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ORIGINAL ARTICLE

The Eight-Week Circuit Resistance Training Decreased the Serum Levels of WISP-1 and WISP-2 in Individuals with Type 2 Diabetes

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ABSTRACT

Background. According to World Health Organization, the global population of diabetes is approximately 463 million people and is projected to exceed half a billion by 2030. There is currently no specific cure for diabetes, but the methods of control and management are advancing. The effect of exercise and physical activity on one of the latest involved factors, WISP-1 and WISP-2, is one of the therapeutic strategies. **Objectives.** This study aims to answer the question of what effect circular resistance training has on WISP-1 and WISP-2 in individuals with type 2 diabetes (T2DM). **Methods.** Among men with T2DM referred to the Diabetes Clinic of Towhid Hospital and the Diabetes Association of Sanandaj, a total of 20 eligible volunteers were randomly assigned to two groups of 10, control and experimental. Circuit resistance training was used in this study for eight weeks, with three non-consecutive sessions per week. The number of sets, intensity, and volume of exercise started with 2 sets at 40% of 1RM (one-repetition maximum) and 15 repetitions in the initial sessions and progressed to 4 sets at 80% of 1RM and 6 repetitions in the final sessions. Rest periods of 20 to 30 seconds between sets and 3 minutes between rounds were considered. WISP-1 and WISP-2 levels were measured via ELISA method. **Results.** WISP-1 and -2 levels in the control group lake a significant change over time, its levels in the experimental group significantly decreased (p=0.029 and p=0.039, respectively). **Conclusion.** Both WISP-1 and WISP-2 likely have an impact on the mechanisms of glucose homeostasis, insulin, insulin resistance, and body weight in individuals with T2DM.

KEYWORDS: ***Resistance Training, Type 2 Diabetes, WISP1, WISP2, Insulin Resistance, Insulin Sensivity.***

INTRODUCTION

The occurrence and prevalence of type 2 diabetes mellitus (T2DM) are still increasing in many parts of the world, which is associated with the rise in obesity and sedentary lifestyle (1). T2DM is a metabolic disorder characterized by high blood glucose levels, insulin resistance, and relative insulin deficiency in the body (2). It leads to various pathological changes such as neuropathy, nephropathy, and retinopathy. A combination of genetic disorders and environmental factors such as physical inactivity and poor nutrition play a role in the development of this disease (3).

On the other hand, insulin resistance, defined as a reduced response of peripheral tissues to the action of insulin, is accompanied by a decrease in the desirable function of muscle cells in glucose uptake in response to insulin secretion from pancreatic beta cells. It is considered one of the main factors contributing to the prevalence of T2DM and its long-term complications. However, this condition is also recognized as one of the main pathological markers of T2DM (4). Improving insulin resistance remains a significant issue in the treatment of T2DM and metabolic syndrome, aiming to discover

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the necessary approaches for better management of insulin resistance.

Adipose tissue is an endocrine organ that secretes various adipokines, some of which contribute to the dysfunction of beta cells and subsequently increase insulin resistance, ultimately creating a foundation for the development of T2DM (5). Researchers have attributed the pathological effects of obesity, including the occurrence of T2DM, to changes in the levels of adipokines (6). So, adipokines have garnered considerable attention for future pharmacological treatment strategies for obesity and its associated metabolic disorders, including T2DM, due to their role in regulating appetite and satiety, energy expenditure, endothelial function, blood pressure, insulin resistance, adipogenesis, fat distribution, insulin secretion, and other functions (7). Recently, WNT signaling pathway-inducing proteins named WISP-1 (CCN4) and WISP-2 (CCN5) have emerged as new adipokines that stimulate cytokine responses in macrophages and play roles in regulating apoptosis as well as a wide range of neurological, musculoskeletal, immune, and cancerous diseases. They have also been identified as a novel cytokine derived from adipose tissue, expressed in subcutaneous and visceral fat, which influences insulin resistance and has important functions in the metabolic state of the body (8, 9).

