Impact of Graded Exercise Intensity on Irisin Secretion, Lipid Profile, and Stress in a Prediabetic Population

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Abstract

Background: *Prediabetes is a growing global health concern characterized by impaired metabolic regulation and elevated risk of progression to type 2 diabetes mellitus. Exercise is a cornerstone of non-pharmacological management; however, the acute physiological effects of varying exercise intensities on metabolic and psychological markers in prediabetic individuals remain inadequately defined. This study evaluates the influence of progressively increasing exercise intensity on cholesterol levels, circulating Irisin concentrations, and perceived stress.* ***Methods:*** *Twenty-two sedentary adults with prediabetes completed four laboratory visits involving treadmill exercise at 50%, 60%, 70%, and 80% of predicted maximum heart rate (PMHR). Exercise duration was fixed at 40 minutes for Visits 1 and 2, and adjusted according to tolerance for Visits 3 and 4. Blood samples were collected pre- and post-exercise to assess total cholesterol and Irisin concentrations. Perceived Stress Scale (PSS-10) scores were recorded before and after each session. Paired t-tests compared pre–post changes across visits.* ***Results:*** *Cholesterol levels decreased significantly after all four exercise intensities (Visit 1: −17.5 mg/dL, $p = 0.002$; Visit 2: −14.5 mg/dL, $p = 0.006$; Visit 3: −12.5 mg/dL, $p = 0.009$; Visit 4: −15.9 mg/dL, $p < 0.001$). Irisin concentrations increased following each session, with significant elevations in Visits 1–3 ($p < 0.05$) and a positive, non-significant trend at Visit 4 ($p = 0.051$). Higher intensities elicited larger Irisin responses despite shorter tolerated durations. PSS scores showed no significant quantitative change ($p > 0.05$), although participants reported subjective improvements in mood and relaxation.* ***Conclusion:*** *Increasing exercise intensity elicits acute and clinically meaningful improvements in cholesterol and stimulates Irisin release in adults with prediabetes, even when higher intensities limit exercise duration. While*

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perceived stress scores remained statistically unchanged, subjective well-being improved across sessions. These findings highlight the metabolic value of tailored intensity-based exercise prescriptions in prediabetes management.

Keywords: Prediabetes, Exercise Intensity, Irisin, Cholesterol, Perceived Stress, Metabolic Health, Aerobic Exercise

INTRODUCTION

Prediabetes (PD) represents an intermediate metabolic state characterized by impaired fasting glucose and/or impaired glucose tolerance, placing affected individuals at substantially elevated risk of progression to type 2 diabetes mellitus (T2DM) and cardiometabolic disease (1,2). The global burden of prediabetes continues to rise at an alarming rate, with recent estimates indicating that more than 470 million individuals may be affected by 2030 (3). In South Asian populations, including Pakistan, the prevalence is disproportionately higher owing to genetic susceptibility, central adiposity, sedentary lifestyles, and dietary patterns (4,5). Importantly, the prediabetic phase offers a critical therapeutic window in which lifestyle modification—particularly structured physical activity—can delay or even prevent progression to overt diabetes (6–8).

Exercise contributes to metabolic regulation through mechanisms involving enhanced glucose uptake, improved insulin sensitivity, reductions in circulating lipids, and modulation of inflammatory pathways (9,10). While the benefits of exercise in T2DM and PD are well-established, growing attention has turned to understanding how exercise intensity specifically shapes acute and chronic metabolic responses. Exercise intensity influences substrate utilization, mitochondrial signaling, hormonal release, and cardiometabolic adaptation, yet its optimal level for individuals with prediabetes remains insufficiently defined (11,12). Identifying intensity-dependent physiological responses is therefore essential for refining non-pharmacological interventions in this population.

