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Original Article

The effect of 12 weeks of Aqua training on RBP4, insulin resistance, and liver enzymes in women with type 2 diabetes

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Abstract

Background & Aims: Retinol-binding protein 4 (RBP4) as an adipokine is involved in regulating insulin function and glucose metabolism. Serum levels of RBP4 have been identified as one of the most effective factors in impaired glucose tolerance and diabetes. Studies have shown that exercise improves metabolic syndrome and hepatotoxicity. But the effects of Aqua training on liver Enzymes in diabetic patients are still unknown. Therefore, the aim of this study was to investigate the effect of Aqua training on RBP4, insulin resistance, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes in women with type 2 diabetes.

***Materials & Methods*:** Forty-four women with type 2 diabetes (57.83± 0.42 years) were selected through available sampling and divided into two groups of control and training. The training group performed the exercise in the water at 60-75% of maximum heart rate for 12 weeks (three sessions per week, 60 minutes each session). Data were analyzed with dependent and independent t-test at the significant level of $p \leq 0.05$.

Results: The results show that 12 weeks of Aqua training significantly reduced RBP4, insulin resistance, and AST and ALT, and improved lipid profiles ($p \leq 0.05$). Also, the result of Independent t-test showed that there is a significant difference between training groups with control in variables of RBP4, insulin resistance, liver enzymes and lipid profiles ($p \leq 0.05$).

Conclusion: Based on the results of the present study, the Aqua training decrease RBP4, that it is associated with improved insulin resistance. Also 12 weeks of Aqua training has an insulin-like effect on diabetic women with changes in liver and metabolic enzymes.

Keywords: Liver Enzymes, Metabolic Indices, Aqua training, Women with Diabetes

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Introduction

Almost 6 percent of the world's population is suffering from type 2 diabetes. One of the major reasons for this disease is the deficiency in insulin secretion, its function or both (1). As a result, the increase in glucose level (Hyperglycemia) leads to malfunctioning in carbohydrate, fat and protein metabolism (1). Also, type 2 diabetes often leads to lipid metabolism disturbances that it cusses hyperlipidemia (1). Hyperlipidemia shows abnormal amounts of fat in the bloodstream. The large amounts of fat in the body can cause problems in metabolism homeostasis (2). Liver, as an important part of the body, is one of the important organs affected by obesity and diabetes (2). The research shows that

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excessive use of calorie causes fat synthesis and increases triglycerides amounts in the liver. When the liver can't decompose this fat in a natural process, the accretion of fat may exceed to 5 percent of liver weight and may lead to fatty liver (3). The accretion of fat in the liver even it happens without inflammation is frequently diagnosed in people suffering from obesity and diabetes and those with other metabolic syndrome parts (3). Diabetes is more frequent in females due to inactivity and the increase of adipose tissue. Adipose tissue secretes a multi-layered protein called adipokine which plays an important role in adjusting insulin action (4). In this regard, retinol-binding protein 4 (RBP-4) is an adipokine derived from adipose tissue which increases resistance to insulin in human and animal systematically (5). RBP4 is a composition with light molecular weight which is secreted by liver, adipocytes and skeletal muscle. RBP4 causes an increase in resistance to insulin through insulin signaling disturbances. This happens in the liver by gluconeogenesis process. This protein carries vitamin A in bloodstream (6).

