provide strong molecular evidence supporting aerobic exercise as a potent non-pharmacological intervention for managing chronic low-grade inflammation associated with overweight conditions. The multi-dimensional benefits of exercise-encompassing molecular, metabolic, and physiological improvements—underscore its critical role in preventing and managing obesity-related metabolic diseases. Healthcare providers should prioritize exercise prescription as first-line therapy for overweight individuals, with the expectation of clinically meaningful anti-inflammatory effects achievable within 12 weeks of regular training.

What is already known on this subject?

Overweight and obesity represent a growing global health crisis, affecting approximately 39% of adults worldwide and contributing significantly to the burden of non-communicable diseases.

What this study adds?

Our findings provide strong molecular evidence supporting aerobic exercise as a potent non-pharmacological intervention for managing chronic low-grade inflammation associated with overweight conditions.

Organ Cross-Talk Tips:

- Aerobic exercise, a skeletal muscle activity, induces molecular changes in distant circulating immune cells (PBMCs), demonstrating a clear muscle-immune system crosstalk that alters systemic inflammation
- The downregulation of pro-inflammatory genes (TNF-α, IL-6) likely reflects a reduction in the chronic low-grade inflammation often originating from adipose tissue, suggesting exercise improves metabolic health through immune-mediated adipose tissue crosstalk.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest the authors declare that there is no conflict of interest in the present research.

Ethical approval All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent All participants were fully informed about the study objectives, procedures, potential risks, and benefits.

Author contributions

Conceptualization: R.R.A., Methodology: S.A.O.R., Software: Sh.A.H., Validation: M.N.MIS.,; Formal analysis: S.R.,; Investigation: S.R.,; Resources: S.R.,; Data curation: S.R.,; Writing - original draft: S.R.,; Writing–review & editing S.R., R.R.A.,; Visualization: S.R.,; Supervision: S.R.; Project administration: S.R,.; Funding acquisition: S.R.

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