One emerging biomarker of exercise-induced metabolic regulation is Irisin, a myokine cleaved from the transmembrane protein FNDC5 and released in response to skeletal muscle contraction (13). Irisin has been shown to promote browning of white adipose tissue, enhance thermogenesis, improve lipid metabolism, and augment glucose homeostasis (14,15). Several studies have demonstrated that both acute and chronic exercise increase circulating Irisin levels; however, the magnitude of response appears dependent on exercise modality, duration, and intensity (16,17). Paradoxically, individuals with prediabetes or obesity may exhibit impaired Irisin signaling—sometimes termed "Irisin resistance"—highlighting the importance of exploring how different intensities of exercise modulate its secretion in metabolically vulnerable populations (18).

In addition to metabolic parameters, exercise plays a key role in psychological well-being. The Perceived Stress Scale (PSS) is a validated measure frequently used to assess psychological stress, which itself is implicated in dysregulated cortisol signaling, insulin resistance, and elevated diabetes risk (19,20). Acute bouts of aerobic exercise consistently demonstrate beneficial effects on mood, perceived stress, and emotional regulation (21). Nevertheless, few studies have examined how varying intensities of exercise influence acute stress responses in prediabetic adults, despite stress being a known accelerator of metabolic dysfunction.

Given these gaps, this study investigates the acute effects of progressively increasing exercise intensity on Irisin secretion, cholesterol levels, and perceived stress in adults with prediabetes. Understanding these intensity-dependent responses may help refine exercise prescriptions tailored to metabolic risk profiles, ultimately contributing to more personalized and effective lifestyle interventions.

METHODOLOGY

Study Design

This study employed an experimental crossover laboratory design, using the same cohort of prediabetic participants who previously completed the timing protocol. The intensity protocol comprised four structured visits (Visits 5–8), each separated by a 7-day washout period to minimize carryover effects. All exercise sessions were executed in a controlled skill-lab environment using a motorized treadmill and continuous heart-rate monitoring.

Participants

Twenty-two prediabetic individuals (aged 25–35 years) who completed the first protocol were included. All participants met the original inclusion criteria, which were HbA1c 5.7–6.4%, fasting glucose 100–125 mg/dL, sedentary lifestyle, and no cardiovascular, endocrine, or musculoskeletal disorders. They also remained medication-free and maintained their routine daily activities throughout the study period.

Exercise Intensity Protocol

The protocol was designed to progressively increase cardiovascular load using predicted maximum heart rate (PMHR): $\text{PMHR} = 220 - \text{age}$

In this protocol, exercise intensity was progressively increased across four sequential laboratory visits. During Visit 1, participants exercised at 50% of their predicted maximum heart rate (PMHR) for a full 40-minute session, and all participants were able to complete the entire duration. In Visit 2, intensity was increased to 60% PMHR, again for 40 minutes, with all individuals completing the full exercise period without difficulty. Visit 3 required participants to exercise at 70% PMHR, during which most participants completed 40 minutes, whereas two participants were only able to sustain 30 minutes due to fatigue and breathlessness associated with the higher intensity. During Visit 4, intensity was further increased to 80% PMHR, and as expected in a sedentary prediabetic cohort, most participants were unable to maintain the full 40-minute session, completing only 20–30 minutes depending on individual tolerance and cardiovascular fitness levels. The progressive increase in cardiovascular load across Visits 1–4 allowed the assessment of physiological responsiveness to varying exercise intensities while maintaining participant safety and adherence.

Exercise intensity was continuously monitored through a Garmin heart-rate belt connected to a metabolic analyzer, ensuring participants remained within their prescribed heart-rate bounds (±5%).

Blood Sampling and Biochemical Analysis

Blood was drawn immediately before and 30 minutes after exercise during each visit. Samples were analyzed for: Human Irisin hormone via ELISA (E-EL-H6120) and Total cholesterol via enzymatic colorimetric assay (DiaTech Diagnostics). Sampling, centrifugation, serum separation, and storage at –80°C followed standardized procedures.

