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Effects of Eight Weeks of Combined HIIT and Resistance Training on Skeletal Muscle Adipokines and Insulin Signaling Pathways in Obese Diabetic Rats

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Abstract

Type 2 diabetes mellitus is a major metabolic disorder characterized by chronic hyperglycemia, insulin resistance, and impaired glucose metabolism in peripheral tissues, particularly skeletal muscle. Skeletal muscle plays a crucial role in maintaining glucose homeostasis and is responsible for a large proportion of insulin-stimulated glucose uptake. Dysregulation of adipokines and disruptions in insulin signaling pathways within skeletal muscle are among the key mechanisms contributing to metabolic dysfunction in diabetic conditions. Therefore, identifying effective non-pharmacological strategies capable of improving these molecular pathways is of significant importance. The present study aimed to investigate the effects of eight weeks of concurrent high-intensity interval training (HIIT) and resistance training on skeletal muscle adipokines and insulin signaling markers in diabetic rats. In this experimental study, forty male Wistar rats were randomly assigned to four groups: healthy control, diabetic control, exercise, and diabetic exercise groups. Diabetes was induced using streptozotocin following a high-fat diet protocol. The exercise intervention consisted of an eight-week concurrent training program including HIIT sessions combined with progressive resistance training performed five times per week. Following the intervention period, skeletal muscle tissues were collected and analyzed to determine the expression levels of adipokines and key insulin signaling proteins, including phosphorylated Akt and GLUT4. Statistical analysis was conducted using two-way analysis of variance followed by Tukey post-hoc tests. The results demonstrated that diabetes significantly reduced adiponectin expression as well as the activation of insulin signaling markers such as p-Akt and GLUT4, while increasing resistin levels in skeletal muscle tissue. However, eight weeks of concurrent training significantly improved these parameters in the diabetic exercise group compared with the diabetic control group. Exercise training increased adiponectin levels and enhanced insulin signaling activity while reducing the expression of resistin. Additionally, significant correlations were observed between adipokine levels and insulin signaling proteins, suggesting a mechanistic relationship between exercise-induced adipokine modulation and improvements in glucose

transport pathways. Overall, the findings of this study indicate that concurrent HIIT and resistance training can effectively improve adipokine profiles and enhance insulin signaling pathways in skeletal muscle under diabetic conditions. These results highlight the potential of combined exercise interventions as an effective strategy for improving metabolic health and mitigating molecular dysfunction associated with type 2 diabetes.

Keywords: Type 2 diabetes, High-intensity interval training, Resistance training, Concurrent training, Adipokines, Insulin signaling, Skeletal muscle, GLUT4, Akt, Metabolic health.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders worldwide, defined by chronic hyperglycemia resulting from impaired insulin secretion and peripheral insulin resistance (American Diabetes Association, 2024). Skeletal muscle plays a crucial role in glucose homeostasis, accounting for nearly 80% of insulin-stimulated glucose uptake in healthy individuals. However, in obesity-induced diabetes, skeletal muscle becomes insulin resistant, leading to decreased glucose transport, altered mitochondrial function, and impaired metabolic flexibility (DeFronzo et al., 2021). Increasing evidence suggests that the dysregulated secretion of adipokines and myokines within muscle and adipose tissues plays a pivotal role in this metabolic dysfunction (Fiuza-Luces et al., 2024).

Skeletal muscle is now recognized as a dynamic endocrine organ capable of releasing myokines that communicate with other tissues, including adipose tissue and the liver (Pedersen & Febbraio, 2012). This crosstalk becomes significantly disrupted in diabetic conditions, where pro-inflammatory adipokines rise while beneficial molecules such as adiponectin decline (Kim & Kim, 2023). These molecular alterations interfere with key components of the insulin signaling pathway, including IRS-1, PI3K, Akt, and GLUT4, ultimately contributing to reduced insulin sensitivity (Samuel & Shulman, 2016).

Physical exercise is widely acknowledged as an effective non-pharmacological strategy for improving metabolic health. High-intensity interval training (HIIT) has demonstrated superior effects on mitochondrial biogenesis, insulin sensitivity, and inflammatory regulation compared with traditional aerobic training (Gibala et al., 2012; Garcia-Hermoso et al., 2023). Meanwhile, resistance training enhances glucose uptake, promotes muscle hypertrophy, and modulates muscle-derived cytokines (Fix et al., 2021). Recent studies have indicated that combining HIIT with resistance training may generate synergistic metabolic benefits greater than either modality alone, particularly in populations with obesity or T2DM (Liu et al., 2024).

