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Article

The Effects of a 12-Month Dried Plum Consumption on Bone Mineral Density and Bone Turnover Markers in Korean Postmenopausal Women with Osteopenia: A Randomized, Open-Labeled, Controlled Study

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Abstract: Consumption of prunes has been shown to slow bone loss after menopause in American women but there is no data on its effects in Asian women. 135 postmenopausal Korean women with osteopenia were randomized to 100g/day of prunes or no prunes with 600U vitamin D and 600mg of calcium for 12 months. Bone density was measured at baseline and 12 months in the lumbar spine, both hips and the L forearm. Serum levels of CTX and P1NP and vitamin D calcium and phosphate were measured at baseline, 6 and 12 months. PTH was measured at baseline if vitamin D was low. Four women dropped out of each group over the 12 months. There was no difference between groups in blood measures or bone density in any region over the 12 month trial. In conclusion 100g/day of prunes has no effect in Korean woman on bone density or bone markers.

Keywords: bone density; DXA; PTX; P1NP; prunes; women

1. Introduction

Osteopenia is a condition associated with as many fragility fractures as osteoporosis because of its higher prevalence [1,2]. According to World Health Organization criteria, osteopenia is defined as BMD as a T-score -1.0 to -2.5, whereas osteoporosis is defined as a T-score -2.5 or lower [1,3]. In the US, 52% of postmenopausal Caucasian women have osteopenia and 20% have osteoporosis [4]. In South Korea, 44% of women aged over 66 years had osteopenia based on data of Korea National Screening Program for Transitional Ages 2008-2011 [5]. Progression of osteopenia and osteoporosis markedly increases the risk of skeletal fractures [6]. The main goal of screening for and treating osteopenia is to prevent the development of low trauma fractures [1,6]. Effective fracture prevention would have a major impact on women's morbidity and an important impact on mortality [1,6].

Osteoporosis may be associated with sarcopenia—a state of low muscle mass and strength, and impaired motor function which increases the risk of falls and fractures. A combination of osteoporosis and sarcopenia is called osteosarcopenia [7]. Osteoporosis and osteoporotic fractures are prevalent conditions among the elderly, which significantly increase morbidity and mortality, a poor quality of life and a substantial economic burden worldwide [8–11]. Direct medical costs of osteoporosis in Americans aged over 50 years was estimated at 13.7–20.3 billion dollars (adjusted to 2005 dollars) [9]. The prevalence of osteoporosis and osteoporotic fractures is growing more rapidly in South Korea than in other countries [8]. The elderly population may be 20% of the total population by 2026 in South Korea, leading to a super-aged country in the near future [12]. In South Korea, a total healthcare expenditure on osteoporosis between 2008 and 2011 increased from \$3,976 million (USD) to \$5,126

million (USD), with an annual increase of 9.2%, which accounted for 16.7% of national healthcare expenditure [8]. Total healthcare costs for osteoporotic women was 6-fold higher than that for osteoporotic men, while the cost per man was 1.5-fold higher than that for women [8].

Current therapies including selective estrogen modulators, anti-resorptive pharmacological agents (e.g. bisphosphonates and denosumab), and the bone-forming pharmacological agents (e.g. teriparatide) are expensive, have some side effects and compliance is variable . Lifestyle modifications including diet (calcium, vitamin D, increased protein, reduced salt and increased fruit and vegetables) and physical activity can reduce the risk of osteoporosis and fractures [13–17].

In a review [18,19] of 5 randomized clinical studies [20–24], 100 g/day of whole prune (dried plum) for 1-year improved bone health indices in postmenopausal women [18,19]. One study showed 50 g/day of prunes for 6 months also was as effective as 100 g/day of prune in preventing bone loss in older, osteopenic postmenopausal women [24]. Currently there are no published clinical data examining the effect of prunes on bone health in Asian women.