Psychological Stress Assessment

Stress was evaluated using the Perceived Stress Scale–10 (PSS-10), administered pre- and post-exercise during each visit. Scores were interpreted as continuous measures of current stress perception.

Statistical Analysis

Paired t-tests were used to compare pre- and post-exercise biochemical values per visit. Significance was set at $p < 0.05$. Mean changes across visits were described to evaluate intensity-dependent response patterns.

Results

A total of 22 participants completed all four intensity-protocol visits. The mean age of the cohort was 34.5 ± 4.14 years, with a slightly higher representation of females (54.5%) compared to males. Baseline anthropometric characteristics indicated an overweight to obese population, with a mean BMI of 30.66 ± 4.41 kg/m², waist circumference of 102.50 ± 12.94 cm, and hip circumference of 105.97 ± 13.14 cm. Glycemic parameters were consistent with prediabetes, reflected by a mean fasting plasma glucose of 112.4 ± 6.8 mg/dL and HbA1c of 5.84 ± 0.14%. All participants reported a sedentary lifestyle, and none were active smokers. A substantial proportion (59.1%) reported a family history of diabetes, aligning with known prediabetes risk profiles. These baseline characteristics support the suitability of the sample for evaluating physiological responses to acute graded-intensity exercise.

Table 1. ***Baseline Demographic and Anthropometric Characteristics of Participants***

Variable	Mean ± SD / n (%)
Age (years)	34.5 ± 4.14
• Male	10 (45.5%)
• Female	12 (54.5%)
Height (cm)	170.3 ± 7.13
Weight (kg)	88.76 ± 15.21
Body Mass Index (kg/m²)	30.66 ± 4.41
Waist Circumference (cm)	102.50 ± 12.94
Hip Circumference (cm)	105.97 ± 13.14
Fasting Plasma Glucose (mg/dL)	112.4 ± 6.8
HbA1c (%)	5.84 ± 0.14
Physical Activity Level	Sedentary (100%)
Smoking Status	0 (0%)
Family History of Diabetes	13 (59.1%)

Cholesterol Response to Increasing Exercise Intensity

Acute bouts of aerobic exercise produced significant reductions in total cholesterol across all four visits (Table 2). During Visit 1 (50% PMHR) and Visit 2 (60% PMHR), all participants successfully completed the full 40-minute exercise session. Post-exercise cholesterol levels were significantly reduced in both sessions (−17.5 mg/dL, $p = 0.002$; −14.5 mg/dL, $p = 0.006$, respectively) (Figure 1A–B).

At higher intensities, completion times varied according to individual stamina. In Visit 3 (70% PMHR), twenty participants completed 40 minutes, while two participants were limited to 30 minutes due to fatigue and breathlessness. Despite this, cholesterol levels again decreased significantly (−12.5 mg/dL, $p = 0.009$) (Figure 1C). The highest exercise intensity, Visit 4 (80% PMHR), elicited the most pronounced exertional fatigue, with most participants tolerating only 20–25 minutes. Nevertheless, this visit demonstrated the greatest reduction in cholesterol (−15.9 mg/dL, $p < 0.001$) (Figure 1D). Collectively, these findings indicate that even when duration is reduced, higher exercise intensities continue to yield favorable acute lipid-modifying effects.

Table 2: ***Cholesterol Levels Before and After Exercise (Visits 1–4)***

Visit	Cholesterol Before (mg/dL)	Cholesterol After (mg/dL)	Mean Difference	p-value
Visit 1	194.5 ± 33	177 ± 16.9	−17.5	0.002
Visit 2	182 ± 23.9	168 ± 11	−14.5	0.006
Visit 3	184 ± 25.6	171 ± 16.9	−12.5	0.009
Visit 4	181 ± 21	165 ± 11	−15.9	<0.001

