

Simultaneous Effect of Resistance Training and *Portulaca Oleracea* Supplementation on Some Biochemical Markers of Bone Dynamics in Women with Type II Diabetes

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ABSTRACT

Background and Objective: Osteoporosis is one of the complications of diabetes. The aim of this study was to determine the impact of resistance training along with *Portulaca oleracea* supplementation on OPG and NFκB levels (bone markers) in women with type II diabetes.

Methods: Overall, 28 women with type II diabetes (44 to 60 years old) were randomly and equally assigned into four groups (supplement, training, training-supplement and control). An eight-week resistance training program (three one-hour sessions per week with one repetition maximum) was performed using three types of bands with different resistances, at 40-50% intensity and 50-70% maximum heart rate. *P. oleracea* seeds were supplemented daily (7.5 grams mixed in yogurt) for eight weeks. The data was analyzed using descriptive statistics, paired t-test and ANOVA.

Results: After 8 weeks, OPG and NFκB levels in the three groups of supplement, training and training-supplement increased and decreased, respectively. The highest change in both variables was observed in the training-supplement group. Moreover, the level of these two variables in the training-supplement group had significant difference with the controls and other groups ($P=0.000$).

Conclusion: As a non-pharmacological therapeutic approach, the regular resistance training and *P. oleracea* supplementation can increase bone formation markers and reduce bone resorption in women with type II diabetes.

Keywords: Type II Diabetes, Resistance Training, *Portulaca Oleracea*, OPG, NFκB.

INTRODUCTION

Diabetes is one of the most common metabolic disorders especially in the elderly, which have debilitating effects on the lives of patients (1, 2). Type II diabetes is growing in the world at an alarming rate. It is estimated that the number of diabetic adults in the world will increase to 300 million in 2025 (3). There are currently 1.5 million diabetic patients in Iran. Approximately 85% of these individuals are type II diabetic patients (4,5). complication (6) and metabolic bone disease, characterized by low bone mass and structural deterioration of bone tissue that leads to increased risk of bone fragility (7). Studies demonstrated high bone resorption rates in both types of diabetes (8). Researchers showed that diabetic women have higher osteoporosis compared to healthy women (9, 10). Almost 28% of women aged over 50 years suffer from osteoporosis (11). Poor diet and therefore receiving less nutrients reduces body storage of iron, calcium, zinc and other essential minerals. The complications caused by these deficiencies will lead to various diseases such as osteoporosis (12). The exact mechanism of bone destruction has not been clearly identified. Recent findings suggested the role of a new molecular system that belongs to tumor necrosis factor (TNF) family in regulation of bone destruction, which includes three key proteins (receptor activator of nuclear factor kappa-B, receptor activator of nuclear factor kappa-B ligand and osteoprotegerin) (13-16). Osteoprotegerin (OPG) is a large glycoprotein that belongs to the TNF α family. This glycoprotein ligand along with receptor activator of nuclear factor kappa-B ligand (RANKL) and its receptor (RANK) form the molecular triad that regulates bone metabolism by controlling osteoclasts. On the other hand, RANKL increases osteoclastogenesis and bone resorption by binding to RANK. OPG neutralizes it and inhibits bone resorption by binding to RANKL (17). As an inhibitor, OPG prevents the RANKL interaction and reduces osteoclastogenesis (18). Nuclear factor kappa-B (NF κ B) is a key signaling pathway involved in the early stages of osteoclast differentiation induced by RANKL (19). It is also considered as an evolutionary family that protects transcription factors in response to environmental changes (20).