Recent studies show AST and ALT are the best indexes for evaluating the status of the liver. When liver cells are damaged, the number and the activity of these enzymes increase in blood (7). AST enzyme is related to the inflammation caused by fat accretion in the liver. Increased level of AST in plasma is related to metabolic syndrome, hyperglycemia, type 2 diabetes, and cardiovascular diseases (7). Several factors can increase the effect of this disease. The most common factors are inactivity, aging, high blood pressure, changes in serum fat contents, and increase in Hemoglobin A1C (HbA1c) (8). Various studies show that exercises and physical activities improve or treat metabolic syndrome, obesity, diabetes, and resistance to insulin (9, 10). Regular exercise decreases cardiovascular risk factor in individuals suffering from type 2 diabetes. It also improves blood sugar adjustment, increases energy consumption, facilitates fat oxidation, and decreases visceral fat. All of them can decrease fat in the liver tissue (11). Physical activity can also increase insulin sensitivity in individuals with or without diabetes. The positive effect of physical activity on decreasing resistance to insulin may be related to the changes in adipokines secretion (12). Based on the current study, individuals suffering from type 2 diabetes should perform regular aerobic exercise with moderate intensity. Also, physical activity and exercise cause secretion of adipokine. The researchers show that the amounts of adipokine are different between type 1 and type 2 diabetes. Some factors such as type of disease, age, gender, changes in blood glucose, and obesity may affect the adipokine levels (13). Tendler et al. (2007) studied patients with fatty liver and found that after 24 weeks of intervention; low-fat diet and physical activity improve weight, body mass index, waist, and amounts of AST and ALT significantly (14). The results of many studies show that physical activities can improve lipid profile, insulin resistance, and RBP4 (15, 16). Lim et al. (2008) reported the decrease of the serum levels of RBP4 after 10 weeks of aerobic exercises with the 60 to 80 percent of maximum oxygen consumption in obese women. The extent of RBP4 changes in middle-aged women is more than young women. The increase in insulin sensitivity caused by exercises has a significant relationship with RBP4 (5). However, Choi et al. (2009) reported that after three months of endurance training, five sessions a week with 60 to 75 percent of maximum heartbeat, there was no significant change in serum levels of RBP4 (17). Moghadasi et al. (2013) reported that aerobic exercises with low and medium intensity had no impact on gene expression or blood density of some adipokines (18). The results of some studies showed that aerobic exercise does not have any desirable effect on the level of blood lipids, glucose, insulin resistance, and RBP4 (19, 20). This contradiction may be due to the selection of the type of exercise and participants. For instance, Cox et al. (2010) compared the effect of swimming and jogging exercises on the fat and lipid profile distribution in the elderly but could not find a significant difference in lipid profile between the two groups (19). Despite the commonly-agreed-upon values of doing exercises, our society is not in desirable status with regard to physical activities. Unfortunately, inactivity is widespread among individuals suffering from type 2 diabetes due to the limitations in doing physical activities (21). Some of these people face difficulties due to obesity, arrhythmia problems, and cardiovascular diseases for doing physical activities on land. Water can provide conditions in which every individual receive resistance suitable based on their need. Also, water can engage both upper and lower parts of the body with appropriate motor domain. Thus, body joints tolerate the least pressure (11, 21). Also, exercise in water affects the whole body, improves cardiovascular conditioning, strengths muscles, endurance, posture, and flexibility at the same time. Your cardiovascular system in particular benefits because swimming improves your body's use of oxygen without overworking your heart (11). There is a low risk for Aqua exercise injuries since we weigh 1/10th less in water and also there is not any stress on bones, joints, or connective tissues due to buoyancy . Moreover, water exercises increase the ability of the elderly to maintain their balance and, thus, decreases the danger of collapsing and breaking bones (22). Since type 2 diabetes is a widespread disease in our country, individuals with this disease are prone to fatty liver, and there are few studies about the effect of doing exercises in water on enzyme levels of fatty liver and RBP4 in the obese suffering from diabetes. Also, Because of the volume of exercises in water is light, 12 weeks of training were used to create compatibility.

One of the reasons we used aqua aerobic exercise is due to the special characteristics of the population studied–patients with type 2 diabetes mellitus. For this population even their daily routine is physically demanding. Aqua aerobic exercise has different benefits: exercising in water requires you to support only 50% of your body weight; the risk of injury is comparatively lower due to its low-impact nature; stress and compression on the joints is less and the resistance offered by water leads to better muscular endurance and tone; the heart rate is maintained at a lower rate than in activities such as cycling and running. It was previously reported that there were no differences in the effects of aerobic activities in the water versus weight-bearing aerobic exercise on land (22). Thus, the present study investigates the effect of doing exercises in water on the amounts of RBP4, insulin resistance, and changes in the liver enzymes in women suffering from type 2 diabetes.

Material and Methodology

Subject:

The present semi-experimental study was conducted on the field and in the laboratory. Based on the exercise protocol, 44 females with type 2 diabetes aged 57.83± 0.42 years old were selected and divided into control group (n=22) and exercise group (n=22). Two participants were excluded from the training group for their irregular participation. Also, two subjects of the control group were excluded since they were not present when blood samples were taken.

Inclusion criteria: Women aged 55-60 years old with no physical exercises in the last two years, BMI more than 30, not taking narcotics and medical or nutritional supplements, not suffering from cardiovascular, respiratory, and orthopedic diseases, and not being banned for taking part in physical activities (11). Exclusion criteria: liver diseases like virus hepatitis B, C, self-immune hepatitis, high blood pressure, cardiovascular diseases, alcohol consumption, and being absent for more than 3 sessions (11). Based on the results of the medical and physical activity questionnaire, the selected individuals had not participated in any regular physical activity for the last

2 years and were at least suffering from type 2 diabetes for 4 years. Before the research began, the participants signed the consent forms.

