The effect of twelve weeks of combined training with and without canagliflozin consumption on fetuin A and fetuin B in type 2 diabetic men

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Abstract

Introduction: Cardiovascular disease, diabetes, and fatty liver are now considered the major causes of mortality in developing countries. The present study investigates the effect of twelve weeks of combined training with and without canagliflozin consumption on fetuin-A and fetuin B in type 2 diabetic men.
Materials and Methods: Forty- four men (25-40 years) who had type two diabitiac were recruited for this study. This is a double-blind study conducted in four groups. For this purpose, diabetic men were divided into four groups of 11 individuals, including control-diabetes, diabetes-medication, diabetes-training, and diabetes-training-supplementation. Every day, 200 mg of canagliflozin and placebo were given to medication-consuming and placebo groups. Blood samples were taken before and 48 hours after the last training session and used for analysis.
Results: Two-way ANOVA results showed a significant difference between groups (P<0.001) for fetuin A-amounts. Bonferroni test results also showed a significant difference between control and training (P = 0.030), control and medication-training (P<0.001), medication-training, and medication (P<0.001) and medication-training and training (P= 0.001) groups. The two-way analysis of variance showed significant differences between groups (P = 0.023) in terms of fetuin B amounts. The post hoc test results showed a significant difference between control and training groups (P = 0.009) and control with training-medication groups (P = 0.007).
Conclusion: According to our results, the administration of a combination program, alongside the use of canagliflozin, on individuals who have type 2 diabetes may have the most significant effect on reducing these hepatokines in people with diabetes.

Keywords: Combined Exercise, Hepatokine, Type 2 Diabetes, Canagliflozin

Introduction

Diabetes is the most common metabolic disease globally, resulting in an overwhelming insulin deficiency or resistance to glucose. There are two major diabetes forms, including type 1 diabetes and type 2 diabetes (1). Type 1 diabetes occurs when insulin-producing beta cells are destroyed in the pancreas and thus are insufficiently produced. Type 2 diabetes is caused by insulin resistance when enough insulin exists. It is usually associated with obesity, which can increase insulin resistance (1-3). As you gain weight and therefore body fat percentage increases, metabolic disorders such as type 2 diabetes, dyslipidemia, or cardiovascular disease are increased, directly related to the release of cytokines and