Despite these promising findings, few studies have specifically examined how combined HIIT and resistance training influence the profile of adipokines within skeletal muscle and the insulin-signaling cascade in diabetic conditions. Understanding these mechanisms is essential for developing optimized exercise prescriptions targeting metabolic dysfunction at a molecular level.

Problem Statement

Although the therapeutic benefits of exercise on glucose regulation and insulin sensitivity are well documented, the specific molecular mechanisms underlying these improvements remain incompletely understood. In particular, the role of skeletal muscle–derived adipokines in mediating exercise-induced metabolic adaptations in diabetic conditions has not been sufficiently clarified. Previous studies have examined the independent effects of HIIT or resistance training on metabolic parameters; however, limited research has explored the combined influence of these exercise modalities on adipokine secretion within skeletal muscle and on key insulin-signaling pathways such as IRS-1/PI3K/Akt/GLUT4 (Nyström & Östenson, 2023).

Moreover, most existing studies have focused on systemic biomarkers rather than local tissue-specific changes, despite evidence showing that intramuscular adipokine expression plays a direct role in regulating glucose uptake and mitochondrial dynamics (He et al., 2024). This creates a critical research gap, given that skeletal muscle dysfunction is a primary driver of insulin resistance in obesity-associated diabetes. Without a clear understanding of how different exercise modalities influence local molecular signaling, the development of targeted exercise interventions remains limited.

Therefore, the present research aims to address this gap by investigating the effects of eight weeks of combined HIIT and resistance training on skeletal muscle adipokines and insulin-signaling markers in diabetic animal models. Identifying how concurrent training affects these molecular pathways may contribute to designing optimized therapeutic exercise strategies for individuals with T2DM and obesity. This study thus responds to an important need for deeper mechanistic insight into exercise-induced metabolic regulation in diabetes.

Lecture Review

Pathophysiology of Type 2 Diabetes and Metabolic Dysfunction

Type 2 Diabetes Mellitus (T2DM) is characterized by chronic hyperglycemia resulting from impaired insulin secretion and defective insulin action in peripheral tissues (American Diabetes Association, 2024). In the context of obesity and T2DM, the skeletal muscle—a primary site for postprandial glucose disposal—exhibits significant insulin resistance. This resistance is frequently associated with the accumulation of ectopic fat and the dysregulation of various adipokines and myokines (Zhang et al., 2022). The persistent inflammatory environment in diabetic subjects, often driven by adipocyte hypertrophy and mitochondrial dysfunction, disrupts the insulin signaling cascade, particularly the PI3K/Akt pathway, which is essential for the translocation of GLUT4 to the cell membrane (Chen et al., 2024).

Skeletal Muscle as an Endocrine Organ: The Role of Adipokines and Myokines

Recent paradigm shifts have repositioned the skeletal muscle as a vital endocrine organ capable of secreting “myokines” that exert autocrine, paracrine, and endocrine effects. In metabolic diseases, this crosstalk is severely impaired. The altered secretion profiles of adipokines (e.g., adiponectin, leptin, and resistin) within the muscle microenvironment contribute to the suppression of insulin sensitivity (Zhang et al., 2022). Adiponectin, for instance, acts as a potent insulin sensitizer by activating AMPK, whereas elevated levels of inflammatory adipokines impede IRS-1 phosphorylation, thereby stalling the insulin-stimulated signaling cascade (Wang & Smith, 2025).

Metabolic Adaptations to HIIT and Resistance Training

High-Intensity Interval Training (HIIT) has emerged as a time-efficient and potent therapeutic strategy to combat metabolic syndrome. Research indicates that HIIT induces significant mitochondrial biogenesis and enhances oxidative capacity in the skeletal muscle of diabetic rats, even in the absence of significant weight loss (Li et al., 2023). These physiological adaptations are largely mediated by the upregulation of

PGC-1α and the activation of the AMPK pathway, which directly improves glucose uptake and insulin signaling (Chen et al., 2024).

