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Evaluating the Effect of Combined Exercise with *Broccoli* Consumption on Fetuin A and B in Men with Type 2 Diabetes

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ABSTRACT

Introduction: Hepatokines are liver-derived proteins that play critical roles in regulating metabolic processes. In individuals with type 2 diabetes, dysregulation of hepatokines, particularly fetuin-A and fetuin-B, has been associated with insulin resistance and increased inflammation. The present study aimed to investigate the effects of a 12-week combined exercise regimen coupled with broccoli consumption on the serum levels of fetuin-A and fetuin-B in men with type 2 diabetes.

Method: This quasi-experimental and applied pre-test and post-test research was conducted on 44 male participants with type 2 diabetes. Participants were randomly assigned to one of four groups (n=11 per group): exercise-supplement group, exercise-placebo group, control-supplement group, and control-placebo group based on individual characteristics. The training protocol involved 45 minutes of resistance exercise at an intensity of 60-70% of one repetition maximum, followed by 30 minutes of aerobic exercise (running) at an intensity of 60-70% of the maximum heart rate. Broccoli was administered in powdered form, with each participant receiving 10 grams per day for a duration of 12 weeks. Blood samples were collected 48 hours prior to the initiation of the training program and again 48 hours after the completion of the final training session to analyze the relevant biomarkers. Intergroup comparisons were conducted using a two-way analysis of variance, while intragroup differences were evaluated using a paired t-test.

Results: The results demonstrated that exercise had a statistically significant impact on plasma levels of fetuin A ($p=0.004$) and fetuin B ($p=0.029$) in men with type 2 diabetes. Moreover, broccoli supplementation also significantly affected plasma levels of fetuin A ($p=0.001$) and fetuin B ($p=0.001$). Additionally, the interaction effect between exercise and broccoli supplementation on the plasma levels of both fetuin A ($p=0.002$) and fetuin B ($p=0.015$) was statistically significant ($p<0.05$).

Conclusion: Regular aerobic exercise significantly reduced fetuin A levels, thereby enhancing insulin sensitivity and improving overall metabolic health. Supplementing the diet with broccoli further supported these benefits by reducing insulin resistance and potentially lowering inflammation through its bioactive compounds. In conclusion, combining aerobic exercise with broccoli supplementation presents an effective strategy to improve metabolic health in men with type 2 diabetes, particularly by modulating key proteins such as fetuin A and fetuin B.

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Introduction

Obesity significantly contributes to the onset and progression of various diseases, with its relationship to type 2 diabetes being particularly noteworthy, as it is considered one of the primary risk factors for developing type 2 diabetes mellitus (1). Diabetes mellitus is a metabolic disorder characterized by elevated blood glucose levels (hyperglycemia), resulting from either inadequate insulin production or dysfunction in insulin action from the pancreas (2). The global prevalence of type 2 diabetes is rapidly increasing, currently affecting approximately 370 million people worldwide, with nearly half of them potentially unaware of their condition (3). Research has linked the adverse effects of obesity, including the development of type 2 diabetes, to alterations in adipokine levels—bioactive substances secreted by adipose tissue (4).

Consequently, hepatokines have garnered significant interest as potential therapeutic targets for obesity and its related metabolic disorders, including type 2 diabetes. This is due to their involvement in regulating a variety of functions, such as appetite and satiety, energy expenditure, endothelial function, blood

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pressure, insulin resistance, adipogenesis, fat distribution, and insulin secretion (5).

The pathological effects of hepatokines, particularly in increasing insulin resistance and contributing to the development of type 2 diabetes, have been well-documented (6). Among these hepatokines, fetuin-A and fetuin-B are notable. The liver plays a crucial role in glucose metabolism, not only through its functions in gluconeogenesis and glycogen synthesis but also by secreting molecules that directly influence peripheral insulin sensitivity. Notably, fetuin-A and fetuin-B, which are primarily produced by the liver, are found at elevated levels in the bloodstream (7).

