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Research Article

THE EFFECT OF CELERY ON BIOMARKERS OF BONE IN MIDDLE-AGED WOMEN

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ABSTRACT
Aging is normally associated with an increased incidence of inflammatory diseases such as osteoporosis. Poor diets resulting in the lower intake of nutrients may result in osteoporosis. The main objective of the present study was to determine the effect of celery on biomarkers of bone in middle-aged women. The present quasi-experimental study was conducted on 30 volunteer overweight women aged 20-44 and randomly divided into two groups: the control group and the celery supplement group. The celery supplement group took 3 celery seed powder capsules with a glass of water every day for 8 weeks. The control group received starch powder (placebo) during the same period. To measure the variables under study, samples were collected from the two groups at baseline and then at the end of the study. The results were analyzed in SPSS-20 using descriptive and analytical statistics. The significance level was set at $P<0.05$ for all the calculations. The results showed that the use of celery supplements in overweight middle-aged women led to a significant decrease in the levels of nuclear factor kappa B (P=0.001), high-sensitivity CRP (P=0.001), alkaline phosphatase (P=0.000) and lipid profile, including triglycerides (P=0.000), LDL-C (P=0.000) and total cholesterol (P=0.000), and also to a significant increase in osteoprotegerin (P=0.000) and HDL-C (P=0.001) levels. According to the results obtained, taking celery supplements can prevent the development of bone diseases in overweight middle-aged women.

Keywords: *Osteoprotegerin, Nuclear Factor Kappa B, Alkaline Phosphatase, Osteoporosis*

INTRODUCTION
One of the adverse outcomes of modern lifestyles is weight gain and obesity (Gaeini and Rajabi, 2014), which is associated with various diseases, including osteoporosis, hypertension, blood disorders, loss of physical strength and loss of the ability to work. The overweight and obese are highly prone to the risk of developing osteoporosis. The factors and conditions reducing ossification markers and increasing bone resorption markers during adolescence result in suboptimal bone mass that may expose the individual to the risk of osteoporosis during adulthood (Health and Services, 2004). Osteoporosis is a serious health problem in most countries. In the United States, almost 26 million people suffer from osteoporosis and over 1.5 million of them suffer from fractures of the spine, the wrist and the pelvis due to this condition. According to studies, about 2.5 million women are prone to the risk of severe osteoporosis and its resultant fractures (Rafieian *et al.*, 2009). Results of another study showed that 28% of Iranian women aged over 50 suffer from osteoporosis and 53% from osteopenia (Rahbar and Nabipour, 2010). Moreover, poor diets resulting in a lower intake of nutrients might lead to a decrease in body reservoirs of iron, calcium, zinc and other essential minerals, and the complications caused by the deficiency of these minerals eventually follow in the form of malnutrition, anemia, zinc deficiency, osteoporosis, reduced work capacity and learning ability, severe physical and psychological changes and internal stress (Montazery Fard *et al.*, 2006). Osteoporosis is a skeletal system disease that is diagnosed by reduced bone mass and thin and brittle bones (Sambrook and Cooper, 2006). Peak bone mass is acquired by the end of adolescence or the early twenties. One way of preventing osteoporosis is therefore to make sure that the strongest possible bones are formed during adolescence (Rahnavard *et al.*, 2006). Osteoporosis begins in early adulthood. From childhood until the age of twenty, more bones are formed than broken down. After the age of thirty, however, the process is reversed for unknown reasons and bone resorption exceeds bone ossification (Cummings and Melton, 2002). Osteoporosis is more prevalent in menopausal women; however, many young girls and women are also at the risk of developing the disease due to inadequate