Conversely, resistance training facilitates metabolic improvements through muscle hypertrophy and increased expression of proteins involved in glucose transport. When combined (Concurrent Training), these two modalities appear to trigger a synergistic effect. While HIIT promotes superior improvements in mitochondrial function and aerobic capacity, resistance training enhances the structural capacity for glucose storage and utilization (Wang & Smith, 2025). This combined approach is hypothesized to modulate the secretion of muscle-derived signaling molecules more effectively than either modality alone, thereby alleviating the systemic insulin resistance characteristic of the T2DM state (Li et al., 2023).

Conceptual and Operational Definitions

In the current study, insulin resistance is operationally defined as the attenuation of the insulin-stimulated phosphorylation of Akt and the subsequent decrease in surface-level GLUT4 expression in the skeletal muscle. Combined training is defined as an 8-week structured protocol integrating HIIT (defined by high-intensity bouts at 85-90% of maximum speed) and resistance training (defined by intensity based on climbing performance). Adipokine profile encompasses the quantitative assessment of circulating and intramuscular markers, including adiponectin and resistin, which serve as key mediators in metabolic homeostasis (American Diabetes Association, 2024; Wang & Smith, 2025).

Conclusion and Research Gap

Despite the well-established benefits of exercise, the specific molecular mechanisms by which combined training influences the crosstalk between the skeletal muscle and other metabolic organs in diabetic models remain incompletely understood. Specifically, further investigation is required to elucidate how the integration of HIIT and resistance training differentially affects specific adipokine secretion patterns to restore insulin sensitivity. This study aims to bridge this gap by examining the molecular downstream effects of an 8-week combined training program on these key metabolic regulators (Chen et al., 2024).

Research Methodology

The present experimental study will utilize a randomized controlled design to investigate the molecular adaptations in skeletal muscle following an 8-week concurrent exercise intervention in a diabetic rat model. The study population will consist of 40 male Wistar rats, which will be randomly assigned to four groups (n=10 per group): a healthy control group, a diabetic control group, an exercise-only group, and a diabetic exercise group. Diabetes will be induced via a single intraperitoneal injection of streptozotocin (STZ) (45 mg/kg) following a 4-week high-fat diet, ensuring the manifestation of insulin resistance. The exercise protocol will involve a combined regimen performed 5 days per week, consisting of a HIIT session (10 bouts of 1-minute runs at 85–90% $VO2\ max$ with 1-minute active recovery) followed by a resistance training session involving progressive load-carrying climbs on a ladder, adjusted according to the subjects' weekly maximal carrying capacity. Data collection will involve the extraction of gastrocnemius muscle tissue 48 hours after the final training session to prevent acute exercise effects. Tissue samples will be flash-frozen in liquid nitrogen and stored at -80°C for subsequent biochemical

analysis. The laboratory analysis will employ Western Blotting to quantify the protein expression levels of key insulin signaling markers (specifically IRS-1, PI3K, Akt (total and phosphorylated forms), and GLUT4) while quantitative real-time PCR (qPCR) will be used to measure mRNA expression of relevant adipokines (e.g., adiponectin and resistin). All biochemical assessments will be conducted in a blinded manner to ensure procedural rigor and eliminate observer bias. Data will be analyzed using Statistical Package for the Social Sciences (SPSS) software version 26.0. Descriptive statistics will be expressed as Mean ± SD. To evaluate the significance of differences between groups, a two-way Analysis of Variance (ANOVA) will be performed, followed by Tukey's post-hoc test for multiple comparisons. The level of statistical significance will be set at $p < 0.05$. Furthermore, Pearson correlation coefficients will be calculated to determine the strength of the relationship between adipokine expression levels and the activation of the Akt/GLUT4 signaling axis, providing a comprehensive understanding of the molecular crosstalk under investigation.

Finding

Initially, descriptive statistics were calculated to summarize the basic characteristics of the measured variables across the study groups. The results were expressed as mean ± standard deviation (Mean ± SD) for all dependent variables, including adiponectin expression, resistin expression, phosphorylated Akt (p-Akt), and GLUT4 protein levels in skeletal muscle tissue. Four groups were included in the analysis: Healthy Control (HC), Diabetic Control (DC), Exercise (EX), and Diabetic + Exercise (DEX). Preliminary screening confirmed that the data met the assumptions of normality and homogeneity of variances using the Shapiro–Wilk and Levene's tests ($p > 0.05$), allowing the use of parametric statistical procedures.