Various studies have shown that exercise is the basis of type II diabetes treatment (21). It is also indicated that exercise prevents and controls the disease and diabetes-induced osteoporosis (22, 23). Additive effects of weight-bearing exercise on bone density are higher than ordinary activities (24). Studies showed that a large amount of body's minerals especially calcium are excreted during endurance activities, which activates osteoclasts and increases the uptake of calcium from bone tissue. Meanwhile, resistance training is a safe stimulant of bone formation because of the high pressure that it exerts on bones (25). Long-term resistance training can decrease the osteoclastic process and reduce diabetes-induced osteoporosis (26). Recent studies considered medicinal plants useful in treatment of type II diabetes. Some medicinal plants have beneficial effects on bone markers, and are considered as alternative treatment strategy for diabetes-induced osteoporosis (27). *Due to its* several properties and by controlling the amount of fat oxidation, *Portolaca oleracea* can show antioxidant and anti-inflammatory effects (28, 29). *P. oleracea* L. is a grass-like plant with small yellow flowers that grows widely in various regions of the world (30). Because of its various constituents such as flavonoids, *P. oleracea* show beneficial effects on type II diabetes (31). It also has a beneficial effect in reducing osteoporosis. This plant is a remarkable source of minerals including calcium and phosphorus, which could have potential role in prevention of bone disorders such as osteoporosis (32, 33). Numerous studies have been conducted on bone markers and the effect of physical activity in diabetics. However, the simultaneous impact of exercise and herbal supplementation has been studied less. Therefore, this study aimed to determine the effect of a period of resistance training along with *P. oleracea* supplementation on bone markers (OPG and NF κ B) in women with type 2 diabetes.

MATERIALS AND METHODS

Participants

This was a semi-experimental study (clinical trial registration number: 2015051772494) with a pretest-posttest design and a control group. The study population included all type

II diabetic women in Sari, Iran. The female volunteers were identified and 28 of them who met the inclusion criteria were enrolled in the study. The age of participants ranged from 44 to 60 years. They had no regular exercise, no supplementation and none of the chronic or acute diabetic complications. Their blood glucose level was higher than 126 mg/dL, and they were taken metformin to lower blood glucose. Written consent was obtained from each participant before the start of the study and the ones who were unwilling to participate were allowed to leave at any stage. The participants were randomly divided into four groups of training, supplement, training-supplement and control (each group included seven individuals) and they were almost matched with age and body mass index (BMI) (Table1).

Resistance training program

Progressive resistance training was performed in groups, three times a week (one hour per session) for eight weeks with 40 to 50% intensity (one-repetition-maximum), and using three types of resistance bonds. The activities included biceps, triceps, upright row, shoulder press, rowing, side bending, leg press, thigh bending, and quadriceps and hamstrings workouts. In the first two weeks, the trainings included 15 minutes warm up, 30 minutes workout and 15 minutes cool-down (28,23).

P. oleracea supplementation

The supplement group and training-supplement group received 7.5 grams of *P. oleracea* seed mixed in 40 grams of yogurt daily with meals (2.5 grams with lunch and 5.2 grams with dinner) for eight weeks. The supplement was prepared weekly in the city of Sari and then weighed and packed for week consumption by the experimental groups. The supplements were provided to the subjects along with necessary recommendations for the amount and timing of consumption. The amount of *P. oleracea* used in this study was calculated based on the average amount of *P. oleracea* seeds consumed in some areas. The necessary recommendations for the amount and timing of consumption were reminded. Moreover, a 2500-3000 kcal daily diet was recommended, which contained 50-55% carbohydrates, 25-30% fat and 10-15% protein (29, 31).

Blood sampling and biochemical analysis

Blood samples were taken before and after the interventions, followed by 12 hours of overnight fasting. For this purpose, 7 ml of blood were taken in the laboratory from the left brachial vein of each subject, between 8 to 10 am and after a half-hour break. Post-test sampling was performed 48 hours after stopping resistance training and taking supplements. The plasma was separated and frozen at -80 °C in order to measure the level of OPG and NFκB. OPG was measured by ELISA and Cusabio kits (China). NFκB was measured using commercial kits (Cayman, USA).

Statistical analysis

The data was first described in terms of central tendency and distribution. Kolmogorov-Smirnov and Levene test were used to determine normality of data distribution and the homogeneity of variances, respectively. Paired t-test was used to evaluate the variations within groups and one-way analysis of variance (ANOVA) was used to compare the means of study variables in the pre- and post-test stages. In addition, Tukey post hoc test was used to detect differences. P-value less than 0.05 was considered as statistically significant.