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adipokines/hepatokines (fetuins). Fetuins were first isolated from human plasma in 1960 and are mainly known as Alpha2-HS glycoprotein (AHSG) and play a role in various pathophysiological functions such as inflammation, osteogenesis of liver cells, and inhibition of vascular calcification by keeping soluble calcium and phosphorus in serum (4). Fetuin-A is mainly produced by the liver. The fatty visceral and subcutaneous adipose tissues also release less fetuin-A; in addition, changes in body fat percentage resulting from a diet and weight loss have been positively correlated with changes in fetuin-A (5). Fetuin-A is an abundant protein in the serum that has recently been shown to be associated with obesity, fatty liver, insulin resistance, and metabolic syndrome (6). In mice suppressed with fetuin-A, an increase in insulin sensitivity, resistance to weight gain, and a decrease in free fatty acid and serum triglyceride levels were observed (7). Recent studies have shown that fetuin-A induces insulin resistance and inflammatory signals through Toll-Like Receptors (TLR) (8). In some cross-sectional studies reporting a positive correlation between Fetuin-A and insulin resistance in people with diabetes, fetuin-A has been reported as an independent indicator of body composition and risk factors; it has also been reported that it predicts the incidence of type 2 diabetes, not considering other factors, at the onset of the disease (9). Fetuin-A increases insulin resistance through the expression of pro-inflammatory factors such as cytokines in monocytes and adipocytes; it also decreases adiponectin expression (10, 11). In their study, Hennig et al. stated that liver hepatocyte A protein's secretion leads to lower levels of inflammation and suppression of adiponectin production in animals and humans. These data indicate the important role of the fatty liver in the pathophysiology of insulin resistance and atherosclerosis (10). Another type of fetuins is fetuin-B, which has recently received special attention due to its structural similarity to that of A. Fetuin B, has been introduced as a novel hepatokinin that contributes to hepatic steatosis and glucose intolerance (12). Blocking of fetuin B in diabetic rats with liver osteogenesis has been shown to improve glucose tolerance and insulin sensitivity; in addition, the association between fetuin-B and inflammation and insulin resistance has also been reported (13). Several studies have reported increased levels of Fetuin-B in non-alcoholic fatty liver patients, individuals with heart disease, and those with type 2 diabetes- as well as obese adults (13, 14). There is a positive correlation between low-density lipoprotein (LDL) levels and this type of hepatokinin with the functional mechanisms of fetuin-B; in addition, a positive correlation has been found between total cholesterol (TC) and fetuin-B, so it may be possible to correlate between fetuin-B and Dyslipidemia (14). Regular exercise has been identified as one of the contributing factors to reduce obesity and related diseases. It has also been proved that training makes insulin sensitivity and insulin resistance in obese or healthy people who have type 2 diabetes better. In a study, it was observed that insulin sensitivity and lipid profile, six months of aerobic training, cause a significant increase in fetuin-A (15). In another study conducted on obese non-diabetic subjects, applying six weeks of aerobic training caused no significant changes in the levels of fetuin-A. It has been suggested that the type of exercise may affect changes in this type of fetuin (16). In another research, it was expressed that while fetuin-A is associated with insulin resistance in diabetic individuals, this correlation does not hold in non-diabetic ones; therefore, this fetuin may be an independent factor in healthy individuals, whose changes is associated with various mechanisms (17). Extensive research is needed to determine the effect of training on

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fetuin, as one of the contributing factors to increased insulin resistance, but the findings are very contradictory. In addition to exercise and physical activity, supplementation effects, medications, and nutritional conditions can also affect diabetes. Canagliflozin is a potent and selective inhibitor of sodium-glucose transport protein 2 (SGLT2) (18). A single-phase study in healthy men showed that a dose of 800 mg (morning) significantly increased the dose-dependent urinary glucose excretion (UGE) and decreased the dose-dependent renal threshold glucose (RTG)(19).

In type 2 diabetic patients, when treatment (100 mg once daily or 300 mg twice daily) was added to insulin for 28 days, RTG level decreased, UGE increased, and hemoglobin A1c (HBA1C), fasting glucose, and body weight soared in comparison with the control group (20). In another 12-week study, adding this substance to metformin showed a significant improvement in glycemic index, low hypoglycemia, and a significant decrease in weight compared to placebo (21). Another study was conducted by applying 100 or 300 mg canagliflozin once daily for 26 weeks on diabetic patients who followed a particular food and training regime, only a significant decrease in HBA1C, fasting blood glucose, and blood pressure was observed compared with placebo(22).

As a supplement that has been shown to have a positive effect on diabetic patients, canagliflozin can have a more significant positive effect on diabetes and related diseases if combined with exercise.

Since these indices play a role in modulating insulin resistance and have a direct relationship with systemic inflammation, in addition; having in mind the fact that it is also little or no research on the effects of training on these indices, it seems necessary to study their changes as a result of sport exercises and canagliflozin consumption. Therefore, this study investigates the effect of combined training along with the consumption of canagliflozin on fetuin-A and fetuin B in diabetic men.