Recent studies have identified the role of WISP-1 as an active marker in the pathophysiology of obesity and T2DM, indicating its potential association with visceral fat accumulation and insulin resistance. Plasma and serum levels of WISP-1 are elevated in obese individuals and are associated with inflammatory markers and insulin resistance (10, 11). In a study, weight loss resulted in decreased expression of WISP-1 in subcutaneous adipose tissue and circulation (10). It has also been reported that WISP-1 levels are significantly increased in individuals with T2DM and gestational diabetes and directly correlate with insulin resistance, fasting glucose, and fasting insulin (12, 13). Additionally, WISP-1 disrupts insulin function in human skeletal muscle cells and mouse liver cells by inhibiting the phosphorylation of insulin receptor, Akt, and downstream glycogen synthase kinase 3β, FOXO1, and p70S6 kinase, suppressing gluconeogenic genes and insulin-stimulated glycogen synthesis. Therefore, excessive expression of WISP-1 may contribute to the pathogenesis and progression of insulin resistance (14). In a study on mice, WISP-1 inhibition resulted in a reduction in insulin resistance induced by a high-fat diet in skeletal muscle cells and also reduced pro-inflammatory factors including nuclear translocation of NF-kB and IκB phosphorylation in the liver (15).

Similarly, WISP-2 is a 29-kilodalton adipokine that has a similar function to WISP-1. Studies have also shown that WISP-2 expression in subcutaneous adipose tissue is increased in obese individuals, indicating a positive association between WISP-2 and obesity (16). In a study by Grünberg et al. (2018), it was demonstrated that WISP-2 expression of WNT-regulated genes is positively associated with obesity markers, hepatic and adipose tissue fat accumulation, and insulin resistance, while showing a negative correlation with whole-body insulin sensitivity, potentially serving as risk markers in the development of T2DM (16).

Moreover, the WNT signaling pathway can limit fat storage and direct lipids away from the liver and muscles, thereby preventing adipogenesis. Therefore, it can contribute to metabolic disorders such as insulin resistance and non-alcoholic fatty liver disease (17). WNT signaling increases insulin resistance through the JNK-JUN kinase cascade and serine phosphorylation of IRS-1. Current studies have shown that WNT signaling plays a crucial role in inflammatory conditions that connect obesity to metabolic complications (18).

On the other hand, physical activity and exercise are among the ways to control and partially treat obesity, diabetes, and related conditions (19-22). Nowadays, the importance of exercise in reducing inflammation and inflammatory factors has received significant attention (23-25). In response to exercise training, adipokines are secreted and these proteins are associated with the metabolic effects of exercise (26, 27). Physical activity leads to increased blood flow, increased capillary density, increased muscle mass, increased glycogen storage capacity due to increased glycogen synthetase enzymes, increased glucose transporter protein in muscle (GLUT4), improved glucose uptake and utilization by muscles, improved insulin sensitivity and efficiency, reduced insulin resistance, increased expression of genes or activities of various proteins involved in the insulin signaling cascade, and results in weight loss and reduced concentrations of adipokines

associated with insulin resistance in sedentary individuals and those with impaired glucose tolerance and diabetes (19-24, 28, 29).

On the other hand, resistance training or weight training has become a common method for improving health and increasing muscle mass (23, 24, 28, 29). Resistance exercises have been introduced as a therapeutic program by the American Heart Association and the American College of Sports Medicine (30). In a study, it was demonstrated that 12 weeks of resistance training led to improvements in metabolic factors such as blood pressure, lipids (total cholesterol and triglycerides), muscle hypertrophy, insulin, and inflammatory markers in sedentary elderly women, and a significant correlation was found between muscle thickness and changes in TNF-α, indicating that muscular hypertrophy is associated with a decrease in inflammatory markers and cytokines (31). Although multiple studies have examined the effects of resistance exercises on adipokines and insulin resistance in healthy individuals and those with diabetes, there is limited information available on the effects of circuit resistance training on serum levels of WISP-1 (CCN4) and WISP-2 (CCN5) in individuals with diabetes. Therefore, the research question of the present study is whether 8 weeks of circuit resistance training an effect on changes has in serum levels of WISP-1 (CCN4) and WISP-2 (CCN5) in individuals with T2DM.

