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CLINICAL TRIAL

Alendronate improves fasting plasma glucose and insulin sensitivity, and decreases insulin resistance in prediabetic osteopenic postmenopausal women: A randomized triple-blind clinical trial

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ABSTRACT

Aims/Introduction: Postmenopausal women receive bisphosphonates for osteoporosis treatment. The effect of these medications on developing diabetes mellitus in prediabetic patients is yet to be investigated. We aimed to determine the effect of alendronate on plasma glucose, insulin indices of postmenopausal women with prediabetes and osteopenia.

Materials and Methods: The present triple-blind randomized controlled clinical trial included 60 postmenopausal women, aged 45–60 years. All patients were vitamin D sufficient. They were randomly enrolled in intervention (70 mg/week alendronate for 12 weeks) and control (placebo tablet per week for 12 weeks) groups. The morning 8-h fasting blood samples were collected at the baseline and follow-up visits to measure the fasting plasma glucose (mg/dL), insulin and hemoglobin A1c (HbA1c). Plasma glucose and insulin concentration were measured 30, 60 and 120 min after the glucose tolerance test. The Matsuda Index, homeostasis model assessment of insulin resistance, homeostasis model assessment of β-cell function and the area under the curves of glucose and insulin were calculated.

Results: The mean (standard deviation) fasting plasma glucose (102.43 [1.46] mg/dL vs 94.23 [1.17] mg/dL, $P = 0.001$), 120-min insulin concentration (101.86 [15.70] mU/L vs 72.60 [11.36] mU/L, $P = 0.026$), HbA1c (5.60 [0.06]% vs 5.40 [0.05]%, $P = 0.001$), homeostasis model assessment of insulin resistance (3.57 [0.45] vs 2.62 [0.24], $P = 0.021$) and Matsuda Index (7.7 [0.41] vs 9.2 [0.4], $P = 0.001$) significantly improved in the alendronate-treated group. There were more statistically significant reductions in fasting plasma glucose (–8.2 [8.63] mg/dL vs –2.5 [14.26] mg/dL, $P = 0.002$) and HbA1c (–0.2 [0.23]% vs –0.09 [0.26]%, $P = 0.015$) observed in the alendronate-treated group than the placebo group during the study course, respectively.

Conclusions: Administration of 70 mg/week alendronate improves fasting plasma glucose, HbA1c and insulin indices in postmenopausal women.

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INTRODUCTION

Diabetes is a serious global health issue, and is a major cause of morbidity, mortality and worldwide economic burden with an annual increase in the prevalence rate[1]. Although the prevalence of diabetes mellitus among the Iranian population is close to the global prevalence (8–9%), it has increased to roughly 20% in women aged 55–65 years[2]. Therefore, any method that can reduce the chance of developing diabetes mellitus in this high-risk group of women by paying more attention to prediabetic patients is highly desirable.

Diabetes mellitus is associated with an increased prevalence of complications, such as nephropathy, cardiomyopathy, retinopathy and vasculopathy[3], mainly caused by generalized capillary dysfunction[4]. Hence, several interventions have been suggested to reduce the incidence rate of diabetes mellitus, such as lifestyle or pharmacological interventions to reduce the risk factors[5,6]. Prediabetes is mainly diagnosed by impaired fasting glucose and/or impaired glucose tolerance[7], defined by hemoglobin A1c (HbA1c) levels of 5.7–6.4%[3]. Generally, 25–50% of patients in the prediabetic state develop diabetes mellitus[8], thus appropriate risk reduction methods and interventions in the prediabetic state can prevent its progression to diabetes mellitus and assist in reducing diabetes-related complications[9,10].