During fetal development, fetuin-A is primarily synthesized by various tissues, but in adults, it is predominantly secreted by the liver, accounting for more than 95% of its production (10). Despite this, fetuin-A is also classified as an adipokine (8). Studies have shown that fetuin-A levels are positively correlated with both fasting and stimulated insulin levels, while exhibiting a negative correlation with insulin sensitivity (9). In animal models, acute injection of recombinant fetuin-A into rats has been shown to reduce tyrosine kinase activity in both muscle and liver tissues. This occurs through the inhibition of autophosphorylation of the enzyme and the suppression of insulin receptor substrate proteins (IRS-1) (10). Fetuin-A acts as a physiological inhibitor of insulin receptor tyrosine kinase and is thus associated with insulin resistance, metabolic syndrome, and an increased risk of type 2 diabetes. Moreover, evidence suggests that fat accumulation in the liver plays a significant role in elevating fetuin-A levels. Research has reported that the reference levels of fetuin-A in the serum of healthy individuals range from 450 to 600 μg/ml, and these levels are independent of gender, although they may be influenced by genetic factors (11). Several studies have further confirmed the pathological effects of this hepatokine, indicating that the injection of fetuin-A can inhibit insulin receptor phosphorylation and the phosphorylation of the insulin receptor substrate, contributing to the development of insulin resistance (11, 12).

In 2019, Karajibani et al. reported that fetuin-A levels were decreased in individuals with type 2 diabetes mellitus. However, the relationship between fetuin-A levels and diabetes appears to be influenced by various unclear factors. When compared to existing literature, the fluctuations in fetuin-A levels among patients with type 2 diabetes suggest a complex, albeit incomplete, role of this hepatokine in the pathogenesis of the disease (13). In a separate study, Saeedi et al. (2021) found that combining broccoli supplementation with an aerobic-resistance training program significantly improved body composition, cardiorespiratory fitness, lipid profiles, glycemic control, and insulin resistance in individuals with type 2 diabetes, compared to baseline measurements. Our findings suggest that this combination of broccoli supplementation and aerobic-resistance training provides additional benefits for individuals with type 2 diabetes. Notably, one key outcome of our study is that the inclusion of broccoli supplements alongside aerobic-resistance training resulted in a more significant increase in VO2peak in patients with type 2 diabetes (14).

Fetuin B is another member of the fetuin family, recognized as a novel adipokine/hepatokine, which significantly increases in hepatic steatosis and plays a role in regulating insulin dysfunction and glucose intolerance (15). Research has also shown a notable increase in fetuin B levels among women with gestational diabetes (16). Furthermore, a positive correlation has been identified between fetuin B levels and insulin resistance, positioning fetuin B as a potential risk factor for both type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) (17). Studies indicate that administering fetuin B to mice leads to impaired glucose tolerance, while reducing its levels improves glucose tolerance. However, researchers have noted that fetuin B does not appear to affect insulin sensitivity or secretion (15). Fetuin B is considered a signaling molecule that links NAFLD with type 2 diabetes, as elevated fetuin B levels in NAFLD are associated with increased fasting insulin levels, which in turn contribute to insulin resistance and the development of type 2 diabetes. Consequently, researchers have concluded that fetuin B facilitates the connection between NAFLD and type 2 diabetes by promoting insulin resistance (18).

Exercise is well-recognized for stimulating the secretion of various hepatokines that play key roles in metabolic regulation. Physical activity can enhance the release of beneficial hepatokines such as FGF21 and follistatin, which are associated with improved insulin sensitivity and reduced inflammation. Studies have demonstrated that both aerobic and resistance training can significantly lower fetuin-A levels in individuals with type 2 diabetes (19, 20). The secretion of these hepatokines is influenced by exercise intensity, with higher-intensity workouts generally leading to a more pronounced effect on hepatokine levels (21).

It has been reported that various forms of exercise can play an effective role in preventing and even improving type 2 diabetes, offering a cost-effective solution (22). Additionally, consuming broccoli has been shown to significantly improve insulin resistance and enhance the beneficial adaptations resulting from exercise, particularly in individuals with type 2 diabetes (23). While the positive effects of exercise and broccoli supplementation on insulin resistance are well-established, there is limited information on the individual effects of each intervention, particularly their combined impact on hepatokines, as investigated in this study. Furthermore, the inflammatory pathways and mechanisms underlying the concurrent effects of exercise and broccoli supplementation in individuals with type 2 diabetes remain unclear. Therefore, the aim of this study was to examine the effects of 12 weeks of combined exercise and broccoli consumption on plasma levels of fetuin A and fetuin B in men with type 2 diabetes. In conclusion, further investigation into how broccoli consumption, in conjunction with exercise, influences hepatokines is crucial for enhancing our understanding of metabolic health, developing effective interventions for chronic diseases, and identifying biomarkers that reflect the dietary impacts on liver function and overall metabolism.