Table 3: ***Irisin Concentration Before and After Exercise (Visits 1–4)***

Visit	Irisin Before (µIU/mL)	Irisin After (µIU/mL)	Mean Difference	p-value
Visit 1	257 ± 166	326 ± 180	69	0.001
Visit 2	289 ± 177	348 ± 185	59.5	0.013
Visit 3	284 ± 164	362 ± 220	78.1	0.002
Visit 4	283 ± 172	320 ± 193	36.9	0.051

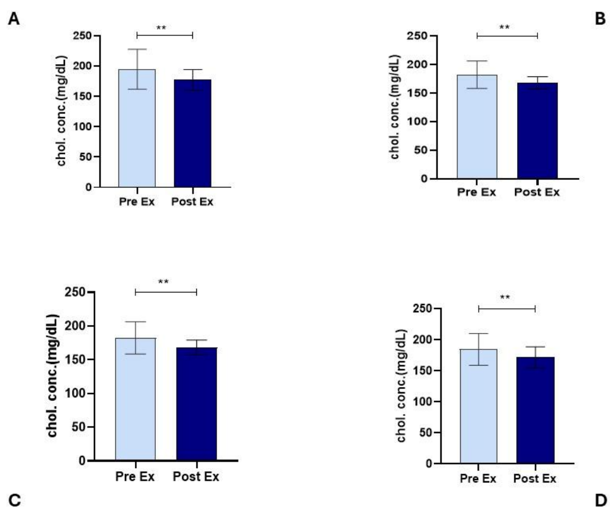

Figure 1: ***Intensity Protocol Cholesterol Concentration***

Panels A–D show cholesterol levels before and after exercise for Visits 1–4. Significant reductions were observed at all intensities ($p < 0.05$, p < 0.005, $p < 0.001$).

Intensity Protocol Human Irisin Concentration

Serum Irisin concentrations increased consistently following each exercise session, with the magnitude of change generally reflective of exercise intensity (Table 3). Significant increases were observed during Visit 1 (50% PMHR) and Visit 2 (60% PMHR), with mean post-exercise elevations of +69.0 µIU/mL ($p = 0.001$) and +59.5 µIU/mL ($p = 0.013$), respectively (Figure 2A–B).

The largest increase occurred in Visit 3 (70% PMHR) (+78.1 µIU/mL, $p = 0.002$) (Figure 2C), coinciding with a higher cardiovascular load. In Visit 4 (80% PMHR), Irisin still increased (+36.9 µIU/mL) but did not reach statistical significance ($p = 0.051$) (Figure 2D). This attenuated response is likely attributable to shortened exercise duration due to participant fatigue rather than the intensity itself. Overall, the pattern demonstrates a robust, intensity-dependent stimulation of Irisin secretion.

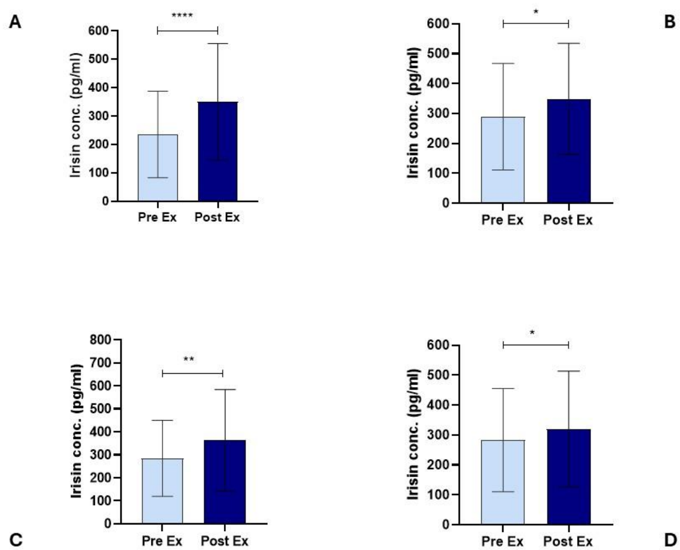

Figure 2: Intensity Protocol Human Irisin Hormone Concentration

Panels A–D illustrate pre- and post-exercise Irisin levels across Visits 1–4. Irisin increased in all visits, with statistically significant elevations in Visits 1–3 ($p < 0.05$, $p < 0.001$).