Materials and Methods

The research is quasi-experimental with pre-test and post-test design with four groups. This study's statistical population included all men aged 25-40 years who had type 2 diabetes in Tehran. Firstly, we referred to diabetes centers and issued a call in offices, institutions, hospitals, municipalities, neighborhood cultural centers, and physicians' offices. The volunteers were then enrolled in the study. The inclusion criteria included: afflicting with type 2 diabetes (individuals whose fasting glucose level was twice as much as 126 mg/dl and their HbA1c was more than 6.5% at the time of the study- they were under the supervision of the physician at the time of the study), lack of cardiovascular, musculoskeletal and metabolic diseases limiting exercise, lack of hypertension, lack of regular exercise activity for the past six months and not receiving insulin. Subjects were asked to complete a questionnaire on preparation for starting a sports activity. Subjects were also examined by a physician to verify their health in order to participate in the exercises. On the other hand, given that individuals with type 2 diabetes are at high risk for heart disease, a cardiovascular specialist approved their participation in the study. Those subjects who used drugs for lowering blood pressure and lipid were excluded from this study. Given that canagliflozinis had been used in the past, a pilot study was conducted on about 20 diabetic patients under the supervision of a physician and the consumed doze was approved based on the previous studies. Indices of the exclusion from the study included a history of serious diabetic complications (such as proliferative diabetic retinopathy, stage 3 or subsequent onset nephropathy, diabetic ketoacidosis, or

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serious diabetic neuropathy), fasting glucose above 270 mg/dl, a sign of using insulin for medication, hereditary uptake of glucose and galactose or renal glycosylation. After providing information, patients selected for diet and training research were included in a four-weeks, blind, placebo-controlled study (match the subjects' nutrition and physical activity). Forty-four subjects were randomly divided into four groups of 11, including training-medication, training, medication, and control. During the meetings, the volunteer participants were introduced to the type of study, its goals and method of implementation, its benefits, and potential risks. Informed consent was obtained from each of the subjects.

Before starting the training program, the participants take part in three sessions of familiarization with the exercises, the principles of exercise safety, and how to use bodybuilding routines. Then the values of a maximum repetition were determined by the Brzeski method. A nurse and a sports trainer were present in all of the sessions. Every training session included 5 minutes of warm-up, 45 minutes of resistance training with 60-70% of maximal repetition, 30 minutes of aerobic training (running) of 60-70% of maximal heart rate. The duration of aerobic exercise was 10 minutes at the beginning of the study, which gradually increased to 30 minutes in the eighth week and remained constant until the end of the study. The workout program eventually ended with the body cooling down. The control group performed their normal daily activities during the 12 weeks of the research program. Resistance training consisted of the upper, lower trunk, and major muscle groups, including leg press, leg flexion, leg extension, chest press, armpit, front arm, and back arm and shoulder. After four weeks, subjects were again tested for one repetition maximum in order to increase the subjects' strength. Aerobic training included running in the gym. Subjects were given the canagliflozin drug 200 mg daily (TA-7284 and JNJ-28431754; Mitsubishi Tanabe Pharma Corporation/Janssen Research & Development, LLC). A food reminder sheet was taken from all the subjects.

In order to measure the biochemical variables, blood sampling was taken after 12 hours of fasting and in two stages 48 hours before the beginning of the program and 48 hours after the last session of intervention. Blood samples were taken from the brachial vein of subjects in the sitting position and collected in EDTA tubes (Ethylene Ediamine Tetraacetic Acid) and then centrifuged at 3500 rpm for 15 minutes at 4 °C. ELISA kits (Epitope Diagnostics, San Diego, CA), and the human ELISA kit (Abcam, Cambridge, MA, USA) was also used for analysis of fetuin A and fetuin B.

Shapirovilk test was used to determine the normality of the data distribution. Bivariate analysis of variance was used to determine the significance of the differences between the variables and their interaction, and if the data were significant, the Tukey post hoc test was used. Results were analyzed at a 95% confidence level ($P<0.05$). Intra-group changes were also assessed using a paired t-test. Data were analyzed using version 25 of IBM SPSS Statistics software.