physical activity, poor nutrition and lack of knowledge about appropriate lifestyles. Many studies have separately shown that being overweight or underweight are both major risk factors for developing osteoporosis in women (Kong *et al.,* 1999). According to many scholars, body weight affects bone mineral density (BMD); (ahmadi *et al.,* 2010). It has been reported that weight loss is associated with reduced BMD (Shivashri *et al.,* 2013). That is to say, weight gain leads to a higher mechanical strain on the bone tissue and consequently decreases calcium removal from the bones and increases BMD (Ramezani *et al.,* 2009). The exact mechanism of bone resorption is yet to be clearly discovered (Magni *et al.,* 2010). Molecular biological research has contributed to the present understanding of the mechanisms and proteins involved in bone resorption (Stejskala *et al.,* 2001). Recent findings have introduced a new molecular system belonging to the tumor necrosis factor (TNF) family for regulating bone resorption, which includes three key proteins, namely RANK, PANKL and osteoprotegerin (Khosla 2001; Lerner 2004; Stejskala *et al.,* 2001; West *et al.,* 2009). Osteoprotegerin is a glycoprotein from the large family of TNFα receptors. Together with the receptor activator of nuclear factor kappa B ligand (RANKL) and its receptor (RANK), this glycoprotein develops a molecular triad that regulates bone metabolism through controlling the osteoclasts. Furthermore, RANKL binds to RANK and thereby enhances osteoclastogenesis and absorption by the bone. Osteoprotegerin binds to RANKL and neutralizes it and consequently inhibits absorption by the bones (Simonet *et al.,* 1997). Osteoprotegerin is an inhibitor that prevents RANKL reactions and consequently reduces osteoclastogenesis (Kostenuik, 2001). NF-kB is a key signaling pathway involved in the primary stages of RANKL-induced osteoclast differentiation (Léotoing *et al.,* 2013) and is known as an evolutionary family protecting transcription factors involved in the response to environmental changes (Hayden and Ghosh, 2004). Studies have shown that the consumption of certain medicinal herbs might be effective in providing an adequate intake of calcium, the elimination of malnutrition and the prevention of bone diseases in overweight and obese women (Tahuri, 2011). One of these valuable medicinal herbs is celery, which contains different vitamins, minerals and nutrients. Celery may have positive effects on the skeletal system's ability to resist fractures and might also increase osteoblast bone markers (Crenshaw *et al.,* 1981). The use of medicinal herbs, including celery, appears to increase bone density (Ebadi, 2007). Although there are very few studies conducted on the effect of celery on human specimens, animal studies have demonstrated the medicinal effects of celery (Leung and Foster, 2003). Studies have shown that celery powder reduces osteoclastogenesis activity in the bone marrow and that it can be used as a calcium-rich nutrient (Crenshaw *et al.,* 1981). Given that previous studies have focused on the medicinal effects of celery and that the majority were conducted on animal specimens, and also since celery consumption in overweight middle-aged women appears to have received less emphasis, the present study was conducted to determine the effect of an 8-week intake of celery supplements on certain biomarkers of bone in overweight middle-aged women.

MATERIALS AND METHODS

The present controlled quasi-experimental study was conducted using the pretest–posttest method. The statistical population consisted of inactive healthy women aged 22-42 residing in Sari, Iran. After making announcements in women's gyms that accepted to cooperate with the researcher, 30 volunteers entered the study after necessary examinations were performed on them and after their compliance with the inclusion criteria was ascertained. The study exclusion criteria consisted of a history of cardiorespiratory diseases, diabetes, high blood pressure, and smoking, using hormones or supplements and orthopedic disorders. Once fully informed of the objectives of the study, participants completed and signed written consent forms. Participants were allowed to withdraw from the study at any stage if they were no longer willing to be part of the study or if they could not tolerate the conditions imposed by the study. To implement the study protocol, participants were randomly divided into two groups: a control group and a supplement group. Participants' height was measured using a metal ruler adjusted perpendicular to a graded wall and while they were leaning straight against it with bare feet and touching it with their heels, hips, shoulder blades and head. Their height was measured twice from the highest tip of the head and its mean was then recorded as their real height. For measuring their weight, participants mounted a digital

scale made in Germany with a ±0.1 kg precision with bare feet and with as few clothes on as possible. Participants' body fat percentage was measured using a body composition analyzer made in Taiwan. The analyzer was sensitive to motions and required the input of certain information, including height, age, gender and the physical activity level (light, moderate and heavy) for measuring body fat percentage. Participants' body fat percentage was measured in fasting conditions and after excretion. Participants were also recommended to stick to their usual diet during the study.

The supplement group took 3 celery powder capsules with a glass of water every day after each of the three main meals for 8 weeks. Each capsule contained 1300 mg of celery seed power, making for a total daily dose of 3900 mg. The control group also took capsules containing starch powder (placebo) administered in the exact same way. Both groups were given capsules of the same shape in similar bottles labeled every week for daily intake without knowledge of their content. It should be noted that participants did not report any complications, including diarrhea, constipation, itching, and skin inflammation and stomach disorders during the course of supplementation.