Table 1. Values of height, weight and BMI variables in research groups (mean ± standard deviation)

Variable		Control	broccoli group	exercise group	exercise - broccoli group
height (cm)		169.53 ± 5.5	171.26 ± 4.8	169.25± 4.61	171.81± 3.81
weight (kg)	Before	90.36 ± 4.56	89.00 ± 3.31	90.09 ± 4.41	90.63 ± 4.90
	After	90.72 ± 3.90	89.18 ± 3.57	83.90 ± 3.53	83.09 ± 3.78
BMI (kg/m2)	Before	31.34 ± 1.13	30.38 ± 1.34	31.51 ± 0.84	31.06 ± 0.82
	After	31.46 ± 0.96	30.43 ± 1.33	30.29 ± 0.74	29.17 ± 0.78

Materials and Methods

The current study is applied in nature with respect to its objectives and employs a semi-experimental methodology. The statistical population of the study consisted of men aged 25 to 40 with type 2 diabetes residing in Tehran (Table 1). Participants were selected using purposive and convenience sampling methods. Initially, information was disseminated by contacting diabetes centers and reaching out to various offices, institutions, hospitals, municipalities, neighborhood centers, clinics, and doctors' offices. Volunteers interested in participating were then registered. The inclusion criteria for the study were as follows: a diagnosis of type 2 diabetes (defined as a history of more than two fasting glucose readings above 126 mg/dL, along with an HbA1c level exceeding 6.5%, and currently under medical supervision); no cardiovascular, musculoskeletal, or metabolic diseases that would limit physical activity; no history of high blood pressure; no regular exercise participation in the past six months; and not being on insulin therapy. Participants were also required to complete a readiness questionnaire for physical activity and undergo a health examination by a physician to confirm their eligibility for the exercise program.

The exclusion criteria included a history of serious diabetic complications, such as proliferative diabetic retinopathy, stage 3 or overt nephropathy, diabetic ketoacidosis, or severe diabetic neuropathy; fasting glucose levels exceeding 270 mg/dL; the requirement for insulin therapy; hereditary malabsorption of glucose and galactose; and renal glycosuria.

A total of 44 participants (mean age: 28.39 ± 2.08 years, mean weight: 89.75 ± 5.14 kg, mean body mass index: 31.1 ± 2.56 kg/m^2) were randomly assigned to one of four groups, with 11 individuals in each group: the exercise plus broccoli group (Exercise + Broccoli G), the exercise group (Exercise G), the broccoli group (Broccoli G), and the control group (Control G).

Determine the Maximum One Repetition Maximum (1RM)

The 1RM (one-repetition maximum) for participants in the resistance training group will be assessed using the Brzycki method. In this process, a weight will be selected that allows the participant to perform a maximum of 6-8 repetitions. The weight lifted will then be entered into the appropriate formula along with the number of repetitions to calculate the 1RM. The training stations will include the following exercises: leg press, leg flexion, leg extension, chest press, lat pulldown, forearm curl, triceps extension, and shoulder press (24).

$$1RM = weight / (1.0278 - 0.0278 \times reps)$$

Exercise Protocol

All training groups participated in a combined aerobic-resistance exercise program three times per week for 12 weeks. The volume and intensity of the exercise regimen were designed based on established guidelines and relevant literature for individuals with type 2 diabetes (25-26). Each session began with a 5 to 10-minute warm-up, followed by 45 minutes of resistance training at an intensity of 60 to 70% of the one-repetition maximum (1RM). This was followed by 30 minutes of aerobic exercise (running) at an intensity of 60 to 70% of the maximum heart rate. The duration of aerobic exercise started at 10 minutes in the first week and gradually increased to 30 minutes by the eighth week, maintaining this duration until the end of the program. Each session concluded with a cool-down period. The control group continued their usual daily activities throughout the 12-week study period (14).

The eight resistance exercises targeted the major muscle groups of the upper body, lower body, and core. These exercises included the leg press, leg flexion, leg extension, chest press, lat pulldown, bicep curl, tricep extension, and shoulder press. After four weeks, participants were reassessed for their one-repetition maximum (1RM) to evaluate strength improvements. The aerobic component of the program involved running on a treadmill in the gym (Table 2).