All statistical analyses were performed by SPSS version 16.

RESULTS

After the eight-week intervention, OPG level significantly increased in subjects in the supplement (16.63%), resistance training (18.75%) and resistance training-supplement (30.63%) groups ($P=0.000$). The control group remained almost unchanged (Figure 1). The results of ANOVA showed that factors of time, group and the interaction between these two had a significant impact on OPG level ($P=0.000$). Overall, these findings showed that concurrent supplementation and resistance training was more effective on OPG level than the other groups. The results showed that NFκB level decreased significantly by 13.81% after eight weeks of *P. oleracea* supplementation, 14.02% after eight weeks of resistance training and 32.84% in the exercise-supplement group ($P=0.000$). The control group remained unchanged. The results of ANOVA showed that both factors of time and group as well as the interaction between these two factors have a significant effect on NFκB level ($P=0.000$), with a higher effect observed in the training-supplement group.

Table 1- Mean and standard deviation (SD) of body composition indices in the study groups

Index Group	Height(Cm)	Weight(Kg)	Age(Years)
Training	159.28±5.08	76.29±4.39	53.28±1.7
Supplement	159.17±6.65	73.5±4.89	52.3±4.08
Training-supplement	159.57±5.25	75.71±5.71	52.57±2.7
Control	160.67±6.54	75.67±9.44	50.17±5.34

Table 2- Changes in the measured variables between 4 groups before and after 8 weeks.

Variable	Groups	Pre-Test	Post-Test	P-Value*	P-Value**
Weight (kg)	Training	76.29±4.39	75.64±4.43	0.000*	
	Supplement	73.5±2.79	72.57±2.51	0.003*	0.033**
	Training-supplement	75.71±5.15	74.86±4.86	0.007*	
	Control	75.67±9.53	75.21±9.07	0.162	
OPG (ng/ml)	Training	3.9±0.29	4.8±0.23	0.000*	
	Supplement	3.91±0.3	4.69±0.3	0.000*	
	Training-supplement	3.94±0.26	5.68±0.18	0.000*	0.000**
	Control	3.86±0.24	3.84±0.2	0.805	
NFKB (ng/ml)	Training	8.27±0.32	7.11±0.32	0.000*	
	Supplement	8.11±0.4	6.99±0.25	0.000*	
	Training-supplement	8.19±0.28	5.5±0.37	0.000*	0.000**
	Control	8.19±0.34	8.19±0.4	1.000	

*changes of variables within groups; ** changes of variables between groups

DISCUSSION

Many studies have shown that diabetes is an important risk factor for osteoporosis (34, 35). Some studies show a direct correlation between bone density and insulin dosage (36). The first findings of the present study showed that level of OPG significantly increased after eight weeks in the supplement (16.63%), training (18.75%) and training-supplement (36.63%) groups. OPG is an anti-inflammatory protein derived from osteoblasts that stimulates osteogenesis (37). Yasuda et al. investigated the effect of OPG on mice with osteoporosis and reported that injection of 100 mmol OPG for four weeks can play an important role in the process of bone calcification, and prevent the osteoclastic process (38). Physical activity is considered a good source for bone turnover, and is recommended for prevention of osteoporosis. The OPG level increases after resistance training leading to prevention of osteoporosis process. Some studies have shown that stimulation of osteoblastic or osteoclastic activity is exercise-dependent (22, 39, and 40). Study of Bergström et al. on postmenopausal women showed that a period of aerobic exercise significantly increases OPG level in the exercise group. Meanwhile, the amount of RANKL in this group decreased, and the rate of osteoporosis in the control group was higher than the training group after a year (22).