Therefore, the aim of this study was to investigate the effects of a 12-month prune consumption on bone mineral density and bone turnover markers in Korean postmenopausal women with osteopenia in a randomized, open-labeled, -controlled design. The primary endpoint was BMD of lumbar spine, forearm, hip and total body using dual-energy X-ray absorptiometry (DXA) at baseline and 12 months. The secondary endpoint was serum vitamin D, serum calcium, serum phosphate, s-CTx and s-P1NP at baseline, 6 and 12 months.

2. Materials and Methods

Subjects

After screening of 217 volunteers, 143 participants with osteopenia were included in this study (Figure 1). The participants were postmenopausal women with osteopenia, aged 50–75 years ,and not on hormone replacement therapy for at least 12 months before initiation of the study This study was performed in the Gyeongsang national university hospital between June 2020 and December 2022. Recruitment was via flyers at public health centers, and hospitals.

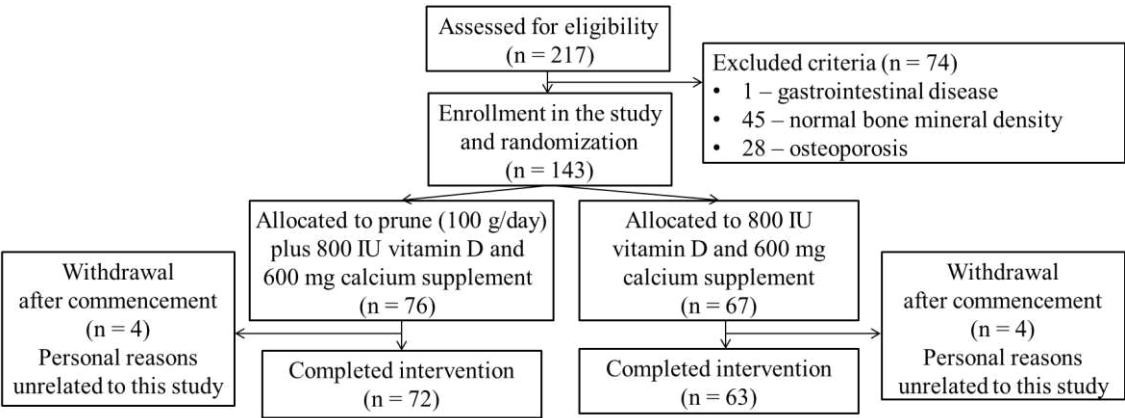


Figure 1. A flow-diagram of the study participant.

Women with a current or recent use (within the last 12 months) of any medications known to alter bone and calcium metabolism, women with abnormal calcium and phosphate or diseases that alter bone and calcium metabolism and women with low vitamin D with elevated parathyroid hormone (PTH) were excluded. Women who regularly consumed prune or prune juice, women with known intolerances to prunes and women who had particular food allergies, women who did not have the national health insurance and women who smoked were also excluded.

The study was performed according to the guidelines of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Gyeongsang National University Hospital (IRB No. GNUH 2020-02-013). Written informed consent was obtained from all subjects involved in

the study. A complete medical history, lifestyle and physical activity surveys were obtained from the participants before commencing the study. The participants were recommended to maintain their usual meal and physical activity pattern.

Study design

Eligible postmenopausal women with osteopenia ($n = 143$) were randomly allocated into a treatment group or a control group: prunes (100 g/day; $n = 76$) plus 800 IU vitamin D and 600 mg elemental calcium or 800 IU vitamin D and 600 mg elemental calcium (control; $n = 67$). Randomization was by an online randomization generator. The calcium amount was based on National Osteoporosis Foundation (NOF)'s daily calcium recommendations – women aged over 50 years need a total of 1,200 mg/day assuming 400-600 mg from diet and 600 mg from supplements[25]

.A daily checklist during the intervention was used in order to monitor compliance. Prunes were gradually incorporated into the participant's diet to ensure tolerance.

Sample size

Determination of the sample size was estimated from the effects on changes in BMD, which was the primary outcome of the trial. Considering several publications [17,21,26], it was expected that a difference between groups of about 1.5% after 12 months with a standard deviation of about 2.5% in total body BMD could be detected between two groups with a power of 80% and two-sided alpha of 0.05 with 45 completers in each group. Thus we aimed to recruit a total of 120 participants to with an expected rate of dropout of 25% during the trial..