Table 2. Aerobic and resistance combined exercise program

Group			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8-12
Aerobic and resistance combined exercise	aerobic exercise	duration (minutes)	10		15	20	20	25	30	30
		intensity (maximum heart rate)	60-65%		60-65%	60-65%	65-70%	65-70%	65-70%	65-70%
	Resistance training		The intensity is 60-65% of one repetition maximum				The intensity is 65-70% of one repetition maximum			

Supplementation

The broccoli supplement was provided as a powder by Sioux Nutrition Company (Irvine, CA, USA), with each participant consuming 10 grams daily for 12 weeks. Participants were instructed to take the supplement after breakfast, with their individual portions distributed at the start of the study. They were directed to open the capsule, dissolve the powder in water, and consume it. For the placebo group, starch powder capsules, colored with chlorophyll, were used (27). Data analysis between groups was performed using a two-way analysis of variance, while intragroup differences were assessed with a paired t-test. All statistical analyses were conducted using SPSS version 22, and results were considered statistically significant at $P<0.05$.

Results

To compare changes in plasma levels of fetuin A and fetuin B across the research groups, a two-way analysis of variance (ANOVA) was performed, with the results presented in Table 3. The analysis revealed significant differences between the groups, with fetuin A showing a p-value of 0.008 and fetuin B a p-value of 0.0001. These findings indicate that 12 weeks of combined exercise and broccoli supplementation significantly affect the plasma concentrations of both fetuin A and fetuin B in men with type 2 diabetes.

Table 3. Two-way analysis of variance test for Fetuin A and Fetuin B serum levels

Variable	Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Fetuin A	Corrected Model Intercept	2.438	3	0.796	3.931	0.020*
	Exercise	12.596	1	12.596	9.854	0.004*
	Supplement	0.365	1	0.372	10.348	0.001*
	exercise * supplement	0.758	1	0.758	11.639	0.002*
Fetuin B	Corrected Model Intercept	1.889	3	0.569	3.598	0.033*
	Exercise	113.458	1	113.458	6.524	0.029*
	Supplement	0.526	1	0.526	8.192	0.001*
	exercise * supplement	0.963	1	0.963	8.369	0.015*

*Significant difference in $P \leq 0.05$

The results showed that exercise significantly affected plasma levels of fetuin A (p = 0.004) and fetuin B (p = 0.029) in men with type 2 diabetes. Additionally, broccoli supplementation had a significant main effect on plasma levels of both fetuin A (p = 0.001) and fetuin B (p = 0.001). Furthermore, the interaction between exercise and broccoli supplementation produced significant effects on the plasma levels of fetuin A (p = 0.002) and fetuin B (p = 0.015). All results were statistically significant at P < 0.05 (Table 3).

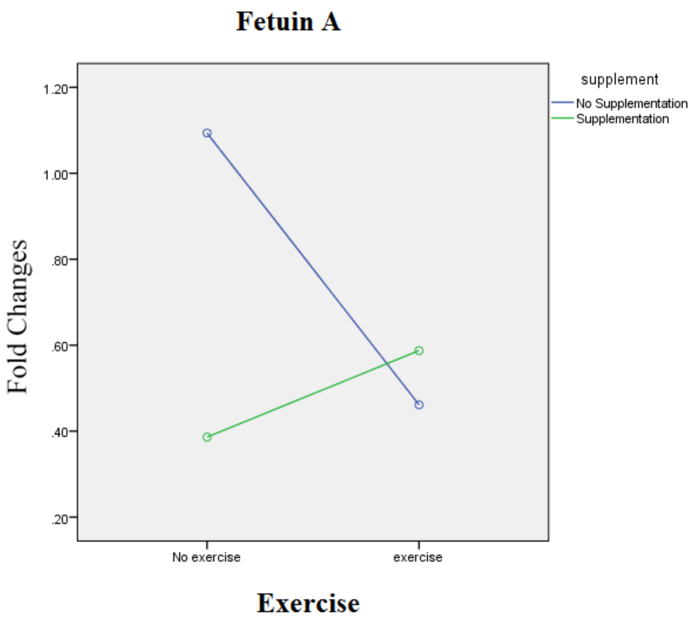

Figure 1. The interaction effect of exercise and supplementation on Fetuin A levels (Fold Change) in men with type 2 diabetes