Pre Ex= before exercise (light bars)

Post Ex= after exercise (dark bars)

Perceived Stress Scale

Perceived Stress Scale (PSS-10) scores were assessed before and after each exercise session across all four visits (Figure 3). No statistically significant differences were observed between pre- and post-exercise scores in any visit ($p > 0.05$). However, participants consistently reported subjective improvements in mood, relaxation, and mental clarity immediately following exercise. These qualitative observations align with established psychological benefits of acute aerobic activity, despite the absence of measurable short-term changes in standardized stress scores.

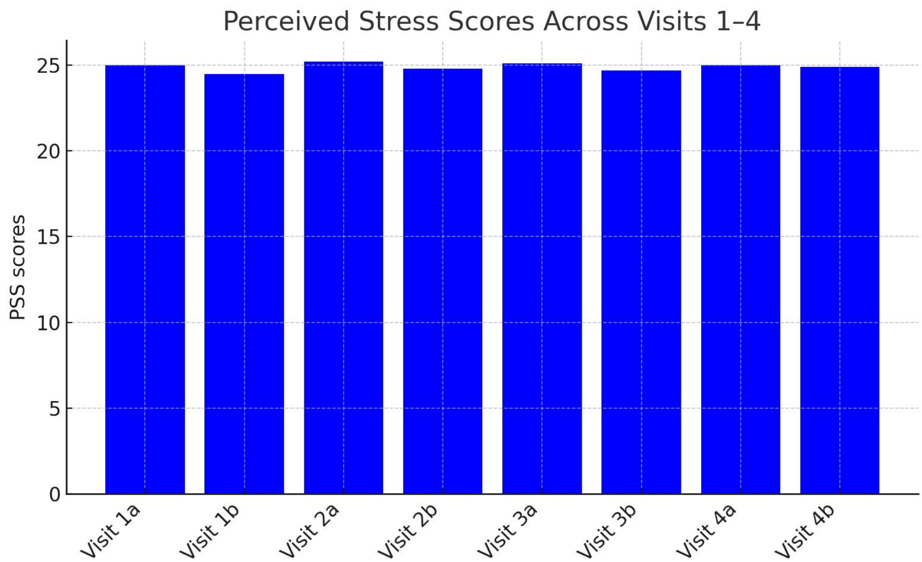

Figure 3: Perceived Stress Scale Scores Intensity Protocol

Recorded via questionnaire given to participants before and after exercise. There was no statistical difference for PSS scores a= before exercise, b=after exercise PSS scores = Perceived Stress Scale scores

Discussion

The present study examined the acute effects of progressively increasing exercise intensity on metabolic and psychological parameters—including total cholesterol, circulating Irisin levels, and perceived stress—in a cohort of sedentary adults with prediabetes. The findings demonstrate three key outcomes: (1) cholesterol levels significantly decreased across all intensity visits, even when higher intensities reduced exercise duration; (2) Irisin concentrations consistently increased following exercise, with the largest rise observed at moderate to high intensities; and (3) although perceived stress scores did not change significantly, participants reported subjective improvements in mood and relaxation. Together, these results highlight that exercise intensity plays an important role in shaping acute physiological responses relevant to metabolic health.

The consistent decline in total cholesterol following each exercise session supports prior evidence that acute aerobic exercise enhances lipid metabolism through increased enzymatic activity, mobilization of fatty acids, and improved hepatic clearance (22,23). Notably, even during Visit 4, where participants performed only 20–25 minutes of exercise at 80% PMHR, cholesterol reduction remained significant and was among the greatest observed in the protocol. This aligns with research demonstrating that exercise dose is influenced both by intensity and duration, and that higher-intensity exercise—even of shorter duration—can produce meaningful acute metabolic benefits (24,25).