Aqua training protocol:

The aqua training used in this study is defined as a training program in which an instructor leads patients with type 2 diabetes in aqua various exercises in water three times a week in 1-hour sessions, for a total of 36 sessions over 12 weeks. The training sessions included the followings: 1) 15 minutes stretching and warm-up in the water including walking backward and forward and to either sided while moving hands, and stretching hand, leg, stomach and back muscles, 2) aerobic basic exercises in the water for 30-45 minutes, and 3) Subjects with gentle walking and simple movements with low intensity and sleep and followings on the water, they were cooled down for 1-14 minutes. (Table 1) (18) . The subject reaches a score of 12–13 for the perceived level of exertion on the Borg 6- to 20-point rating scale. All the stages of the exercise for this study were done in a shallow swimming pool. Moderate to moderate/vigorous intensity of the exercise was attained via self-monitoring of reserve heart rates during the class. Based on the resting heart rate and maximal heart rate, the training heart rate was set to 50–75% of reserve heart rate based on the Tanaka et al. equation (23).

Table 1. Aqua training protocol

Time	Warm-up (15 min)	Aerobic exercises (30 min)	Cool-down (15 min)
Weeks 1-3	Walking around the pool and stretching	Doing basic aerobic exercises	Gentle walking and simple movements with low intensity and sleep and followings on the water
Weeks 4-6	Walking in the water with legs bent, walking in the water fast	Walking fast in the water and doing basic aerobic exercises	Gentle walking and simple movements with low intensity and sleep and followings on the water
Weeks 7-9	Walking to the sides in the water	Doing aerobics in the water	Gentle walking and simple movements with low intensity and sleep and followings on the water
Weeks 10-12	Walking in the water with legs bent and to the sides	Doing aerobics in the water	Gentle walking and simple movements with low intensity and sleep and followings on the water

The height (cm) of the subjects was measured using Meter strip, and weight was measured by digital Scale made in Germany with 0.1 kg accuracy. Body fat percentage and BMI were measured by Composition logic / Body fat analyzer Body made in South Korea. Heart rate was measured by Polar device model F1tm made in Finland. Also, the exercise time was measured by a digital stopwatch with 0.01 second accuracy. In order to measure biochemical variables, blood samples were taken from the weeks 8 to 10 at set-point and also 48 hours after the last exercise session with 12 hours of fasting. The blood samples were taken from each participant for 5 cc of vein while seated and rested. The samples were poured into lab pipes containing EDTA for the plasma separation. Then, there were put into the centrifuge machine for 15 minutes. Blood biochemical factors including Cholesterol, TG, LDL, HDL, alanine aminotransferase, and aspartate aminotransferase were measured through the enzymatic method and by the biochemical auto-analyzer device using kits made in Pars Azmoon Co. The insulin (while fasted) was measured through Elisa method using Mercudia kits made in Sweden. Hba1C amount was measured through turbidimetric method using kits made in Pars Azmoon Co. and by biochemical auto-analyzer device. RBP4 was measured through Enzymatic-Elisa method using RBP4 kits (sensitivity: 0/01) (Zelbio, made in Germany). Resistance to insulin was done through HOMA-IR method after glucose and insulin had been measured (24).

HOMA-IR= glucose (mmol/l) × serum insulin (mU/l) ÷ 22/5

Data Analysis:

After Kolmogorov-Smirnov test, dependent and independent t-tests were used to establish inter-group and intra-group differences in the distribution of measured variables. SPSS version 19 was used to analyze data ($p < 0.05$).

Results

The results of independent t-test showed that there were no significant differences between the two groups in the pre-test in terms of anthropometric and biochemical variables ($p>0.05$). Comparison of inter-group interventions showed that after 12-week-intervention of training in the water, BMI and weight decreased significantly ($p< 0.05$). Also, comparisons of the intra-group interventions showed that training and control groups were not significantly different in terms of these indexes ($p< 0.05$).

The results of independent t-test in training group showed that the levels of serum insulin, insulin resistance, liver enzymes (AST and ALT), and RBP4 decreased significantly after Aqua training ($p< 0.01$). These differences were not significant in the control group ($p>0.05$).