Anthropometric data

A medical history was obtained at the beginning of this study. The international physical activity short survey and anthropometric data were collected at baseline, 6 and 12 months. Body height (cm) was measured to the nearest 0.1 cm. Body weight (kg) was measured to the nearest 0.1 kg with the participant wearing light clothing without shoes. Body height and weight were measured using a stadiometer with scales (DS-103, Dongsahn JENIX, Seoul, Korea). Blood pressure and pulse pressure were measured once on the right upper arm in seated position using an automatic electronic sphygmomanometer (HBP-9020, OMRON Healthcare, Kyoto, Japan).

Measurements of bone mineral density

BMD of lumbar spine (L1-L4), L forearm, R and L hip and total body were assessed at baseline and at the end of the study using dual energy X-ray absorptiometry (DXA; Discovery Wi, Hologic Inc., Bedford, MA, USA). Osteopenia ($-2.5 < T\text{-score} < -1.0$) and osteoporosis ($T\text{-score} \leq -2.5$) were diagnosed using the World Health Organization (WHO) Asian T-score criteria [3]. Densitometer accuracy was evaluated by performance of phantom scans on the dates of data acquisition.

Measurements of bone turnover markers

Venous blood samples were collected after an overnight fast at baseline, 6 and 12 months. PTH levels were measured in women with low vitamin D (< 50 nmol/L) at baseline. s-P1NP level was measured using Elecsys total P1NP assay (Roche Diagnostics, Mannheim, Germany) by E170 module immunology analyzer (Roche Diagnostics). s-CTx level was measured using Elecsys β -CrossLaps kit (Roche Diagnostics, Mannheim, Germany) by electrochemiluminescence assay (ECLIA; Roche Diagnostics, Mannheim, Germany). Serum 25(OH)D level was measured using Elecsys vitamin D total electrochemiluminescence binding assay (Roche Diagnostics, Mannheim, Germany) by Cobas 8000 e602 analyzer (Roche Diagnostics). Serum calcium level was measured using colorimetric (NM-BAPTA method) by Roche Cobas 8000 module c701/702 (Roche Diagnostics). Serum phosphorus level was measured using a commercial kit on a Cobas 8000 (Roche Diagnostics, Mannheim, Germany). Serum PTH level was measured using ECLIA (Roche Diagnostics, Mannheim, Germany) on a E170 module immunology analyzer (Roche Diagnostics).

Statistical analysis

The statistical analyses were performed with SPSS 27.0 (IBM, Chicago, IL, USA). BMD (lumbar spine, hip, forearm and total body) (baseline and 12 months), age, height, weight, BMI, blood pressure, pulse rate, physical activity and lab tests (s-CTx, s-P1NP, serum calcium, serum phosphorus and serum vitamin D) (baseline, 6 and 12 months) were tested for normality with the Kolmogorov-Smirnov test, Q-Q plots and histograms. Data was analyzed by repeated measures ANOVA with and without covariates of age, BMI, t score quartile and prune compliance and activity scores. The chi-squared test was used for categorical variables. Change data are presented as means $\pm$ standard deviation (SD). Statistical significance level was assumed at $P < 0.05$.

3. Results

Baseline characteristics of the study participants

As shown in **Figure 1** and **Table 1**, of the 217 postmenopausal women who were screened, seventy six participants in test group (dried plum group) and sixty seven participants in the control group were enrolled and four volunteers dropped out of each group over the 12 month period. The mean age of all participants were 60.9 ± 5.8 years. Moderate and high physical activity (5 days per week or more) were non-significantly higher in the prune group while walking 5 days per week or more was similar in both groups. There was no statistically significant difference in demographic characteristics between groups (**Table 1**). Compliance to the prune consumption was over 90% in all participants.

Table 1. Demographic findings of the participants who completed (n=135).

