The Effect of 8 Weeks Aerobic Training and Vitamin C on Creatine Kinase of Serum Levels in Type 2 Diabetes Patients

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Abstract

Objective: Diabetes mellitus is a metabolic disorder associated with impaired serum skeletal muscle pain enzymes levels. The purpose of this study was to investigate the effect of 8 weeks aerobic training with and without vitamin C consumption on serum levels of Creatine Kinase (CK) in type 2 diabetic patients (T2DM).

Materials and Methods: In this clinical trial 45 women (30-45 years) with T2DM were randomly assigned into one of these 3 groups: aerobic training (3 sessions a week for 45 minutes), aerobic training with 250 mg/day vitamin C supplementation and control (without exercise and vitamin C). Fasting serum levels of CK were measured before and 24 hours after the last exercise session. The results were analyzed using descriptive and inferential statistics (analysis of variance, LSD post hoc test, dependent T test for hypothesis testing) by SPSS19 software.

Results: Aerobic training as well as aerobic training plus vitamin C reduced significantly concentrations of CK compared to the control (*P*-value= 0.037, *P*-value= 0.017) respectively. However, There were no significant differences in CK levels between intervention groups (*P*-value= 0.899).

Conclusion: This study showed that aerobic exercise with or without vitamin C supplementation is effective in reducing CK levels in T2DM. So, in order to reduce at least one of the markers of muscle damage (CK), aerobic exercises are recommended in T2DM, in the absence of contraindications.

Keywords: Aerobic exercise, vitamin C, Creatine kinase, Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is the most common metabolic disease characterized by hyperglycemia due to insulin deficiency and resistance (1). Diabetes increases the levels of DNA, proteins, and lipids oxidation level by increasing oxidative stress in different tissues (2). Free radicals are created in T2DM patients via glucose oxidation, non-enzymatic glycation of proteins followed by oxidative degradation of glycated proteins. Tissues and enzymes can be damaged by increasing the number of free radicals and

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simultaneously reducing defensive mechanisms against it (3,4).

High activity of Creatine Kinase (CK) in blood is considered as an indicator for increasing cells activity, particularly muscle cells (5). An increase in serum CK does not only indicate an increase in muscle cells activity but also indicates damage to skeletal muscle cells (6). There are various theories about bruising and muscle damage, the most important of which are the theory of inflammation and the theory of tissue rupture. Inflammation is a response to muscle damage caused by the movement or flow of plasma proteins and leukocytes into the tissue, which is associated with pain, swelling, and limited mobility associated with muscle contraction and increased plasma CK enzymes (7), and according to the tissue rupture theory, when the sarcomere is disturbed, the enzymes CK and lactate dehydrogenase (LDH) are released into the blood. CK and LDH are involved in the non-aerobic pathway of adenosine triphosphate (ATP) production. CK is a key enzyme in muscle cell metabolism that accelerates the binding of creatine to phosphate or vice versa. Increased physical activity increases plasma CK (6). it has also been shown that daily intake of 500 mg of vitamin C for two weeks in healthy young women did not affect the oxidative stress markers after moderate intensity exercise (8) and consumption of vitamin C and E can reduce aerobic exercises-induced muscle damage in women (9).

Antioxidants could reduce oxidative stress produced by free radicals and, consequently, diminish the cell injuries. Vitamin C (Ascorbic acid), a potent antioxidant, is a water-soluble vitamin presents in the cytosolic composition of the cells which functions as an electron donor to vitamin E during oxidative stress in the cell membrane (10). Furthermore, vitamin C may compete with glucose in bonding to the amine group of proteins which could reduce glycated products (11). Based on these evidences vitamin C might potentiate effects of exercise in the prevention of muscle injury (11). The aim of this study was to investigate the combination effect of vitamin C on aerobic exercise on serum CK levels in T2DM.

Materials and Methods

In this clinical trial 45 women (30-45 years), with T2DM from Diabetes Clinic of Bouali Hospital in Zahedan were randomly assigned into 3 groups: training group (along with vitamin C placebo) that mean age was 35.45 years old and mean BMI was 31.60 (N= 15), Training plus vitamin C group, mean age was 33.43 yr, mean body weight was 78.53 kg and mean BMI was 31.92 (N= 15) and control group (without exercise and taking vitamin C), mean age was 37.13 yr, mean body weight was 78.27 kg and mean BMI was 31.95 (N= 15). The consent form was completed by the patients to participate in the research project.

The inclusion criteria were: diagnosis of diabetes within the previous year, no consumption of vitamins, supplements and drugs that affect muscular system(for example, statins category pharmaceutical), lack of micro- or macro- vascular complications of diabetes, liver or muscular diseases and ability to stay in the protocol for at least 8 weeks. Patients that participate in any other exercise program rather than the protocol, absence of more than 2 sessions per week and those who discontinued vitamin C consumption were excluded from study.