Results

The results of the two-way analysis of variance showed that there was a significant difference for the amount of fetuin-A between-group ($P<0.001$), time ($P<0.001$), and group-time interaction ($P<0.001$). Bonferroni test results showed a significant difference between control and exercise ($P = 0.030$), control and medication-training ($P<0.001$), medication and medication-training ($P<0.001$) and medication-training with training ($P<0.001$). In addition, intra-group changes showed that there was a significant decrease in fetuin-A in the

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medication (P = 0.008), training (P = 0.002), and training-drug medication(P<0.001) (Figure 1). The results of two-way analysis of variance showed that there was a significant difference for the amount of fetuin B between group (P = 0.023), time (P<0.001) and group-time interaction (P = 0.005). Bonferroni test results showed that there was a significant difference between control and training groups (P = 0.009) and control and training-medication groups (P = 0.007). In addition, studying intra-group changes showed that there was a significant decrease in fetuin B in the training group (P = 0.031) and training-medication group (P<0.001) (Figure 2).

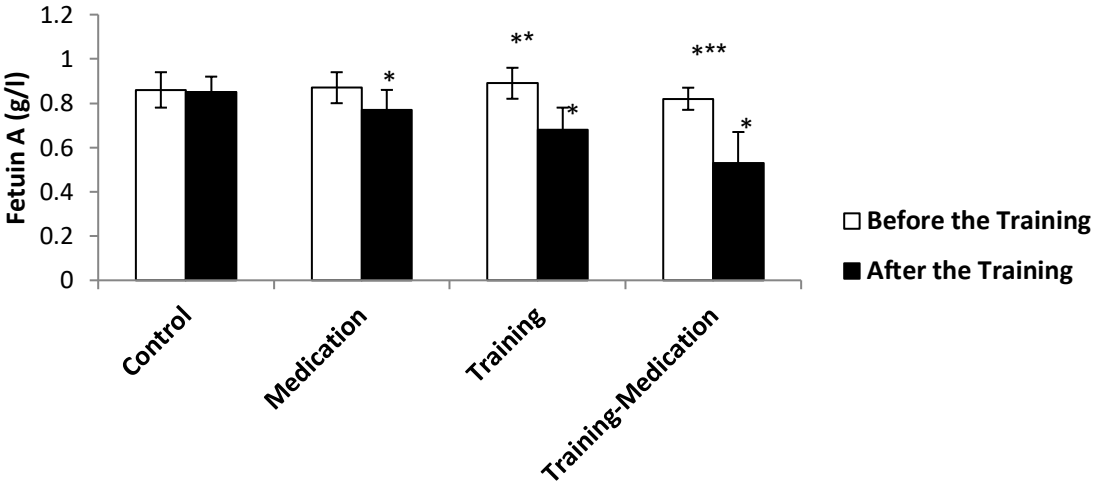

Figure 1. Plasma concentrations of fetuin A in the control, medication, training and training-medication groups. *Significant difference in pre-test and post-test values of medication, training and training-medication groups. **Significant difference between training group and control group.
***Significant differences between the medication-training group and the training, medication and control groups. Data have been shown as mean ± standard deviation.