Various studies show that high pressure in resistance trainings is a safe stimulus to osteogenesis. Exercise training increases osteoblastic activity and OPG level by exerting mechanical pressure on bones. Increased serum OPG level after a period of exercise neutralizes the increased osteoclastic activity (22, 41). Study of Marques et al. indicated that eight months of resistance training increases bone mineral density, while OPG and RANKL remain unchanged after resistance training and aerobic exercise (42). This is inconsistent with the findings of the present study, which could be due to differences in intensity, duration and type of trainings, as well as physical fitness and age of the participants in the two studies (43, 44). Some studies have also shown that medicinal plants, as dietary supplements are good source of minerals such as calcium that also increase calcium absorption rate. Medicinal plants increase osteoblastic activity and ultimately reduce osteoporosis by increasing the level of OPG (45). In this study, eight weeks of *P. oleracea* consumption significantly increased OPG. It is reported that calcium and phosphorus present in *P. oleracea* have an essential role in normal and better functioning of the bone structure. Moreover, antioxidant

components of *P. oleracea* activate calcium-dependent paraoxonase 1 enzyme. Thus, *P. oleracea* is also effective on intracellular calcium and in this way may activate the bone formation factors (44, 46). In this regard, Gao et al. indicated that *P. oleracea* supplementation for 12 weeks inhibits bone resorption, and increases calcium and OPG activity (43). In the present study, eight weeks of supplementation, training and supplementation in combination with resistance training significantly reduced NFκB levels by 13.81%, 14.02% and 32.84%, respectively. In fact, the reduction of NFκB indicates the decreased activity of the osteoclastic cells (47). Diabetic patients are more susceptible to osteoporosis compared to healthy individuals, which may be due to increased activity of NFκB. In this regard, Austin et al. found that increased NFκB level increases the osteoclastic activity (47). By changing the level of RANK, RANKL and OPG, and imbalancing in the expression of these molecules, osteoporosis increases NFκB, osteoclast formation and ultimately bone resorption (48, 49). Recent studies show that resistance training can help prevent the process of osteoporosis by reducing the activity of NFκB. In this regard, Bergström et al. showed that a one-year period of exercise significantly decreased the activity of NFκB and RANKL in postmenopausal women (40). It seems that both resistance training and aerobic exercise have similar impact on the osteoclastic process, so that the mechanical pressure of resistance training on bones changes the osteoclastic process of NFκB (39, 47, and 50). However, several studies have reported increased level of NFκB immediately after a physical activity. Schenk et al. showed that a period of physical activity prevents NFκB activity in humans, but the effect of aerobic exercise on NFκB activity in individuals with normal glucose and insulin resistance is not clear (51). Tantiwong et al. investigated the impact of eight weeks of training on non-diabetics and showed that unlike endurance training, intense aerobic exercise increases NFκB activity (52). Rivas et al. demonstrated that intense exercise

training in the elderly leads to 60% increase in phosphorylation of the pro-inflammatory transcription factor NFκB (53). Increased, decreased or unchanged level of NFκB is expected after exercise, depending on the type and intensity of physical activity, fitness and early NFκB plasma level of participants and their adaptability to trainings (52). On the other hand, diabetic individuals have the highest level of NFκB activity, therefore it is likely that exercise may not increase the activity of NFκB because the threshold has been already triggered (47, 54). Studies also showed that using medicinal plants as a non-drug treatment is useful for the prevention of osteoporosis. Recent studies have shown that medicinal plants can prevent osteoporosis by reducing the NFκB activity. Lee et al. showed that a period of *P. oleracea* supplementation significantly reduces NFκB and RANKL activity in postmenopausal women. They also stated that *P. oleracea* is among the medicinal plants that inhibit NFκB and prevent the osteoclastic process and osteoporosis (45).

CONCLUSION

As a non-pharmacological therapeutic approach, regular resistance training and *P. oleracea* consumption can independently increase bone formation markers and decrease bone resorption in diabetic women. However, supplementation in combination with exercise is far more effective than these two methods separately. Based on the results of this study, *P. oleracea* supplementation with resistance training is recommended for improvement of bone markers in women with type II diabetes, as a step towards reduction of bone disorders in this group of people.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding this manuscript.

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