To measure the variables under study, 5 ml blood was drawn from participants' left brachial vein while in a seated position after 12 hours of fasting first at baseline and then at the end of the study (i.e. after 8 weeks). Blood sampling was performed in the morning on both occasions. The blood samples collected were immediately poured into tubes containing EDTA anticoagulant and centrifuged at 3000 rpm for 15 minutes to separate the plasma. The separated plasma was transferred into a microtube and frozen at -80°C. The major blood variables examined in this study included NF-kB, osteoprotegerin, alkaline phosphatase, high-sensitivity CRP (hs-CRP) and lipid profile. Commercial kits made by Cayman in the US were used to measure TN-kB.

The serum osteoprotegerin level was measured using the ELISA method and with commercial kits made by Cusabio in China. Serum alkaline phosphatase, hs-CRP and lipid profile were measured using the enzymatic method and diagnostic kits made by Pars Azmoon in Iran. Data were analyzed through descriptive and analytical tests. The independent *t*-test was used to examine intergroup changes and the dependent *t*-test to examine intragroup changes. The Smirnov–Kolmogorov test was used to examine the normal distribution of the data and Levene's test to examine the homogeneity of variances. All statistical analyses were performed in SPSS-20 and the level of significance was set at $P<0.05$ for all the calculations.

RESULTS AND DISCUSSION

The findings showed the minimum mean age, height and weight to pertain to the celery supplement group. Table 1 demonstrates participants' details by group.

Table 1: Characteristics of the participating research groups

Group	Control	Celery Supplement
Age (year)	38.33±5.79	38.8±3.88
Weight (kg)	67.37±6.93	69.37±5.49
Height (cm)	159.13±5.44	160.67±6.82

After the 8-week period, mean body mass index (BMI) decreased from 27.03 to 25.53 in the group receiving celery powder as a supplement while it did not change in the control group.

The results of the present study showed that 8 weeks of using celery supplements by the middle-aged women led to a significant reduction in their plasma lipid profile levels except in the case of HDL-C, which had increased. Table 2 demonstrates participants' lipid profile details before and after the intervention.

Table 2: Participants' lipid profile details before and after the intervention

Variables	Group	Before	After	%	P Value
LDL-C	Supplement	93.15	79.35	14.81% ↓	0.000 *
	Control	92.06	93.13	1.1% ↑	0.246
HDL-C	Supplement	37.53	42.6	11.9% ↑	0.026 *
	Control	36.46	37.2	1.9% ↑	0.421
Total Cholesterol	Supplement	194.12	173.41	10.66% ↓	0.000 *
	Control	193.8	194.9	0.5% ↑	0.584
Triglyceride	Supplement	165.4	154.8	6.4% ↓	0.000 *
	Control	166.07	167.53	0.8% ↑	0.301

Results

The results also showed a significant reduction in the celery supplement group's mean hs-CRP after 8 weeks, decreasing from 3.89±0.28 pg/dl to 2.99±0.39 (P=0.001). In the control group receiving starch powder as a placebo, mean hs-CRP showed a slight increase from 3.90±0.25 pg/dl at baseline to 3.93±0.32 pg/dl after the 8-week period; however, the difference was not statistically significant (P=0.724). Figure 1 shows OPG levels in participants.