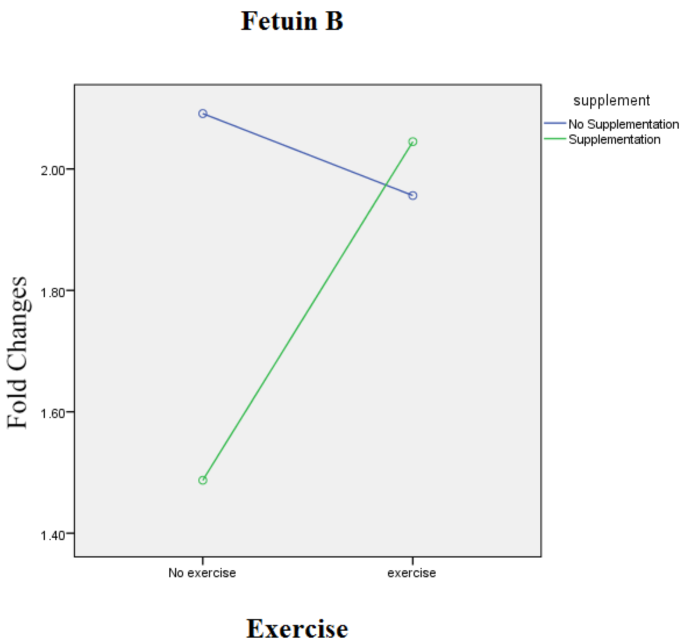

Figure 2. The interaction effect of exercise and supplementation on Fetuin B levels (Fold Change) in men with type 2 diabetes

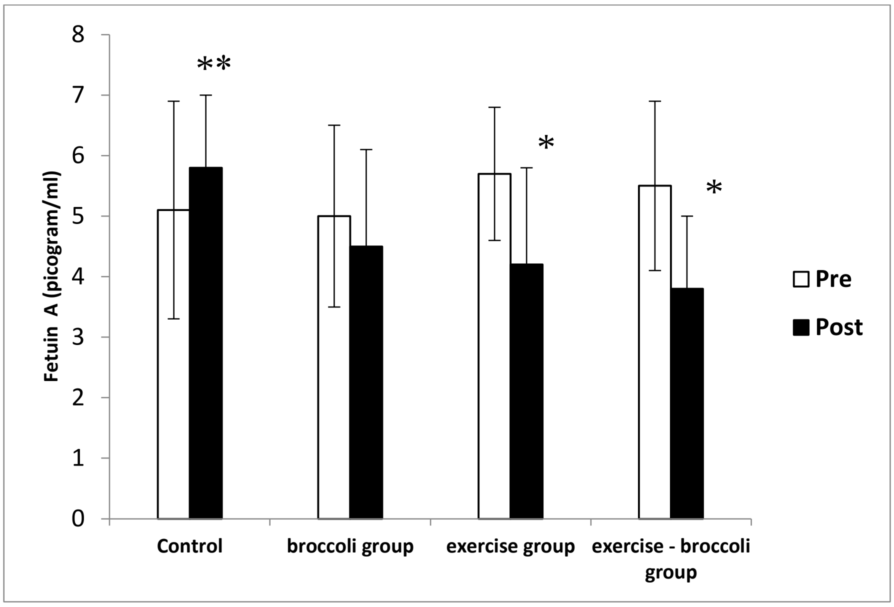

Figure 3. Fetuin A serum values. * sign of significant difference between pre-test and post-test in exercise and supplementary exercise groups, ** sign of significant difference between control group and exercise and supplementary exercise group.