Variables		Prune group (n=72) N (%)	Control group (n=63) N(%)	P- value
Age (year)	Mean $\pm$ SD	60.3 $\pm$ 6.1	61.5 $\pm$ 5.6	0.9
	Baseline	16 (23)	19 (32)	0.3
BMI over 25	6 month	16 (23)	20 (31)	0.3
	12 month	17 (24)	14 (23)	0.3
	Baseline	16 (29)	7 (13)	0.09
Moderate or high physical activity on 5 or more days per week	6 month	16 (29)	10 (19)	0.4
	12 month	16 (29)	9 (17)	0.2
	Baseline	47 (66)	45 (73)	0.4
Walking 5 days or more per week	6 month	50 (70)	42 (68)	0.4
	12 month	56 (79)	43 (70)	0.2

BMI, body mass index; SD, standard deviation.

Changes in BMD at 1 year of follow-up for study participants

Table 2 presents the changes of BMD at each site from baseline to 12 months for prune and control group. The change in BMD of total lumbar spine was -0.015 ± 0.024 g/cm² for the prune group and -0.011 ± 0.025 g/cm² for the control group ($P = 0.3$). The change in BMD of left total hip was -0.007 ± 0.025 g/cm² for the prune group and -0.004 ± 0.033 g/cm² for the control group ($P = 0.5$). The change in BMD of total forearm was -0.008 ± 0.012 g/cm² for prune group and -0.007 ± 0.015 g/cm² for control group ($P = 0.7$).

Table 2. Changes in BMD and T-score at 1 year of follow-.

Variables	Total (n = 135)		Prune group (n = 72)		Control group (n = 63)		P
	Mean	SD	Mean	SD	Mean	SD	
Lumbar spine BMD							
L1 (g/cm ²)	-0.013	0.033	-0.013	0.036	-0.013	0.030	0.9
L2 (g/cm ²)	-0.012	0.039	-0.015	0.039	-0.009	0.038	0.4
L3 (g/cm ²)	-0.015	0.040	-0.019	0.036	-0.010	0.043	0.2
L4 (g/cm ²)	-0.013	0.036	-0.014	0.031	-0.012	0.042	0.7
Total (g/cm ²)	-0.013	0.025	-0.015	0.024	-0.011	0.025	0.3
Left hip BMD							
Neck (g/cm ²)	-0.004	0.024	-0.006	0.024	-0.002	0.023	0.4
Troch (g/cm ²)	-0.001	0.019	-0.001	0.020	-0.001	0.018	0.9
Inter (g/cm ²)	-0.006	0.032	-0.007	0.031	-0.004	0.033	0.6
Total (g/cm ²)	-0.005	0.023	-0.007	0.025	-0.004	0.022	0.5
Right hip BMD							
Neck (g/cm ²)	-0.004	0.028	-0.005	0.023	-0.003	0.033	0.7
Troch (g/cm ²)	0.000	0.018	-0.001	0.017	0.001	0.019	0.5
Inter (g/cm ²)	0.004	0.031	0.002	0.029	0.005	0.033	0.5
Total (g/cm ²)	0.001	0.023	0.000	0.022	0.003	0.024	0.4
Forearm BMD							
UD (g/cm ²)	-0.005	0.016	-0.006	0.015	-0.004	0.018	0.6
MID (g/cm ²)	-0.008	0.014	-0.008	0.013	-0.007	0.015	0.6
1/3 (g/cm ²)	-0.011	0.017	-0.011	0.017	-0.011	0.017	0.9
Total (g/cm ²)	-0.008	0.013	-0.008	0.012	-0.007	0.015	0.7
Total body BMD (g/cm²)	-0.008	0.021	-0.008	0.020	-0.007	0.023	0.7

BMD, bone mineral density; Inter, intertrochanter; MID, mid-distal radius; Neck, femoral neck; SD, standard deviation; Troch, trochanter; UD, ultra distal radius.