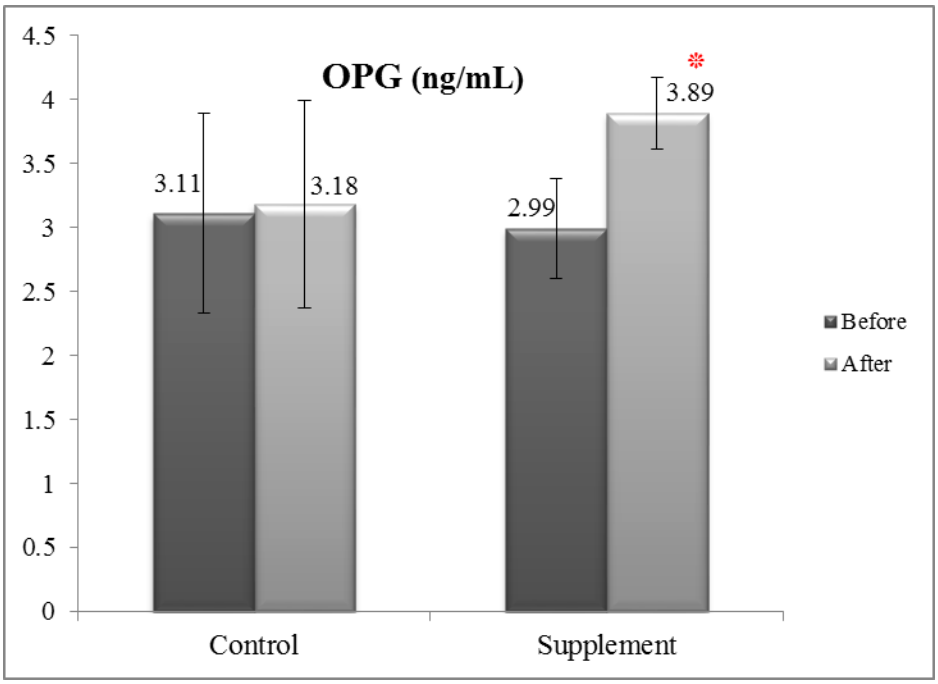

Figure 1: OPG levels in participants

The findings of the present study showed a significant increase in osteoprotegerin levels after 8 weeks of using celery supplements (P=0.001); however, the marker showed almost no changes in the control group

(P=0.949). The statistical analyses showed that the intergroup changes in OPG levels were significant after the intervention (P=0.013). Figure 2 shows participants' NF-kB levels.

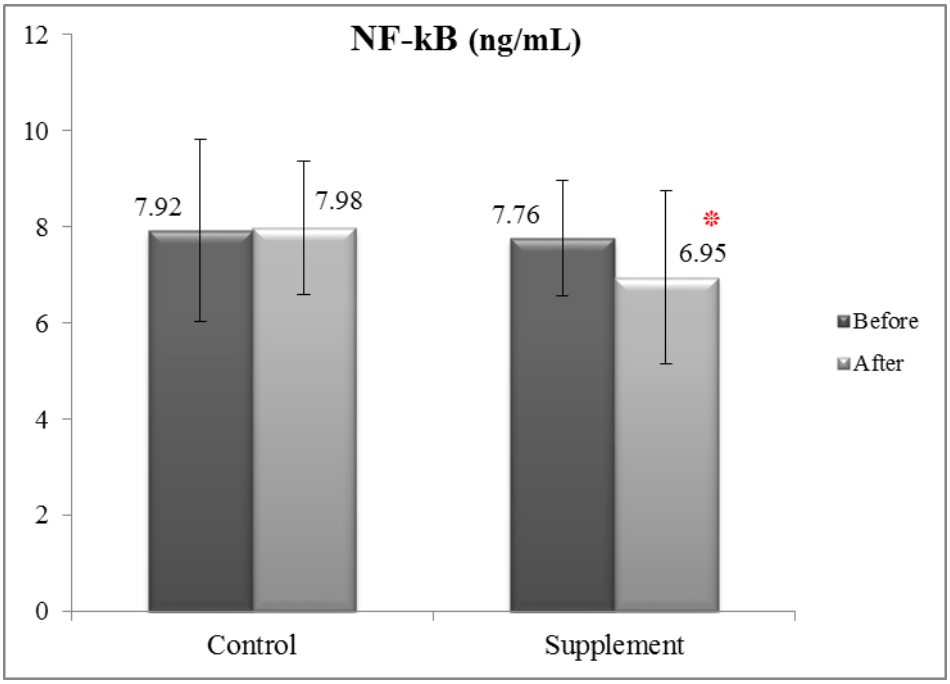

Figure 2: NF-kB levels in participants

The findings showed a significant reduction in NF-kB levels in the supplement group after 8 weeks of taking celery supplement (P=0.001); however, no significant changes were noticed in the control group (P=0.668). The statistical analyses showed a significant difference between the two groups in terms of changes in their TNF-kB levels after the intervention (P=0.020). Figure 3 shows participants' alkaline phosphatase levels.