Another significant and prevalent cause of morbidity and mortality in postmenopausal women is osteoporosis, characterized by substantial bone loss, resulting in increased risk of fractures[11], which imposes a great cost and impairs the quality of life of the affected patients[12]. Bisphosphonates, specifically alendronate and risedronate[13], are in the first line of treatment for osteoporosis with few adverse effects[14], and efficiently suppress bone resorption and prevent fractures. Bisphosphonates have also shown antitumor effects[15] and lipid profile modification[16]. Recent population-based studies have suggested a 50% reduced risk of type 2 diabetes mellitus with the use of bisphosphonate, but it has not yet been proven clinically[17,18]. Studies carried out on mouse models have suggested that reduced bone turnover can regulate insulin sensitivity[19,20]. A population-based cohort study showed that the use of alendronate decreased the incidence of diabetes[21]. However, no clinical trial study has yet investigated the effect of antiresorptive therapies on fasting glucose, weight and diabetes incidence. The aim of the present study was to determine the effect of bisphosphonates on metabolic indices (fasting plasma glucose [FPG], insulin, homeostasis model assessment of insulin resistance [HOMA-IR], homeostasis model assessment of β-cell function [HOMA-B], Matsuda Index) of postmenopausal women with prediabetes and osteopenia. We opted for patients with osteopenia, because it is unethical to deprive osteoporotic patients of proven treatment.

METHODS

Study design

The present triple-blind randomized controlled trial was carried out in the Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, between 20 March 2016 and 21 December 2016. The study was approved by the ethics committee of the Isfahan University of Medical Sciences (code: Ir.mui.rec.1395.3.292) and registered in the Iranian Registry of Clinical Trials (code: IRCT2016101530309N1). This study was carried out in accordance with the ethical standards placed in the 1964 Declaration of Helsinki and its later amendments. Among all patients who were referred to the Isfahan Endocrine and Metabolism Research Center, 60 eligible postmenopausal women (amenorrhea for at least 12 months), aged 45–60, with prediabetes and osteopenia (bone densitometry with a T score of −1.5 to −2.4, diagnosed by dual-energy X-ray absorptiometry (Hologic 2008 model; Orlando, FL, USA) and normal serum level of vitamin D were recruited (25-hydroxyvitamin D >20 ng/mL). Those patients who had renal failure, unattended the follow up, received corticosteroid therapy or medications that affect carbohydrate or lipid metabolism including metformin, pioglitazone, statins, beta blockers, anti-inflammatory and angiotensin-converting enzyme inhibitors, were excluded from the study. The patients were under surveillance throughout the entire study and were followed up carefully. According to the patients' declarations, they took no additional medications without informing the research team, and patients who had to use other drugs at any time during the study were excluded. The sample size was determined to be 30 patients in each group based on previous studies, considering 10 people for loss to follow up[22], with $\alpha = 0.05$ and $\beta = 80\%$. Eventually, 40 people were enrolled for the study. The patients' enrollment diagram is shown in Figure 1.

All participants gave informed consent, and were randomized into the intervention and placebo groups using the block randomization method. The intervention group received 70 mg/week alendronate (Dr. Abidi Company, Tehran, Iran), and the control group received a placebo (produced by the Pharmaceutical Faculty of the Isfahan University of Medical Sciences in the same size, shape and color). The Pharmaceutical Faculty allocated codes of A and B to these medications, and revealed the codes to the research team after completion of the clinical study. One tablet per week for 12 weeks was prescribed for patients to take in the morning while fasting with a glass of water, and patients were instructed to remain in the non-supine position for at least an hour after taking the tablet. The patients were randomly assigned to treatment arms on a 1:1 basis to receive alendronate or a placebo. The research team members who were recording the data, the physicians who examined the patients and the person who was giving medications to the patients with codes A and B according to the randomization block groups were all blind to the group allocations. A member of the research team contacted the patients every 2 weeks to ensure the patients were taking the pills, therefore the included participants that completed the study protocol had complete adherence to the medications. Two blood samples were collected from each participant at the baseline and at the end of the follow-up period; after 8 h of overnight fasting, FPG, insulin, HbA1c and 25 hydroxyvitamin D_3 were measured. The