MATERIALS AND METHODS

Research Method. This study was conducted in a semi-experimental design using pre-and post-test assessments for the measurement of variables in two control and experimental groups.

Participants/Patients. Twenty volunteers men with type 2 diabetes from the diabetes clinic of Towhid Hospital and the Diabetes Association of Sanandaj were randomly assigned to two control and experimental groups (each n=10). The inclusion criteria for participation in the study were age between 45-55 years, fasting blood glucose levels between 100 and 250 mg/dL, oral medication with metformin, and a history of diabetes for more than five years. The exclusion criteria included complications related to type 2 diabetes (such as neuropathy, nephropathy, retinopathy, cardiovascular complications, joint discomfort, and diabetic foot ulcers), a history of hypoglycemia in the past two months, depression, smoking and alcohol consumption, insulin injections, changes in antidiabetic medications, blood pressure higher than 160/95 mm Hg, and regular participation in any form of exercise training in the past six months.

The selection process of participants was supervised by a specialist diabetes physician. It is also worth mentioning that no changes were made to the patient's medication, including antidiabetic drugs, during the eight-week exercise period.

After explaining the study protocol and relevant procedures, the participants provided written consent to participate in the research. During the exercise period, the participants were asked to refrain from engaging in other physical activities and to control their diet according to recommendations. In the end, three individuals from both groups decided to withdraw from the study. The present study was conducted under the ethical guidelines of the 1975 Helsinki Declaration and was registered and approved by the Ethics Committee of Allameh Tabataba'i University (Code: IR.ATU.REC.009).

Measurements. Determination of anthropometric indices and of maximal strength (1RM) was conducted one week before the initiation of the exercise program in three separate non-consecutive sessions. The measurement of anthropometric indices, including weight, height, and BMI, was performed. Weight was measured using a digital scale with minimal clothing, barefoot, and with an empty bladder. Height measurement was taken in a standing position without shoes using a wall-mounted stadiometer. BMI (Kg/m^2) was calculated using the formula "weight divided by height squared." The participants' maximal strength (1RM) was determined using the Brzycki formula. Measurement of blood variables was performed 48 hours before the first- and 48 hours after and last-exercise sessions. The participants arrived at the laboratory in a 12-hour overnight fasting state, and under laboratory conditions, 10 ml of blood was taken from the antecubital vein in a seated position. After centrifugation and separation of serum samples, they were stored at a temperature of -20°C for future assessments. The serum levels of WISP1 and WISP2 were measured using an ELISA method kit with sensitivity = 0.06 ng/ml (Zelbio, Germany).

Exercise protocol and implementation method. Before the start of the training program, during familiarization sessions, the participants were fully instructed on the resistance exercise

machines, proper performing of each exercise, correct breathing during exercises, and how to increase or decrease weights on each machine.

The CRT used in this study was conducted for eight weeks, with three non-consecutive sessions per week. Each training session lasted an average of 60 minutes, consisting of a 10-minute warm-up period (including light jogging and stretching exercises), 40 minutes of resistance training using weight machines, and a 10-minute cool-down period (including stretching exercises). The CRT program included exercises with 10 machines (bench press, seated leg press, seated shoulder press, lying leg curl, bicep curl, calf raise, seated row, lat pulldown, spinal extension, triceps pushdown) performed in a circuit. Initial sessions started with 2 circuits and increased to 4 circuits in the final sessions. The training intensity (volume) started at 40% of 1RM (15 repetitions) in the initial sessions and ended at 80% of 1RM (6 repetitions) in the final sessions. A rest period of 20 to 30 seconds was taken between each exercise, and a rest period of 3 minutes was given between each circuit (Table 1).