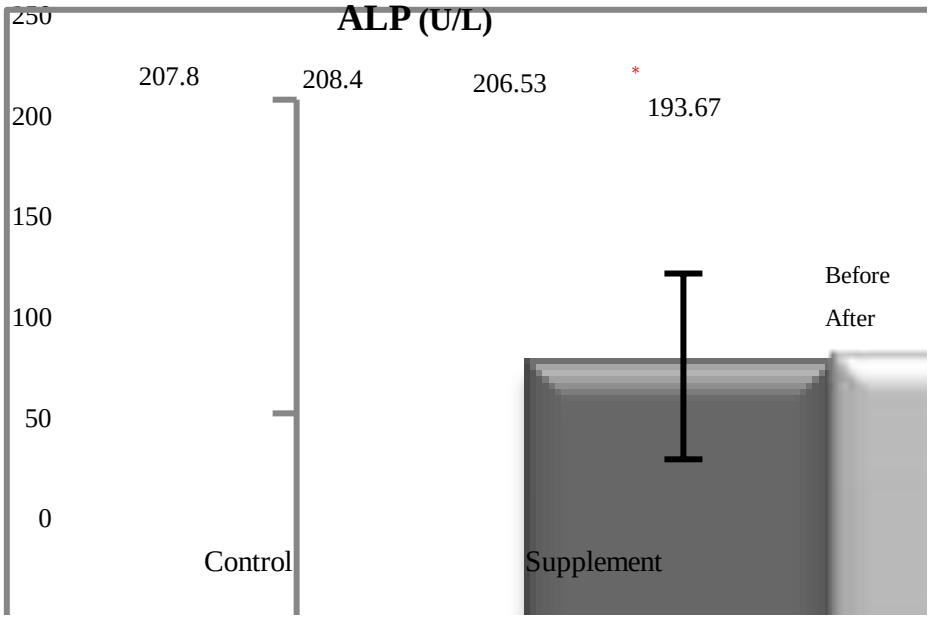

Figure 3: Alkaline phosphatase levels in participants

The findings showed a significant reduction in alkaline phosphatase levels in the supplement group after 8 weeks of taking celery supplement (P=0.000); however, the changes in the control group were not statistically significant (P=0.736). The statistical analyses showed a significant difference between the two groups in their alkaline phosphatase levels after the intervention (P=0.000).