Table 2. Physiologic indexes in the exercise and control groups

variable	Control group		Aqua training group	
	Basic status	After 12 weeks	Basic status	After 12 weeks
BMI (kg/m2)	33.2 ± 0.24	32.58 ± 0.87	33.14 ± 0.18	29.76 ± 0.43
Age (yrs.)	57.33 ± 0.25	57.33 ± 0.25	58.33 ± 0.27	58.33 ± 0.27
Height (cm)	159 ± 0.25	159 ± 0.25	160 ± 0.14	160 ± 0.14
Weight (kg)	82.45 ± 0.22	82.39 ± 0.44	81.92 ± 0.28	76.98 ± 1.01
Body fat percentage	31.62 ± 0.17	31.50 ± 0.18	31.54 ± 0.15	27.50 ± 0.32

Weight, fat percentage, and BMI were measured in both groups before 12-week-intervention. Table 2 shows that the changes were significant in the Aqua training group.

Table 3. Comparing the mean of RBP4, lipid profile, and liver enzymes before and after the training

variable	Control group		Aqua training group	
	Basic status	After 12 weeks	Basic status	After 12 weeks
RBP4 (mm/L)	248.5±4.25	245.6 ± 0.44	247.71 ± 0.55	* 207.22 ± 0.73
AST (unit/L)	28.63 ± 1.32	28.6 ± 0.11	28.01 ± 0.47	* 24.26 ± 0.24
ALT (unit/L)	32.91 ± 0.53	33.30 ± 0.37	33.25 ± 0.17	* 27.47 ± 0.6
HbA1C (%)	7.57 ± 0.13	7.92 ± 0.37	7.66 ± 0.15	* 6.1 ± 0.15
Insulin resistance	6.40 ± 0.11	6.60 ± 0.13	6.45 ± 0.10	* 5.36 ± 0.02
Insulin (mU/l)	15.56 ± 0.14	15.55 ± 0.1	15.56 ± 0.16	* 13.13 ± 0.12
Cholesterol (mg/dl)	176.49 ± 0.27	175.31 ± 2.2	176.9 ± 0.51	* 166.36 ± 0.83
Triglyceride (mg/dl)	176.54 ± 0.59	178.1 ± 0.4	176.23 ± 0.71	* 157.2 ± 1.40
HDL -C (mg/dl)	45.28 ± 0.77	45.28 ± 0.77	45.36 ± 0.30	* 48.56 ± 2.21
LDL-C (mg/dl)	116.88 ± 0.51	116.4 ± 65.87	117.8 ± 0.43	* 102.61 ± 0.99

* changes were significant in the Aqua training group ($p < 0.05$).

Discussion and Conclusion

The results of the present study showed that 12 weeks of aqua exercise training decreases RBP4 and lipid profile including cholesterol, triglyceride, LDL and increased HDL-C. The intervention of aqua exercise also decreased ALT and AST liver enzymes in women suffering from type 2 diabetes.

Serum levels of RBP4 decreased significantly in the training group as compared with the control group. RBP4 is an adipokine associated with obesity and type 2 diabetes. Increasing RBP4 causes a decrease in Phosphoinositide 3-kinase and this action increases the risk of insulin resistance. Thus in this study, a decrease in RBP4 can effect insulin resistance by inhibiting the decrease of PI3k. Also the training can upregulate PI3K independent pathway. In other words, a mechanism that affected insulin resistance can inhibit the decrease of PI3K by decreasing RBP4. RBP4 also increases liver gluconeogenesis (40) and blood glucose; however, it has the negative effect on the secretion of beta cells (26). The results of the present study show that there is a positive relationship between RBP4 and insulin resistance. Also, the findings show that exercise training is the best agent between RBP4 and insulin resistance. In line with these results, Graham et al. (2006) investigated the effect of 4 weeks of aerobic training in participants suffering from diabetes and reported a significant decrease in RBP4 and a significant increase in insulin sensitivity (25). Since RBP4 is secreted from liver, visceral fat, Subcutaneous and muscle tissues, and given the study of Mansouri et al. (2014) that reported the decrease in the expression of RBP4 in visceral fat and not liver after endurance training, it seems that the training capable of affecting this tissue and making change in the physical status of participants can play a role in decreasing serum levels of this adipokine. Studies show that the most common lipid in type 2 diabetes increased triglyceride and the decreased HDL-C. The second risk factor for cardiovascular diseases increases the level of triglyceride and LDL-C (45, 12). In fact, various studies found a strong relationship between RBP4, triglyceride, and resistance to insulin (46, 27, 28). Some studies, however, don’t support this relationship. Sun et al. found that RBP4 density was higher in postmenopausal females than pre-menopausal females. Thus, the status of menopause can be an important factor in the density of RBP4 plasma (29). Therefore, the level of estrogen decreases at the menopause stage. This changes amount or percentage of fat which overcomes lipid metabolism. This change can be due to the level of RBP4 in plasma resulted from adipocytes (30). Training can decrease RBP4 levels. Also researchers found that training with appropriate intensity can have a positive effect on lipid profile and decrease the mortality rate (32). The results of this study showed that aqua training decreases triglyceride, cholesterol, and LDL-C and increases HDL-C. These results are consistent with findings of Koomar et al. (2012). However, they are different from the results of the study conducted by Michelle et al. (2006) (33, 34). Some researchers believe that weight loss can decrease triglyceride and cholesterol in subjects suffering from type 2 diabetes (34). Thus, a decrease in lipid profile and weight, as observed in this study, can decrease the level of serum RBP4 (4, 6).