Table 1. Protocol of 8 weeks of circuit resistance training

	Week 1			Week 2			Week 3			Week 4			Week 5			Week 6			Week 7			Week 8		
Session	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Intensity	40%	40%	45%	45%	50%	50%	55%	55%	60%	60%	60%	65%	65%	65%	70%	70%	70%	75%	75%	75%	80%	80%	80%	80%
Repetition	15			12			10			10			8			8			6			6		
Set	2			2			3			3			3			4			4			4		

Statistical Analysis. Mean plus/minus standard error of mean was used as descriptive statistics. Inferential statistical analysis using repeated measures-analysis of variance (ANOVA). The LSD test was used to test the main effects of the interaction effect of GROUP×TIME. The acceptable significance level was less than 0.05 ($p<0.05$). SPSS software was used to analyze the data.

RESULTS

Descriptive statistics for the morphological profile of the samples are summarized in Table 2.

WISP1. The interaction effect of time×group was significant ($F = 807.5$, $p = 0.029$, $\eta^2 = 0.28$). In other words, while the control group did not show a significant change in WISP-1 over time, the experimental group demonstrated a significant decrease in WISP-1 levels after 8 weeks of circular resistance training (Graph 1).

WISP2. The interaction effect of time×group was significant ($F = 123.5$, $p = 0.039$, $\eta^2 = 0.26$). In other words, while the control group did not show a significant change in WISP-2 over time, the experimental group exhibited a significant decrease in WISP-2 levels after 8 weeks of circular resistance training (Graph 2).

DISCUSSION

The present study aimed to investigate the effect of an eight-week circuit resistance training on the serum levels of WISP1 and WISP2 in individuals with type 2 diabetes. The findings demonstrated a significant decrease in WISP1 and WISP2 levels. On the other hand, in the previously published data from this study, the experimental group showed a significant decrease in fasting blood sugar (FBS) compared to the control group; an insignificant change in insulin levels; and a significant reduction in insulin resistance (29). Furthermore, the research findings indicated that body weight and BMI had a significant decrease in experimental group compared to the control group (29).

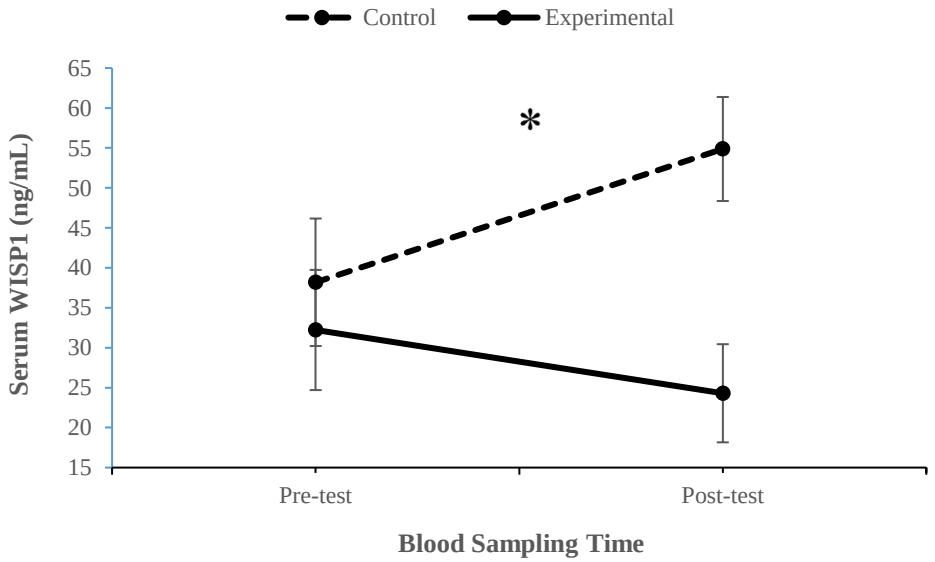
Very few studies have examined the effects of exercise training on serum WISP-1 levels in individuals with type 2 diabetes (32, 33). However, no research has been conducted regarding the effects of exercise training on the adipokine WISP-2. About the effects of exercise training on WISP-1, a study by Bahreini et al. (2017) demonstrated that eight weeks of continuous aerobic and interval training, three days a week at intensities of 60% to 75% of maximum heart rate, led to a decrease in serum WISP-1 levels and insulin resistance in overweight girls (32). Additionally, Chang et al. (2009) showed in a study examining the effects of resistance and aerobic exercise on serum WISP-1 levels in individuals with breast cancer that 12 weeks of exercise training resulted in a reduction in serum WISP-1 levels and insulin resistance,