Discussion

The world's elderly population is growing and, as commonly known, aging is normally associated with an increased incidence of inflammatory diseases, such as hypertension, diabetes and osteoporosis. Poor diets followed by a reduction in the intake of nutrients reduces body reservoirs of iron, calcium, zinc and other essential minerals; complications arising from these deficiencies result in diseases such as malnutrition, anemia, zinc deficiency and osteoporosis. Changes in lifestyle and the use of natural antioxidants available make for an effective therapeutic method for the adult and middle-aged population, including women who often have to deal with menopause and its subsequent complications. Proper nutrition can also reduce the risk of bone diseases through controlling the body fat mass, cholesterol levels and oxidative stress and through decreasing bone resorption (Ahmadi *et al.,* 2010; Montazery *et al.,* 2006). Part of the present study focused on examining the effect of an 8-week regimen containing celery supplement on participants' lipid profile. LDL-C levels decreased significantly in the supplement group after the 8 weeks (P=0.000); however, the control group did not show any significant changes with regard to this type of cholesterol (P=0.246). A study conducted by Rafeian *et al.,* (2008) Titled "the effect of Kelussia odoratissima Mozaff. on blood lipid in patients using Lovastatin: a clinical study" revealed a reduction in serum LDL after two weeks and one month of using Kelussia odoratissima Mozaff.; however, there were no statistically significant differences between the two groups in their rate of reduction. The LDL to HDL ratio decreased in both groups (Rafieian *et al.,* 2009). Results of a study conducted by Lair *et al.,* (2011) showed that the use of the alcohol extract and the seeds of celery at the dose of 200 mg/kg and 400 mg/kg of body weight reduces LDL in rats, which is consistent with the findings of the present study (Leung and Foster, 2003). Participants' total cholesterol levels also decreased significantly with the use of celery powder supplement (P=0.000); however, the control group showed no significant changes in this regard (P=0.584). The results of different studies attribute a cholesterol-reducing effect to certain components of celery seeds (Newall *et al.,* 1996). Asgari *et al.,* (2003) conducted a study on the effect of Kelussia odoratissima Mozaff. on the development and progress of Atherosclerosis in rabbits on a high-cholesterol diet and concluded that the plant was effective in preventing the development and progress of fatty streaks (Asgari *et al.,* 2004). Consistent with the results of the present study, cholesterol levels also reduced with a diet containing celery in studies conducted by Rafeian *et al.,* (2008) and Lair *et al.,* (2011). Similar results were also obtained in the analysis of participants' serum triglyceride levels. Serum triglyceride levels decreased significantly in the supplement group after the 8 weeks (P=0.000); however, no significant changes were observed in the control group (P=0.301). This finding was also consistent with the results of similar studies conducted (Leung and Foster, 2003; Rafieian *et al.,* 2009). Analysis of the other plasma lipid content, that is, high-density lipoprotein (HDL-C), showed that a regimen containing celery supplements could increase the level of this fraction. In the present study, the 8-week use of celery powder supplement led to a significant increase in HDL-C levels in the supplement group (P=0.001); however, the control group did not show any significant changes with regard to this type of cholesterol (P=0.421). The results of the study conducted by Rafeian *et al.,* indicated an increase in HDL levels in the supplement group and its decrease in the control group (Rafieian *et al.,* 2009), which was consistent with the results of the present study. Quoting Asgari, Rafeian *et al.,* stated that the use of Kelussia odoratissima Mozaff. in hypercholesterolemia rabbits did not change mean HDL levels at the end of the study, which is not consistent with the results of the present study (Rafieian *et al.,* 2009). Moreover, the results of the study conducted by Lair *et al.,* (2011) was consistent with those of the present study, which revealed a significant increase in HDL levels (Leung and Foster, 2003). With its flavonoid content, antioxidant effects and statin-like effects, celery appears to reduce harmful blood fat and consequently result in weight loss. Part of the effectiveness of celery in reducing the risk of the development of bone diseases in

women might therefore be attributed to its ability to reduce plasma lipid levels and to subsequently lead to weight loss (Rafieian *et al.,* 2009). The present study also examined the effect of using celery supplements on hs-CRP levels in overweight middle-aged women. The findings revealed a significant decrease in the supplement group (P=0.001) and the lack of significant changes in the control group (P=0.724). The researcher was unable to find any studies conducted on the effect of celery on this factor; however, results of the present study revealed a reduction in hs-CRP levels and might thus denote that the use of celery supplements reduces inflammatory processes and is therefore effective in the promotion of health and the reduction of different diseases related to inflammation. The analysis of the use of celery supplements on osteoprotegerin (OPG) levels in the middle-aged women participating in the study showed a significant increase in the supplement group (P=0.000); however, no significant changes were noticed in the control group in this regard (P=0.949). Osteoprotegerin deficiency is indicative of osteoporosis. Osteoprotegerin acts through binding to its natural ligand –osteoprotegerin L, also known as RANKL. Through this binding, osteoprotegerin L inhibits the activity of RANK, a critical osteoclast receptor for differentiation, activity and survival of osteoclasts. The ceasing of osteoprotegerin secretion causes a deep osteoporosis, thereby showing the crucial physiological role of this protein in the regulation of bone resorption. The secretion of osteoprotegerin and osteoprotegerin L from osteoblasts and stromal cells by various hormones and cytokines is often regulated reciprocally. Excessive osteoprotegerin L increases bone resorption while excessive osteoprotegerin inhibits the process. Osteoprotegerin also inhibits bone resorption in a variety of animal diseases, including osteoporosis caused by ovariectomy, malignant humoral hypercalcemia and experimental bone metastasis (Kostenuik, 2001). Powell *et al.,* (2011) conducted a study on the relationship of osteoporosis with adipose tissue leptin and osteoprotegerin in patients with chronic obstructive pulmonary disease (COPD) and concluded that patients with both COPD and osteoporosis have less leptin in their adipose tissue and serum levels compared to people with normal bone mineral density. The adipose tissue leptin and osteoprotegerin are both variables related to bone mineral density. These results show that leptin and osteoprotegerin act as mediators of fat mass and bone mineral density in patients with COPD. Although overweight and obese individuals are at a higher risk of several chronic diseases, such as cardiovascular diseases, diabetes, hypertension and cancer, some reports show that obesity may actually protect against osteoporosis (Pobeha *et al.,* 2011). The results of a study conducted by Hossein *et al.,* (2008) performed on 279 women who were referred to a bone densitometry center for the assessment of their bone status showed no relationship between osteoprotegerin and LDL-C (Hossein *et al.,* 2009). Nezami *et al.,* (2011) studied the effect of lovastatin on serum osteoprotegerin in patients with diabetes type II nephropathy. Thirty men with diabetes type II nephropathy used 20 mg of lovastatin every day for 90 days. Their osteoprotegerin and RANKL levels were measured at baseline, after 90 days of using the supplement and finally 30 days after stopping lovastatin and then compared against one another. The results showed osteoprotegerin to have significantly increased after 90 days of using lovastatin and to have significantly decreased 30 days after stopping it. RANKL levels also measured at the same points first decreased and then increased significantly in both cases (Nezami *et al.,* 2012). These findings denote that celery can prevent potential bone diseases in middle-aged women through the significant increase of their osteoprotegerin levels. Another part of this study examined the effect of celery supplements on NF-kB. The results showed that 8 weeks of using celery supplements led to a significant reduction in the level of this marker in the middle-aged women (P=0.001) while changes in the control group were not significant (P=0.668). NF-KB is a key signaling pathway involved in the initial stages of RANKL-induced osteoclast differentiation (Léotoing *et al.,* 2013) and is known as an evolutionary family protecting transcription factors involved in the response to environmental changes (Hayden and Ghosh, 2004). Sen and Baltimore (1986) revealed the contribution of NF-kB to a variety of biological processes, including immune response, inflammation, proliferation and apoptosis (Xiao, 2004). NF-kB signaling pathways play a role in osteoclast differentiation and bone homeostasis and are proposed as a therapeutic objective for rheumatoid arthritis (Hayden and Ghosh, 2004). Struska *et al.,* (2011) studied the RANKL/RANK/OPG system and bone status in underweight girls with anorexia nervosa. The study was conducted on 91 girls with anorexia