Laboratory results of the study participants

Table 3 presents the mean and SD of the difference in serum bone biomarkers (CTx, P1NP, vitamin D, calcium and phosphorus) from baseline to 6 months and baseline to 12 months. The change in serum CTx, a marker of bone resorption, was -0.042 ± 0.13 ng/mL for prune group and -0.046 ± 0.16 ng/mL for control group between baseline and 6 months ($P = 0.9$). Between baseline and 12 months changes in serum CTx were -0.045 ± 0.15 ng/mL for prune group and -0.024 ± 0.17 ng/mL for control group ($P = 0.6$). Changes in serum P1NP, a marker of bone formation, were -4.03 ± 14.1 ng/mL for prune group and -5.1 ± 14.4 ng/mL for control group between baseline and 6 months ($P = 0.7$). Changes in serum P1NP were -2.15 ± 14.4 ng/mL for prune group and -2.42 ± 16.0 ng/mL for control group between baseline and 12 months ($P = 0.9$). Changes in serum vitamin D were 4.7 ± 6.9 ng/mL for prune group and 6.0 ± 6.7 ng/mL for control group between baseline to 6 months ($P = 0.4$).

Table 3. Laboratory results of the study participants (n=135).

Variables		Total	Prune group	Control group	P-value
CTx (ng/mL)	6 month - baseline	-0.044 ± 0.15	-0.042 ± 0.13	-0.046 ± 0.16	0.9
	12 month - baseline	-0.035 ± 0.16	-0.045 ± 0.15	-0.024 ± 0.17	0.6
P1NP (ng/mL)	6 month - baseline	-4.60 ± 14.2	-4.03 ± 14.1	-5.14 ± 14.4	0.7
	12 month - baseline	-2.3 ± 15.0	-2.15 ± 14.4	-2.4 ± 16.0	0.9
Vit D (ng/mL)	6 month - baseline	5.3 ± 6.7	4.7 ± 6.8	6.0 ± 6.7	0.4
	12 month - baseline	5.5 ± 7.3	4.7 ± 8.4	6.3 ± 5.9	0.3
Ca (mg/dL)	6 month - baseline	0.06 ± 0.4	-0.01 ± 0.3	0.1 ± 0.4	0.08
	12 month - baseline	-0.1 ± 0.4	-0.2 ± 0.4	-0.05 ± 0.42	0.2

P	6 month - baseline	0.03 ± 0.6	0.06 ± 0.6	-0.01 ± 0.	0.6
(mg/dL)	12 month - baseline	-0.06 ± 0.5	-0.08 ± 0.5	-0.04 ± 0.5	0.7

Ca, calcium; CTx, C-terminal telopeptide of type 1 collagen; P1NP, procollagen. type 1 N propeptide; Vit D, vitamin D; P, phosphorus.

4. Discussion

This study examined the effect of 100g/day of prunes for 12 months on BMD and bone turnover markers of Korean postmenopausal women with osteopenia in a randomized, open-labeled, controlled design. No effects were seen with prunes in either serum markers or BMD at any site.

In the first human studies using prunes Arjmandi et al[20] randomly assigned fifty-eight postmenopausal women not on hormone replacement therapy (HRT) to consume either 100 g dried plums or 75 g dried apples daily for 3 months. In comparison with corresponding baseline values, only dried plums significantly increased serum levels of insulin-like growth factor-I (IGF-I) and bone-specific alkaline phosphatase (BSAP) activity. The two groups however were not significantly different from each other. Hooshmand et al. [21] investigated the effect of prune intake (100 g/day) on BMD in postmenopausal women with osteopenia compared to dried apple intake for 12 months in 162 women. Both groups received 500 mg calcium plus 400 IU vitamin D daily. A total of 100 participants completed the study, with 45 in the prune group and 55 in the dried apple group. In this study [21], bone biomarkers [bone-specific alkaline phosphatase (BALP), osteocalcin (OC), tartrate-resistant acid phosphatase-5b (TRAB-5b) and C-reactive protein (CRP) at baseline, 3, 6 and 12 months] and BMD (whole body, lumbar spine, hip and femoral neck at baseline and at the end of the study) were measured. This study showed that BMD in the prune group significantly increased at the ulna and spine BMD compared to the dried apple group. No differences were seen between groups in serum markers [21]. In a second paper RANKL and sclerostin were measured but there was no difference between groups[22]. In a small study prunes had no additional effect to resistance training in bone turnover markers over 6 months in breast cancer survivors[23].