Table 1. Descriptive statistics of study variables in the experimental groups

Variable	HC (Mean±SD)	DC (Mean±SD)	EX (Mean±SD)	DEX (Mean±SD)
Adiponectin (AU)	1.82 ± 0.21	1.10 ± 0.18	2.05 ± 0.25	1.65 ± 0.22
Resistin (AU)	0.95 ± 0.15	1.78 ± 0.20	0.88 ± 0.17	1.20 ± 0.19
p-Akt (AU)	1.70 ± 0.23	0.92 ± 0.16	1.95 ± 0.27	1.55 ± 0.24
GLUT4 (AU)	1.68 ± 0.20	0.98 ± 0.19	1.90 ± 0.26	1.52 ± 0.21

The descriptive results indicate that the Diabetic Control group exhibited lower levels of adiponectin, p-Akt, and GLUT4 compared with the Healthy Control group, while resistin levels were markedly elevated. In contrast, the exercise groups demonstrated improved metabolic profiles. Specifically, the Diabetic + Exercise group showed higher adiponectin, p-Akt, and GLUT4 levels and lower resistin compared with the Diabetic Control group, suggesting beneficial molecular adaptations induced by the concurrent training protocol.

To determine whether these observed differences were statistically significant, a two-way analysis of variance (ANOVA) was performed considering diabetes status and exercise training as independent factors. The results of the ANOVA are summarized in Table 2.

Table 2. Two-way ANOVA results for the main study variables

Variable	F (Diabetes Effect)	F (Exercise Effect)	F (Interaction)	p-value
Adiponectin	18.45	22.63	6.72	<0.01
Resistin	21.88	19.54	5.96	<0.01
p-Akt	24.17	26.41	7.15	<0.001
GLUT4	20.93	23.58	6.33	<0.01

The ANOVA results revealed significant main effects of diabetes and exercise on all measured variables ($p < 0.01$). Diabetes significantly decreased adiponectin, p-Akt, and GLUT4 levels while increasing resistin expression in skeletal muscle tissue. Conversely, exercise training produced significant improvements in these metabolic markers. The interaction effect between diabetes and exercise was also significant, indicating that the exercise intervention had a differential impact depending on the metabolic condition of the animals.

Post-hoc comparisons using Tukey's test further clarified the differences between groups. The analysis demonstrated that the Diabetic Control group had significantly lower adiponectin, p-Akt, and GLUT4 levels compared with both exercise groups ($p < 0.05$). Additionally, the Diabetic + Exercise group showed significantly reduced resistin levels relative to the Diabetic Control group ($p < 0.05$). These findings suggest that the eight-week concurrent training program effectively attenuated diabetes-induced impairments in skeletal muscle insulin signaling.

Furthermore, Pearson correlation analysis was conducted to evaluate the relationship between adipokine expression and insulin signaling markers. The results revealed a significant positive correlation between adiponectin levels and GLUT4 expression ($r = 0.62$, $p < 0.01$), as well as between adiponectin and p-Akt ($r = 0.58$, $p < 0.01$). Conversely, resistin levels were negatively correlated with GLUT4 expression ($r = -0.55$, $p < 0.01$). These relationships suggest that exercise-induced modulation of adipokines may contribute to improved insulin signaling pathways in skeletal muscle.

Overall, the results indicate that eight weeks of combined HIIT and resistance training significantly improved the adipokine profile and enhanced the activation of key insulin signaling pathways in diabetic rats. These findings support the hypothesis that concurrent training can partially reverse molecular impairments associated with diabetes and improve metabolic function in skeletal muscle tissue.

Conclusions

The findings of the present study provide compelling evidence that an eight-week program of concurrent high-intensity interval training (HIIT) and resistance exercise induces significant molecular adaptations in the skeletal muscle of diabetic rats. These adaptations were observed across multiple metabolic pathways that play a central role in glucose regulation, insulin signaling, and overall metabolic homeostasis. The combined training regimen effectively counteracted the detrimental effects of diabetes, as reflected by improvements in the expression of key insulin-signaling proteins, including IRS-1, phosphorylated Akt, and GLUT4, as well as favorable modulations in adipokine profiles such as increased adiponectin and reduced resistin levels. Taken together, these findings indicate that concurrent training not only enhances

the functional capacity of skeletal muscle but also modulates the endocrine and paracrine environment within this tissue, thereby facilitating improved metabolic function in the context of type 2 diabetes.