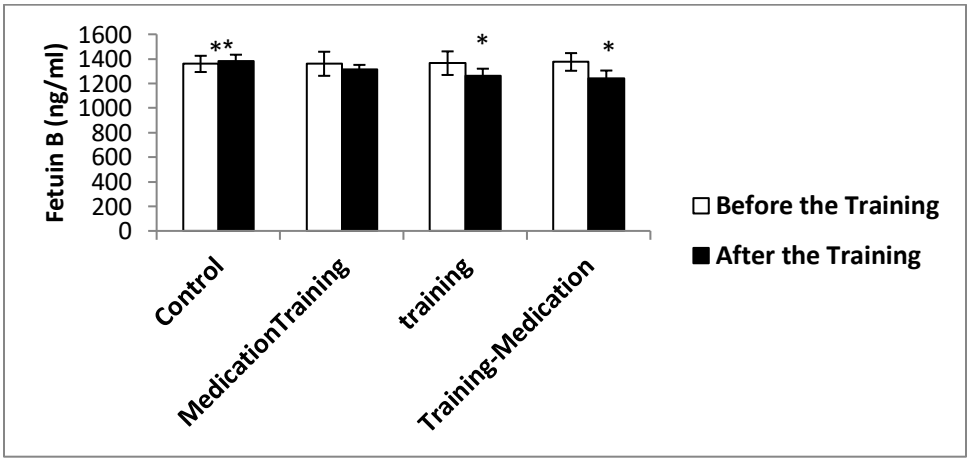

Figure 2. Plasma concentrations of fetuin B in the control, medication, training and training-medication groups.
*Significant difference in pre-test and post-test values of medication, training and training-medication groups.
**Significant difference between training group and control group.
***Significant differences between the medication-training group and the training, medication and control groups. Data have been shown in the form of mean ± standard deviation (P <0.05).

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Discussion

Metabolic disorders such as type 2 diabetes are directly linked to the release of cytokines and adipokines/hepatokines (photosynthesis). One of the most important findings of our study was a significant decrease in fetuin-A in the three groups of medication, training, and medication-training; this decrease was significantly greater in the medication- training group than the other two ones. Studies regarding the effect of training on fetuin-A are limited and reliant on aerobic exercise, and conflicting results have been shown in this regard. In one study, weight loss decreased due to increased physical activity, and the resultant decreased fetuin-A levels were positively correlated with a decrease in liver fat content (26). In another study, obese older men and women showed a decrease in fetuin-A levels after 12 weeks of aerobic exercise, associated with improved body composition and metabolism (27). Contrary to our findings, fetuin-A, aerobic capacity, body composition, and insulin sensitivity were evaluated in a study of obese non-diabetic patients after six months of aerobic exercise. fetuin-A was positively correlated with body fat and negatively correlated with insulin sensitivity. After six months of aerobic exercise, despite a significant increase in insulin sensitivity and lipid profile, there was a significant increase in the levels of fetuin-A, and a positive correlation between fetuin-A and aerobic capacity was reported (15). Also, 12 weeks of aerobic training did not significantly change the levels of fetuin-A in obese older men and women (27). Regarding the correlation between fetuin-A and the indices involved in type 2 diabetes, a research has shown that fetuin-A is associated with insulin resistance in diabetic individuals. Thus, fetuin-A may be an independent factor in healthy individuals; whose changes are related to different mechanisms (17). In mice with suppressed fetuin-A, increased insulin sensitivity, resistance to weight gain, and decreased serum free triglyceride and fatty acid levels were observed. Fetuin-A reduces lipogenic pathways in adipose tissue by inhibiting the PPARγ signaling pathway and promotes lipolysis (28); in addition, it acts as an adapter protein for activating the Toll-like-TLR4 receptor (TLR4) to induce signaling inflammation and insulin resistance. In cell culture models, it has been observed that fetuin-A binds to insulin receptors and inhibits tyrosine kinase phosphorylation and insulin signaling (29). It has also been shown to inhibit glucose transporter type 4 (GLUT-4) function in C2C12 muscle cells by inhibiting the insulin receptor by reducing AS160 phosphorylation (30). Research has attributed the decrease in post-exercise fetuin-A to glycemic recovery after exercise made due to changes in insulin resistance in muscle or liver cells (27). Since some studies have not reported a direct relationship between insulin resistance and fetuin-A, this fetuin may indirectly modulate skeletal muscle glucose uptake by affecting CHO oxidation (glycolysis, Krebs cycle, and oxidative phosphorylation) (27). A meta-analysis paper also reported several possible mechanisms for decreasing fetuin-A after exercise, including reduction of liver fat by down-regulating sterol regulatory element-binding protein-1c and regulation of receptor γ expression level of peroxisome proliferator-activated receptors, reduction of hepatic hyperglycemia by modulating reactive oxygen species through inhibiting pro-inflammatory mediators and activating protein kinase B (or Akt) and phosphorylation of AS160 substrates that improve glucose tolerance and decrease insulin resistance (31). Other findings showed a significant decrease in fetuin-B levels in the training and training-medication groups and a significant increase in the control group compared to two training and training-medication groups. Consistent with