In training plus supplementation and training groups, exercises were initiated with warming up for 5 minutes (soft running, combined hand and foot movements and tensile movements), followed by 35 minutes of main exercises (running at 50 to 60% of maximum heart rate) and finally, 5 minutes of cool down (return to the initial state), under direct supervision that repeated for 45 minutes 3 days in a week for 8 weeks (12).

The training plus supplementation group, consumed 250 mg (per day) of vitamin C tablet (Oswah pharmaceutical Company, Iran). The training group was prescribed the same amount (250 mg/day) of the vehicle. Both vitamin C and placebo were consumed just 2 hours prior to exercise (12).

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Prior to initial blood sampling the participants were asked not to participate in any physical activity for 48 hours thereafter; 10 ml of venous blood was obtained two hours before the exercise via anti-cubital vein. Again, twenty-four hours after the last exercise session, blood samples were collected as mentioned previously. The sera were separated by centrifugation in 2000 rpm for 15 minutes and were frozen at -70 °C until further analyses. The serum level of creatine kinase enzyme was measured by the auto-analyzer device using available kits. To measure vitamin C level, In accordance with the instructions of the vitamin C assay kit, 200 µl of the sample was firstly combined with 200 µl of Lysic Buffer and completely mixed with 20 µl of concentrated sulfuric acid then, centrifuged at 15000 × g for 10 minutes and stored at -20 °C and measured at 500 to 530 nm.

Statistical analyses

Descriptive statistics were used to express the data. Furthermore, Kolmogorov-Smirnov test was used to investigate the normal distribution of data. To compare changes in variables after interventions and between groups, paired T-test and One-way analysis of variance (ANOVA) complemented with appropriate post hoc test e.g. LSD were used respectively. All statistical analyses were performed using SPSS software (SPSS Inc. Chicago, IL, USA), version 19 and *P*-value< 0.05 was set to be significant.

Ethical considerations

This study was approved by the ethical committee of Zahedan University of Medical Sciences (Code: IR.ZAUMS.RES.1397.180).

Results

As shown in table 1 there was no significant difference before intervention among groups regarding age, BMI, vitamin C levels and CK levels. The results (table 2) showed that CK serum levels were significantly decreased using an aerobic training exercise and in combination of vitamin C.

The results showed that serum creatine kinase levels decreased significantly after 8 weeks of aerobic exercise as well as after 8 weeks of aerobic exercise plus vitamin C intake

Table 1. Changes in the subjects' variables (mean ± standard deviation) before and after the exercise intervention

Indicator group	Training +Placebo		Training + Vitamin C		Control		*P*-value Between groups Before intervention
	Before	After	Before	After	Before	After	
Age (year)	35.45 (±4.62)	_	33.43 (±3.72)	_	37.13 (±5.67)	_	0.505
Height (cm)	154.09 (±3.26)	_	157.07 (±6.16)	_	156.67 (±5.41)	_	0.402
Weight (kg)	74.90 (±6.25)	71.45 (±4.92)	78.53 (±6.11)	76.12 (±6.32)	78.27 (±7.35)	78.68 (±6.15)	0.322
Body mass index (kg/m^2)	31.60 (±1.4)	30.14 (±2.2)	31.92 (±0.9)	30.94 (±1.6)	31.95 (±2.0)	32.11 (±2.3)	0.112
The concentration of vitamin C (µ mol /l)	10.56 (±9.27)	11.67 (±9.33)	9.98 (±11.27)	12.36 (±10.86)	10.46 (±8.19)	11.36 (±9.23)	0.61
Creatine Kinase u/l	247.70 (±48.96)	224.69 (± 39.31)	249.84 (±52.46)	215.59 (±46.81)	272.80 (± 28.01)	275.41 (±29.32)	0.971

Table 2. The results of one-way ANOVA to compare Creatine Kinase Serum levels between groups (After the intervention)

Variable	Group	Before	After	*P*-value Within groups	*P*-value Between groups
Creatine kinase (U/L)	Training +Placebo	247.70 (±48.96)	224.69 (± 39.31)	0.037	0.035*
	Training +Vitamin C	249.84 (±52.46)	215.59 (±46.81)	0.017	
	Control	272.80 (± 28.01)	275.41 (±29.32)	0.899	

* The difference between group 1 and group 3 was lower
*There was no difference between group 1 and group 2
*There was little difference between group 2 and group 3

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compared to the control group. Recent studies have shown that 5 to 8 weeks of aerobic exercises increase the blood flow and subsequently may amplify lactate and H^+ clearance, function of the sarcoplasmic reticulum network and ionic regulation (13). Furthermore, higher activity of intramuscular pumps, in turn, can reduce the level of CK as an indicator of muscular injury (13). Additionally, increasing cortisol secretion during exercise could increase excretion of vitamin C from the adrenal glands and ultimately reduce creatine kinase serum levels (8). Exercise may also increase expression of a gene related to insulin like growth factor(IGF-II) in myocytes; played a protective role in muscles (14).