This study also showed a decrease in the amount of ALT and AST in the training group after 12 weeks of aqua training. A decrease in liver enzymes can increase the sensitivity of liver to insulin, increase liver oxidation, decrease lipogenic enzymes and consequently decrease liver fat (56). The decrease in the liver fat can enhance its function and improve the activity of the liver enzymes (35). Regular training increases daily energy consumption, fat oxidation in skeletal muscles and hepatocyte mitochondrion, burning of visceral fat and help reinforce response to insulin in the adipose tissue. The result show that release of fatty acids decreases liver enzymes and fat deposit and increases fat oxidation in the liver (35). Training can stimulate lipid oxidation and control their synthesis in the liver, these finding are in line with those of Izadi et al. (2011). They studied the effect of 8 weeks of aerobic training and diet intervention in individuals suffering from type 2 diabetes. In both groups, the weight and TG of subjects decreased significantly, also, in the diet group with training, fasting insulin and liver enzymes decreased significantly (36). One of the most important reasons for the different results is related to the training duration, diet, and calorie received. The function of liver enzymes changes due to these factors (36). Studies showed that intensive training for a long time can lead to the damage of liver cells and the release of AST and ALT in the blood. The high plasma activity can be associated with the change in muscle membrane, muscle glycogen discharge, lipid peroxidation of the cell membrane and the damage due to mechanical processes (30). Samelman et al. (2000) found that endurance training prevents ALT and AST activities in rats through HSP70 (37). The training improves cardiovascular status, endurance, and body composition. The decrease in visceral fat can be an important contribution to health. The changes in blood and hormone indexes of subjects suffering from type 2 diabetes can be related to the biochemical effects of water.

An individual's organism releases heat 4 times more in water (38). Overall, the findings show the positive effect of 12 weeks of Aqua training on RBP4 and liver enzymes amounts in women suffering from type 2 diabetes. There might be some unknown factors contributing to the issue. A small population and program length were among the limitations of this study. Thus, we suggest more studies with larger population investigating different training programs and diets for individuals suffering from type 2 diabetes.

Glucose transfer to skeletal muscle is carried out through glucose transport proteins, and the glucose transporter-4 (GLUT-4) is the most important isoform in the skeletal muscle that is affected by muscle contraction and insulin. Insulin activates the transfer of glucose transporters- 4 from the depth to the cell surface through complex signal cascades. One of the mechanisms responsible for reducing blood glucose during and after training in people with insulin resistance is the transfer of glucose-4 transducers from the cytoplasm to the membrane surface of muscle cells in type 2 diabetic patients. So that the muscle contraction through the activation of the protein kinase activated by AMP causes the transfer of GLUT-4 from the depth to the cell surface. Generally, type 2 diabetes mellitus disturbs GLUT-4 from the depth to the cell surface, which is stimulated by insulin. Both aerobic and aqua training, increase the frequency of glucose transporters- 4 and absorption glucose in type 2 diabetic patients. Aerobic and aqua training in water (with long period) can increase the effect of this agent on RBP4, BMI, and liver enzymes.

Also one of the restrictions and weaknesses of this study was related to our inability to control daily physical activity and nutritional status ofsubjects, therefore researchers are recommended to consider this issue in further studies.

Conclusion

Use of aqua training for patient with type 2 diabetes have an important effect on index of liver enzymes, lipid profile and also RBP4 in women with type 2 diabetes and it can help inhibit the progression of insulin resistance.

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