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our findings in a study of type 2 diabetic men, individuals were assigned to endurance and resistance training groups. After eight weeks of intervention, a decrease was observed in both fetuin-A and fetuin-B levels, and this decrease was significantly higher in the resistance training group. In this study, it was reported that the decrease in fetuin-A and fetuin-B correlates with lower blood glucose and insulin resistance in individuals with type 2 diabetes. It was also announced that the level of fetuin-A and fetuin-B increases the probability of type 2 diabetes more than twice a decrease in fetuin-A and fetuin-B correlates with lower blood glucose and insulin resistance in individuals with type 2 diabetes (32). One study reported that secretion of fetuin-B by hepatocytes isolated in mice afflicted with hepatic steatosis increased and impaired glucose homeostasis in humans and rodents. It has also been suggested that fetuin-B protein reduces insulin function in the body and implicates in the development of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (33). Regarding the functional mechanisms of fetuin-B, a positive correlation has been noted between LDL levels and this type of hypokine; in addition, a positive correlation has been shown between total cholesterol (TC) and fetuin B (14). Therefore, aerobic or resistance training may have a role in decreasing fetuin B by reducing their insulin resistance, increasing insulin sensitivity, and lowering plasma or hepatic lipid levels.

In addition to exercise training, the use of supplements or adjuvants in recent years has received much attention in the control or treatment of type 2 diabetes. Canagliflozin is one of the drugs that is used to control the disease and has been considered as a supplement that has been shown to have a positive effect on diabetic patients; its main effect is on the function of renal tubules. About half of diabetic patients develop symptoms of kidney damage in their lifetime. Diabetic nephropathy is the most common renal complication of diabetes. Diabetic nephropathy is said to be a progressive increase in the excretion of protein (albuminuria) from the urine, which has been seen in chronic diabetic patients, leading to a decrease in renal function and ultimately to renal failure (34, 35). Normally 90% of the filtered glucose in the kidney glomeruli is reabsorbed by the curved tubes close to the kidney nephrons. The trigger for this uptake is SGLT2. Canagliflozin inhibits the carrier and thus prevents glucose uptake and excretion in the urine. This type of function results in hyperglycemia in patients with hyperglycemia (36). Thus, this drug may have a role in reducing glucose and increasing insulin sensitivity in type 2 diabetic patients or non-diabetic patients with renal impairment (36). Studies have also shown that weight loss due to canagliflozin administration has been shown to decrease with HbA1c and systolic blood pressure in diabetic patients (37). Another study has also shown that canagliflozin improves insulin resistance and beta-cell function. In vitro conditions in this study, it was shown that part of the islets of Langerhans treated with canagliflozin was resuscitated to alpha and beta cells compared with the control group, which was attributed to reduced beta-cell apoptosis (38). In our study, the medication group did not show a significant change in fetuin-B levels. Investigating the functional mechanisms of this drug and fetuin-B requires further studies, but available evidence may suggest that fetuin-B or canagliflozin may act independently of insulin resistance or the dose of canagliflozin was insufficient to affect fetuin-B.

Conclusion

This study showed that twelve weeks of combined training with canagliflozin significantly reduced fetuin-A and fetuin-B in the training and medication- training

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groups. In general, given the positive effects of conglafluzine as a supplement for diabetic patients, it can positively affect the improvement of diabetes and related diseases if it is consumed concomitant with exercise training. Aerobic exercise reduces urinary protein excretion by lowering blood glucose and blood pressure. It also reduces insulin resistance and increases insulin sensitivity. On the other hand, resistance exercise has a positive effect on glomerular filtration rate. Its effects on insulin sensitivity have been reported. Therefore, our results suggest that a combined plan with canagliflozin consumption may significantly affect type 2 diabetes by reducing inflammatory markers and controlling diabetes.

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