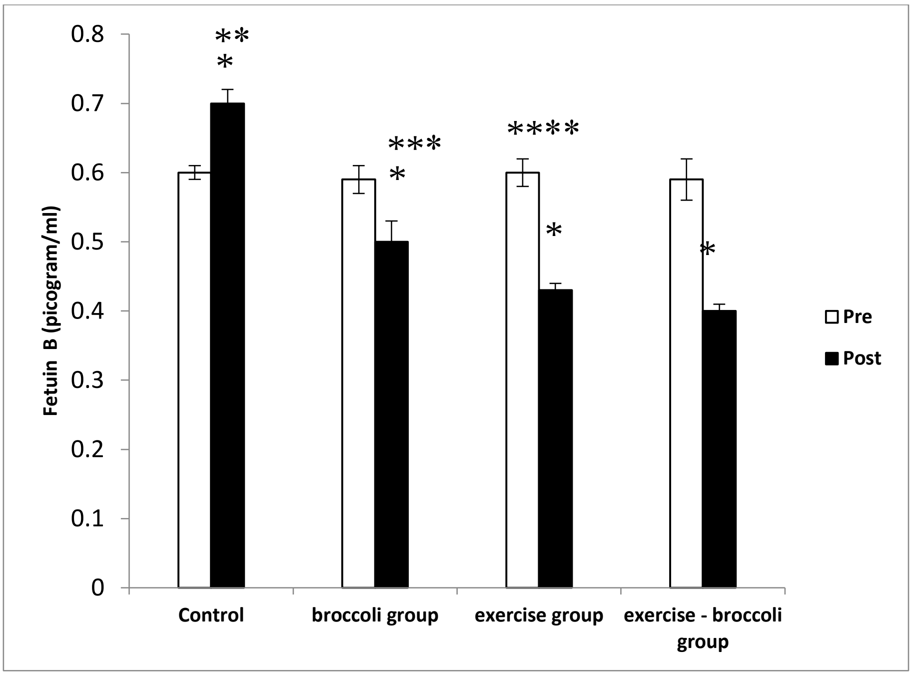

Figure 4. Fetuin B serum levels. * sign of significant difference between pre-test and post-test in the research groups, ** sign of significant difference between the control group and supplement, exercise and supplement training groups, *** sign of significant difference Supplementary group with exercise group and supplementary exercise. ****. The sign of a significant difference between the training group and the supplementary training group

Discussion

One of the key findings of this study was the significant reduction in fetuin A and fetuin B levels after 12 weeks of combined exercise in men with type 2 diabetes. This observation aligns with several studies. For instance, one study reported a significant decrease in fetuin A levels after 8 weeks of aerobic and combined training compared to a control group (28). Another investigation found that weight loss through dietary changes and physical activity in children with metabolic syndrome also led to lower fetuin A levels (29). Additionally, a meta-analysis by Ramírez-Vélez et al. (2019), which reviewed the effects of aerobic exercise on fetuin A levels in obese individuals, those with type 2 diabetes, and older adults, included 189 studies and revealed that 78 of these studies reported a significant reduction in fetuin A levels, particularly among participants with lower body mass index (30). Fetuin A is recognized as a protein that connects fatty liver disease, insulin resistance, metabolic syndrome, and obesity (31). In cellular models, fetuin A was shown to bind to insulin receptors, inhibiting tyrosine kinase phosphorylation and disrupting insulin signaling pathways. In experiments with mice treated with fetuin A, researchers observed decreased serum free fatty acid and triglyceride levels, reduced weight gain, and improved insulin sensitivity (32).

Studies have shown that fetuin A promotes insulin resistance and inflammatory responses through Toll-like receptor (TLR) pathways (33). The mechanisms responsible for the reduction of fetuin A following exercise are multifactorial, including decreased liver glucose toxicity through modulation of reactive oxygen species, inhibition of pro-inflammatory mediators (34), reduction in intrahepatic fat, and positive regulation of proliferative peroxisome proliferator-activated receptor gamma (35). Additionally, the activation of protein kinase B (Akt) and the phosphorylation of its substrates indicate improvements in glucose tolerance and reductions in insulin resistance (36). Elevated levels of fetuin B have been observed in patients with cardiovascular disease, type 2 diabetes, non-alcoholic fatty liver disease, and obesity (37). Fetuin B is primarily associated with glucose intolerance (38). In diabetic obese rats with hepatic osteogenesis, blocking fetuin B resulted in improved glucose tolerance. Moreover, a positive correlation has been identified between inflammation, insulin resistance, and fetuin B levels (15).

In another study, fetuin B levels were found to be elevated in women with gestational diabetes compared to healthy pregnant women (39). Several studies have also demonstrated a positive correlation between fetuin B levels and LDL and total cholesterol (40, 41). Research has shown that both aerobic and resistance training in individuals with type 2 diabetes lead to significant reductions in fetuin A and fetuin B levels, with resistance exercise resulting in a more pronounced decrease compared to aerobic exercise. This suggests that exercise training can alleviate certain symptoms of type 2 diabetes, including the dysregulation of hepatokines such as fetuin A, fetuin B, and FGF-21. Exercise enhances insulin sensitivity by inhibiting the natural inhibitor of insulin receptor tyrosine kinase in the liver and improving the synthesis activity of GLUT4, glycogen, and hexokinase. Additionally, it facilitates glucose delivery to muscles (42). Furthermore, high-intensity interval training in women with fatty liver has been shown to significantly reduce levels of fetuin B and RBP4 (41).

Conclusion

The findings of this study indicated that 12 weeks of combined exercise resulted in a significant reduction in both fetuin A and fetuin B levels in men with type 2 diabetes. Notably, the reduction was more pronounced when broccoli was consumed alongside the exercise regimen. Given the more significant effects of the combined exercise and broccoli supplementation on these hepatokines and adipokines, it is advisable for individuals with type 2 diabetes to incorporate both broccoli consumption and combined exercise into their routine. This approach may help control, or even improve, diseases related to insulin resistance and metabolic dysfunction.

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