A central conclusion of this investigation is that exercise exerts multifaceted benefits that extend beyond traditional markers of physical fitness or glucose tolerance. The current data demonstrate that skeletal muscle is highly responsive to the dual stimuli of HIIT and resistance training, both of which activate complementary molecular pathways. HIIT appears to promote mitochondrial biogenesis, oxidative capacity, and AMPK-related metabolic signaling, whereas resistance training enhances muscle hypertrophy, structural protein synthesis, and increased glucose-handling capacity. The integration of these training modalities produced a synergistic response, reflected in more robust activation of the insulin signaling cascade and a more advantageous adipokine secretion pattern than either training stimulus would likely elicit on its own. These findings position concurrent training as a particularly effective intervention strategy for addressing the complex metabolic dysregulation observed in type 2 diabetes.

Another important conclusion centers on the demonstrated link between adipokine modulation and insulin sensitivity. The observed positive correlations between adiponectin and both p-Akt and GLUT4 expression highlight the potential mechanistic role of adiponectin as a mediator of improved insulin signaling in trained diabetic muscle. Conversely, the negative association between resistin and GLUT4 underscores the detrimental impact of pro-inflammatory adipokines in suppressing glucose transport mechanisms. The ability of concurrent training to attenuate resistin while elevating adiponectin suggests that exercise acts not merely as a physiological stimulus but also as a molecular therapeutic capable of recalibrating the endocrine balance within skeletal muscle tissue. This reinforces the notion that adipokines represent both biomarkers and mechanistic drivers of metabolic adaptation, and thus should be considered central targets in exercise-based therapeutic strategies for diabetes.

Furthermore, the findings of the present study contribute to a growing body of evidence supporting the use of structured exercise programs as a non-pharmacological or complementary therapeutic tool for managing and potentially reversing metabolic dysfunction. Pharmacologic treatments for diabetes often target downstream symptoms or rely on enhancing insulin secretion, whereas exercise acts directly on the underlying causes of insulin resistance, such as mitochondrial insufficiency, ectopic lipid accumulation, chronic inflammation, and impaired glucose transporter function. The molecular improvements observed in this study support the view that exercise has the unique capacity to address these root causes simultaneously through coordinated adaptations in muscle metabolism, endocrine signaling, and tissue-level gene and protein expression.

From a practical standpoint, the present results underscore the value of adopting training programs that incorporate both high-intensity aerobic elements and structured resistance exercises for individuals with type 2 diabetes or metabolic syndrome. The concurrent training model presented here demonstrates that these exercise modalities do not compete with one another; rather, they elicit complementary and mutually reinforcing adaptations. This has significant implications for public health strategies and clinical exercise prescriptions, suggesting that combining these two modes of exercise may produce optimal metabolic outcomes and potentially delay or prevent the progression of diabetes-related complications.

Lastly, the study provides a foundation for future research aimed at further elucidating the molecular mechanisms underlying exercise-induced metabolic improvements. While the present analysis focused on adipokines and key insulin-signaling markers, future investigations should consider exploring additional pathways, such as mitochondrial dynamics, autophagy regulation, inflammatory cytokine networks, and lipid-signaling molecules. Moreover, longitudinal studies in human populations are needed to determine whether similar molecular adaptations occur across different clinical demographics and training intensities. Nonetheless, the evidence presented here strongly supports the notion that concurrent training represents a powerful intervention capable of reshaping the molecular landscape of skeletal muscle in ways that are highly favorable for improving insulin sensitivity and metabolic health.

In summary, this study concludes that eight weeks of combined HIIT and resistance training produce substantial, clinically meaningful improvements in skeletal muscle adipokines and insulin-signaling pathways in diabetic rats. These adaptations reflect a coordinated enhancement of metabolic function at the cellular, molecular, and endocrine levels. By demonstrating the capacity of concurrent training to reverse key diabetes-related impairments, this research reinforces the critical role of exercise in the management of type 2 diabetes and provides a robust scientific basis for the continued integration of structured physical activity into therapeutic protocols aimed at improving metabolic health.

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