ultimately increasing insulin sensitivity in individuals with breast cancer (33). Therefore, it can be stated that there is a close relationship between serum WISP-1 levels and insulin sensitivity. Adipokines play a fundamental role in regulating insulin sensitivity in peripheral tissues. WISP-1 is a newly recognized adipokine that is produced by various tissues, including adipocytes. Recent evidence suggests that the adipokine WISP-1 has prominent metabolic effects and plays an important role in modulating insulin sensitivity, with its increase leading to insulin resistance. Thus, the circulating level of WISP-1 and its expression in tissues have a direct association with the promotion and progression of insulin resistance and may be the major factor in obesity and insulin resistance (34). On the other hand, recent studies indicate the role of WISP-1 as an active marker in the pathophysiology of obesity and type 2 diabetes mellitus (T2DM), indicating its potential as a marker of visceral fat accumulation and insulin resistance. Plasma and serum levels of WISP-1 are increased in obese individuals and are associated with inflammatory markers and insulin resistance (10).

Table 2. Characteristics of participants

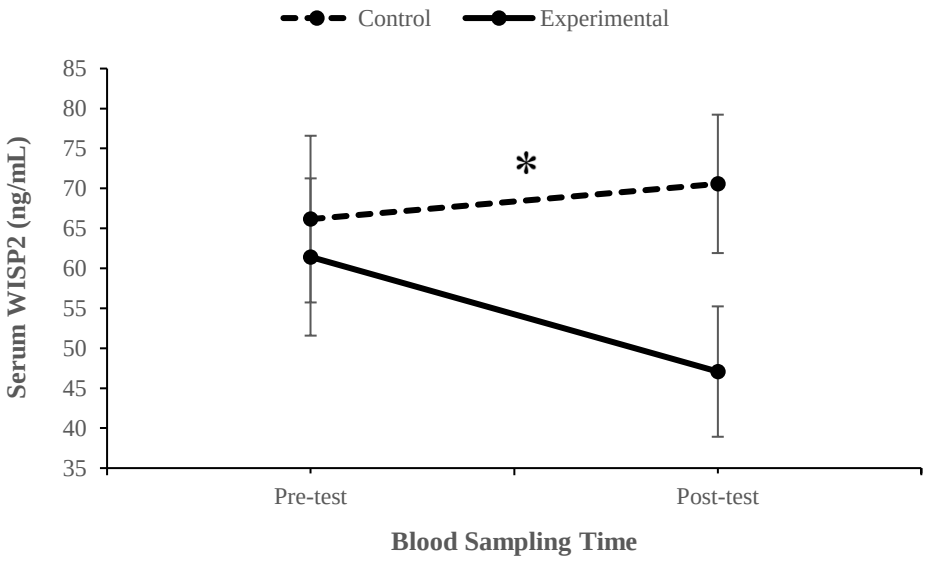
Groups	Age (year)	Body Height (cm)	Body Mass (kg)	BMI (kg/m^2)
Control (n=8)	51 ± 1	174 ± 2	83.56 ± 4.01	27.43 ± 0.98
Experimental (n=9)	50 ± 1	166 ± 2	83.96 ± 3.78	30.12 ± 0.92

BMI: Body mass index. Mean ± SEM.



Graph 1. Serum WISP1 in adaptation with eight-week circuit resistance training (CRT) in men with type 2 diabetes. *: a significant effect of CRT at $p < 0.05$.