nervosa and 29 healthy girls with a mean age of 13-18, showing a decrease in their NF-kB (Ostrowska *et al.,* 2012). Reduced NF-kB following an 8-week regimen of celery showed the positive effect of celery on preventing bone disorders, in particular, osteoporosis. The last part of the present study examined the level of alkaline phosphatase activity in participants' blood flow. The results showed a significant reduction in the level of alkaline phosphatase activity in the supplement group after the intervention (P=0.000); however, no significant changes were observed in the control group (P=0.736). In their study, Shivasherry *et al.,* (2013) stated that the use of celery powder at the dose of 500 mg/kg of body weight significantly reduced alkaline phosphatase levels in rats (Shivashri *et al.,* 2013), which was consistent with the results of the present study. In a study conducted by Taher *et al.,* (2007) on the effect of the hydroalcoholic extract of celery and dill on the activity of hepatic enzymes in rats revealed that the administration of the extract of either of the herbs decreases alkaline phosphatase activity (Taher *et al.,* 2007), which was consistent with the results of the present study. Dolyn *et al.,* (2011) conducted a study on the effect of limited calorie intake on bone mass in growing mice. They divided 57 weaned 3-week-old male mice into two groups: the calorie restriction (CR) group and the normal diet (N) group. Compared to group N, the CR group showed lower serum leptin levels by 52% and 88% at the age of 6 weeks and 12 weeks. Moreover, the CR group was smaller and had a lower bone mineral density and trabecular and cortical bone properties. Ossification markers (ALP) were lower in the CR group compared to the other group while bone resorption markers (CTX) were higher compared to group N. The results indicate that calorie restriction is associated with skeletal disorders and low levels of leptin in growing mice (Devlin *et al.,* 2010). The results of the present study showed that the use of celery supplements decreased the levels of alkaline phosphatase, NF-kB, plasma lipid including total cholesterol, triglycerides and LDL-C and increased osteoprotegerin and HDL-C levels. It therefore appears that the intake of celery supplement can prevent the development of bone diseases in overweight middle-aged women through its positive mechanisms. Further studies conducted on this topic are recommended to increase the sample size so as to achieve more accurate results.

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