Jonior et al (2013) showed that aerobic training reduced glucose levels in diabetic rats, CK levels increased and indicated more muscular damage (15), which is inconsistent with this research results. Padravand et al (2013), in a study showed that there was a significant increase in the enzymes (CK, LDH) activities after 6 weeks of progressive endurance exercises (16). In another study Hashemi et al (2009) showed that swimming can reduce pathological changes and improve muscle tissue damage in cases of diabetic myopathy (17). Foroohi et al (2017) showed that vitamin C supplementation decreased the serum CK and CRP levels compare to the placebo group 48 hours after the exercise (18). The results of this study are consistent with the results of this study.

In all studies, it was found that the results of exercise with vitamin C supplementation were more significant than the effects of supplementation alone. In this regard, the present study showed that in the group of exercise plus vitamin C, creatine kinase decreased more than the group of exercise and placebo, although this difference was not significant. Perhaps this difference would have been significant if vitamin C intake or the duration of the aerobic exercise protocol had been longer. Glucose strongly inhibits the uptake of dehydroascorbic acid (DHA), which is the oxidized transportable form of vitamin C. Therefore; hyperglycemia in diabetes would be expected to cause vitamin C deficiency within the cell. DHA uptake into the cells is accomplished through glucose transporters, GLUT1 and GLUT3, which transport DHA in competition with glucose, and this effect may be overcome by a large intake of vitamin C (19) on the other hand, aerobic exercise lowers blood sugar levels in diabetes.

Lacks of a group with supplementation of vitamin C but without aerobic training together with a small sample size are potential limitations of current study. It is suggested that other studies investigate these issues in future researches.

Discussion

The findings of this study showed that among the personality factors, only neuroticism negatively predicted adherence to medication in individuals with T2DM. Indeed, individuals who rated high on this personality trait were less likely to comply with their medication. This finding is in line with those of previous studies, indicating that individuals with some specific personality traits, such as neuroticism, were disposed to non-adherent behavior (25).

For example, in their study on individuals with T2DM, Novak et al. (2017) found that higher neuroticism was linked to lower levels of medication adherence (17). Similarly, in another research, a negative relationship was observed between some personality factors, such as neuroticism, and compliance with therapeutic medications (15).

A possible explanation for this finding is that individuals with high scores on neuroticism tend to worry and cannot follow their medication or diet regimens. Previous research has also shown that people influenced by these personality characteristics tend to engage in health-compromising behaviors, such as smoking which pose more risk to their health (26), and adhere loosely to disease management suggestions (27).

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While the results of this study are in agreement with those of most previous studies, there are a few studies the results of which are not in line with those of the present research. For instance, in one study on individuals with T2DM in Iran, a positive association was observed between neuroticism and HbA1C level (24). This discrepancy in results can be explained by differences in demographic and social factors of the participants of this study and those of other studies.

Also, diabetes self-management is complex and difficult and it seems unlikely that patients with neuroticism be successful at it. Furthermore, diabetes complications can lead to functional limitations and reduce the quality of life (28). In terms of conscientiousness, no significant association was observed between medication adherence and this personality trait in the present study.

This finding is contrary to those of most previous results, which indicated that patients who were high on conscientiousness were more compliant with treatment. For instance, in one study, Molloy et al. (2014) found that a higher level of conscientiousness was associated with better medication adherence (29).

Regarding other personality factors, including agreeableness, extraversion, and openness, the results of this research did not indicate any significant association between these three factors and medication adherence. Previous research has reported mixed results on the relationship between these three personality characteristics and adherence to treatment. While some studies showed the significant association between the personality traits and compliance of treatment (25,30), other studies did not find any significant relationship between the aforementioned factors and medication adherence (31).

The study has some limitations. First, the cross-sectional methodology and in studies with this type of design, it is almost impossible to explore cause-effect. Moreover, the role of demographic variables, such as gender and age was not investigated in this study because the sample size was not large enough to include these variables into the model. Finally, in this study, medication adherence was assessed by a questionnaire, but to have a precise evaluation of adherence medication, the assessment of the HbA1C level should also have been considered.

It is hoped that the results of this study, which examined the role of personality traits in medication adherence, can help clinicians to identify individuals with poor self-management adherence and provide them with necessary instructions, care, and therapy. Clinical practitioners are recommended to consider the role of personality traits in adherence to treatment and provide patients with effective interventions when necessary.

Conclusions

According to finding in this study, aerobic training with or without vitamin C supplementation decreases creatine kinase serum levels in patients with type 2 diabetes mellitus which could prevent muscle injury in these patients.

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Conflict of Interest

No potential conflict of interest relevant to this study was reported.

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