Furthermore, regarding blood glucose levels and WISP, it can be mentioned that glucose storage as glycogen in muscles and liver occurs through insulin, which maintains the normal level of plasma glucose (34). There is evidence showing that WISP1 has inhibitory effects on glycogen synthase and suppresses glycogen synthesis (14). Wang et al. (2012) demonstrated that the activity of adipokine WISP1/CCN4 is associated with the inhibition of glycogen synthase kinase β3 (35). Horbelt et al. (2018) showed that WISP-1 inhibits insulin-stimulated glycogen synthesis and suppresses unregulated gluconeogenic gene expression, resulting in a decrease in glycogen levels in tissues (14). In a study by Liu et al. (2020), it was shown that the level of WISP-1 increased in overweight pregnant women with gestational diabetes compared to overweight individuals with normal blood glucose levels. It was also demonstrated that the level of WISP-1 is positively and directly associated with fasting blood glucose and systolic blood pressure (36). It has also been reported that WISP-1 levels are significantly increased in individuals with T2DM and gestational diabetes and are associated with insulin resistance, fasting glucose, and fasting insulin (13).



Graph 2. Serum WISP2 in adaptation with eight-week circuit resistance training (CRT) in men with type 2 diabetes. *: a significant effect of CRT at $p < 0.05$.

Furthermore, regarding serum insulin levels and WISP, studies have shown that excessive expression of WISP1 inhibits insulin receptor substrate (IRS) and protein kinase B (Akt) phosphorylation, disrupting insulin signaling in hepatic cells (36). Sahin Ersoy et al. (2017) reported that adipokine WISP-1 disrupts insulin signal transduction, leading to insulin resistance in pregnant women with gestational diabetes (13). Jung et al. (2018) also reported that WISP-1 significantly suppresses insulin signaling through the nuclear factor JNK, leading to JNK phosphorylation in adipocytes and hepatic cells of mice (15). On the other hand, Mirr et al. (2021) have shown that WISP-1 can be considered as one of the key adipokines involved in glucose homeostasis (37). They confirmed the growing evidence that WISP-1 plays a role in a complex network consisting of body overweight, insulin sensitivity disorders, and ultimately, T2DM (37). They also suggested that WISP-1 expression in adipocytes is negatively associated with insulin sensitivity and appears to involve mechanisms that impair insulin sensitivity, including glycogen synthesis inhibition, disrupted insulin signaling, and promotion of an inflammatory state (37).

However, very few studies have examined the role of WISP-2 in diabetes and insulin resistance. Grünberg (2015) demonstrated in a study on mice that the expression of WISP2 and other WNT activation markers in subcutaneous adipose tissue of humans is increased, which is associated with hypertrophic obesity, metabolic syndrome, insulin resistance, and visceral fat accumulation (16). In line with this, Hamresch and colleagues stated that the expression of CCN5/WISP2 is associated with WNT-regulated genes such as CYCLIND1, insulin resistance, and markers of hypertrophic obesity. Additionally, CCN5 / WISP2 had a positive correlation with markers of ectopic fat accumulation (e.g., liver fat or subcutaneous /visceral fat) and a negative correlation with whole-body insulin sensitivity, indicating a risk factor for T2DM (38). These findings suggest that WISP2 may play a role as a marker in metabolic syndrome, insulin resistance, obesity, and T2DM.

CONCLUSION

The findings of the current study demonstrated that eight weeks of circuit resistance training (3 sessions/week) with intensities of 40%-80% of 1RM and 15-6 repetitions/exercise resulted in a significant decrease in resting levels of WISP-1 and WISP-2 of men with T2DM. This is likely to contribute to the improvement of fasting blood glucose levels and insulin resistance.

APPLICABLE REMARKS

- Circuit resistance training (at least 8 weeks, 3 sessions/week) with low to moderate intensity prescribed for the reduction of fasting blood

glucose and insulin resistance of men with T2DM and without retinopathy, neuropathy, nephropathy, and etc.

AUTHORS' CONTRIBUTIONS

Study concept and design: Seyed Morteza Tayebi. Acquisition of data: Milad Golmohammadi. Analysis and interpretation of data: Seyed Morteza Tayebi, Milad Golmohammadi. Drafting the manuscript: Seyed Morteza Tayebi, Milad Golmohammadi. Critical revision of the manuscript for important intellectual content: Ayoub Saeidi, Ramin Shahghasi. Statistical analysis: Seyed Morteza Tayebi. Administrative, technical, and material support: Seyed Morteza Tayebi, Ramin Shahghasi. Study supervision: Seyed Morteza Tayebi, Ayoub Saeidi.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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