De Souza et al. study[27,28] evaluated the effects of prune intakes (50 g/day and 100g/day) on BMD and bone turnover in postmenopausal women for 12 months. A total of 183 participants completed, 46 subjects in the 100 g/day prune group, 67 subjects in the 50 g/day prune group and 70 subjects in the control group (0g/day prune) were completed. All study participants received 1200 mg calcium plus 800 IU vitamin D3 daily. This study measured BMD (lumbar spine, hip and total body) at screening, 6 and 12 months and also assessed bone biomarkers (P1NP, CTx, IGF-1 and vitamin D) at baseline, 6 and 12 months[27]. Using 50g of prunes per day a diet by time effect was seen in total hip BMD ($p=0.017$) but no other bone area with an intention to treat analysis. Using a completors analysis at 12 months the effect on % change in BMD was stronger with a 1.1% fall in the control group and a 0.27% fall in the prune group ($p=0.011$). With 100g/day power was reduced by dropouts and a significant variation in the response so that the diet by time interaction was $p=0.287$ despite the mean difference between groups being similar (0.005) in the 50 and 100g groups. In the participants who completed the full 12-mo intervention, there was no difference in percent change in total hip BMD for the control compared with the 100-g prune groups [$-1.1 \pm 0.2\%$ compared with $-0.23 \pm 0.4\%$, $P = 0.131$].

With both prune groups combined a group $\times$ time interaction was borderline significant for total hip BMD ($P = 0.051$). In the participants who completed the full 12-mo intervention, the control group lost $1.1 \pm 0.2\%$ BMD at the total hip compared with the pooled prune group, who lost $0.25 \pm 0.2\%$ [$P = 0.007$]. No significant effects were seen with prune supplementation in blood biomarkers.

Given the negative results from this study in Korean women and the negative results with the 100g supplementation in the De Souza study we have a quandary. Previous studies using 100g of prunes have shown no ill effects of this amount American women while in the De Souza study it appears some volunteers have no response to it while others had a large response given the mean change and the SD in this group. Does this variation in response to the higher dose reflect pre-existing intake of polyphenols with no response (or a negative response) in those individuals with a high intake of fruits and vegetables and/or tea and coffee? Does this response also explain the negative

effect in Korean women who would be expected to have a much higher intake of polyphenols than American women. We assume that Korean women have quite different microbiota to Caucasian women in the USA given the geographical microbiome data[29] and the microbiome in Japanese[30] and this may influence the response to prunes. Increased plant intake and polyphenol-rich green tea intake in addition to a Mediterranean diet has been shown to modulate the microbiome [31]. The microbiome has been related to bone density and susceptibility to osteoporosis in women.[32]. Prunes appear to modulate inflammation in preclinical studies[33] as well as change the gut microbiota[34]. Polyphenol intake is related to bone density while coffee intake is related to bone density in Korean[35] and Chinese women[36] with polyphenol metabolites also related to bone density in the latter study. One particular polyphenol, resveratrol, increases bone density in Australian women but this may be partly due to its estrogenic action[37]. One area of inconsistency in the high plant, high polyphenol hypothesis is the finding that vegetarian and especially vegan women in the Oxford EPIC study have a higher fracture rate than omnivores even after adjusting for BMI, protein and calcium intake[38].

It is difficult to understand the varying effects of prunes on different regions in different studies with no consistency apparent. Certainly in the De Souza study where only hip BMD was different there is no suggestion of an effect on total body or lumbar spine BMD nor is any effect on hip BMD seen in the other studies.

Conclusions

In conclusion, in Asian women 100g/day of prunes is not beneficial. Given the results for the 50g/day group in American women it is possible this dose of prunes may be beneficial in Korean women

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