Previous studies have shown similar intensity-dependent responses. For instance, Grandjean et al. reported that high-intensity aerobic exercise facilitated greater post-exercise lipid oxidation compared to moderate-intensity training (26). Likewise, high-intensity interval training (HIIT) has been associated with improvements in dyslipidemia in individuals with metabolic risk factors (27). Our results extend this literature by demonstrating that these beneficial lipid responses also occur acutely in a prediabetic population, even when exercise capacity limits full session duration at higher intensities.

Irisin is increasingly recognized as a key mediator linking muscle contraction to systemic metabolic outcomes. In our study, Irisin levels increased significantly after Visits 1–3 and showed a non-significant but positive trend in Visit 4. The attenuated response at the highest intensity likely reflects shortened exercise exposure rather than diminished physiological capacity for Irisin secretion. Prior work indicates that Irisin release correlates with both exercise intensity and total muscular workload, suggesting that reductions in exercise duration could partially blunt the expected rise (28–30).

Nevertheless, the robust increases in Irisin in the earlier visits reinforce the hormone’s role in metabolic regulation through browning of white adipose tissue, enhancement of thermogenesis, and improved glucose homeostasis (31,32). Importantly, individuals with obesity or prediabetes may exhibit altered Irisin dynamics, sometimes described as “Irisin resistance,” where baseline levels are elevated but responsiveness to exercise is reduced (33). Our findings, however, demonstrate preserved responsiveness in this cohort, indicating that Irisin-mediated pathways remain viable targets for lifestyle-based metabolic interventions.

Despite no statistically significant change in PSS scores across visits, participants consistently reported subjective reductions in tension and improved mood following exercise. This discrepancy between quantitative and qualitative outcomes has been noted in prior studies, where acute exercise elicits immediate affective benefits not fully captured by standardized scales (34,35). The PSS is designed to measure stress appraisal over the preceding month and may therefore lack sensitivity to detect rapid, session-specific changes (36). Nonetheless, psychological improvements following exercise—whether measured objectively or reported subjectively—are meaningful, particularly given the bidirectional relationship between stress and metabolic dysfunction (37).

The findings from this study underscore the value of modulating exercise intensity to optimize metabolic outcomes in prediabetic adults. Moderate intensities (50–70% PMHR) elicited the greatest combined improvements in cholesterol reduction and Irisin elevation, while higher intensity (80% PMHR) remained beneficial but limited by exercise tolerance. These observations support tailored exercise prescriptions that account for individual stamina, comorbidities, and behavioral readiness. Importantly, even short sessions at higher intensities produced favorable lipid changes, suggesting that flexible strategies may help individuals with low baseline fitness achieve clinically relevant benefits.

From a public health perspective, integrating intensity-based exercise recommendations into diabetes-prevention programs may enhance their effectiveness, particularly in regions such as South Asia where metabolic risk is high and physical inactivity is prevalent. Key strengths of this study include the use of objective biochemical markers, controlled laboratory conditions, and a progressive design allowing direct comparison of multiple intensity levels. However, several limitations warrant consideration. The sample size was modest, limiting generalizability. The study assessed only acute responses, and long-term adaptations may differ. Additionally, Irisin assays remain imperfect, with some variability across commercial kits, potentially affecting measurement precision. Finally, psychological outcomes may require alternative scales designed to capture acute emotional responses.

Conclusion

In summary, progressively increasing exercise intensity produces significant acute improvements in cholesterol and stimulates Irisin release in adults with prediabetes, even when higher intensities shorten exercise duration. Although perceived stress scores did not change significantly, participants experienced subjective psychological benefits. These findings emphasize the metabolic value of structured aerobic exercise and highlight the importance of intensity-based prescription in prediabetes management. Future research should explore long-term adaptations to repeated exposure at varying intensities and examine how these responses translate into diabetes-prevention outcomes.

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