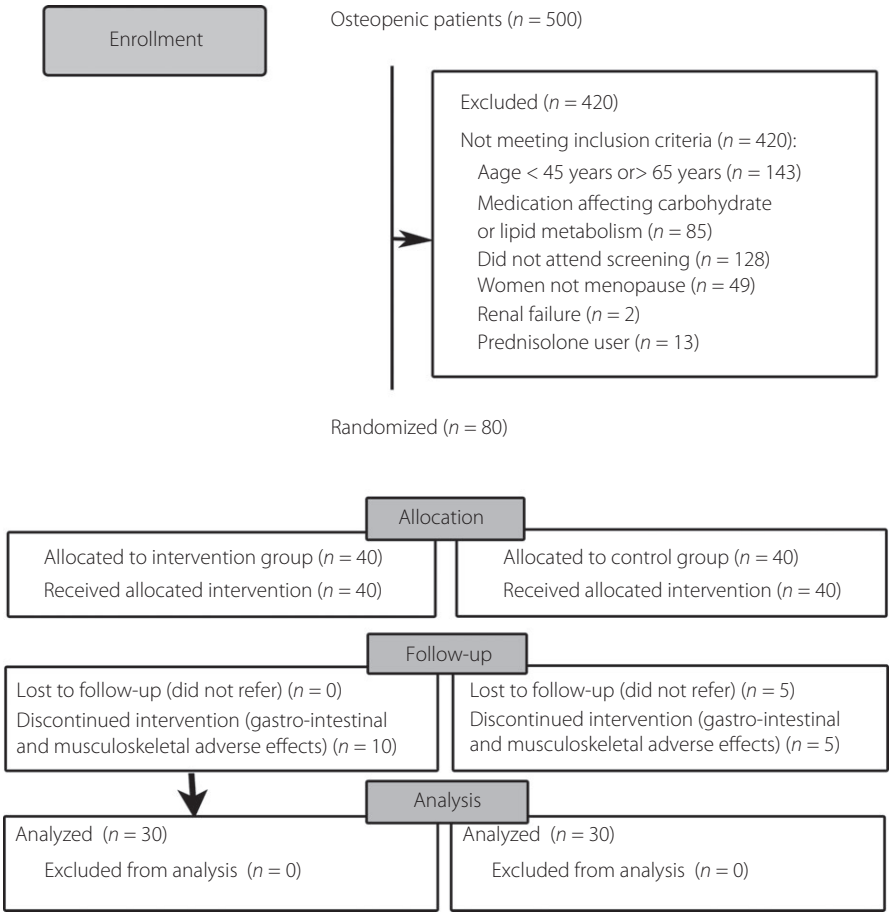

Figure 1 | Consort flow diagram for enrollment of participants in the study.

glucose tolerance test was carried out by using 75 g glucose, and the blood samples were collected before and after 30, 60 and 120 min to measure plasma glucose and insulin. Insulin sensitivity and resistance were calculated using the Matsuda Index and HOMA-IR, respectively. The Matsuda Index was calculated by: 10,000/square root of (fasting glucose [mg/dL] × fasting insulin [mIUl/L]) × (mean glucose [mg/dL] × mean insulin [mIUl/L] during oral glucose tolerance test [OGTT]) and HOMA-IR was defined as: (fasting glucose [mmol/mL] × fasting insulin [mIUl/L]) / 22.5. B-cell function was measured using HOMA-B, defined as: 20 × fasting insulin [mIUl/L] / (fasting plasma glucose [mmol/mL] − 3.5)[23].

Plasma glucose levels were measured by colorimetric enzymatic method using photometric single-point measurement. The insulin levels were measured by sandwich chemiluminescent immune assay (DIAPLUS insulin–96 test; Siemens, Munich, Germany). Interassay coefficients of variation were 0.9 for glucose and 1.9 for insulin, and their intra-assay coefficients of variation were 1.5 and 2.53, respectively. HbA1c was measured using the chromatography ion exchange approach. Vitamin D (25 hydroxyvitamin D_3) concentration was assessed by direct competitive chemiluminescent immunoassay (IDS, Boldons, UK).

Statistical analysis

The continuous quantitative variables are reported as the mean and standard error or the median (interquartile range). Normality of data was evaluated using the Kolmogorov–Smirnov test and Q-Q plot. Log transformation was used for all positive skewed data including HbA1c and HOMA-IR. The independent samples *t*-test was used for comparing the quantitative baseline data between two groups. In order to detect within-group differences in the biochemical characteristics, paired samples *t*-test was used and analysis of covariance (ANCOVA) was carried out to determine the differences between two groups, adjusted by baseline values. The changes in glucose and insulin concentrations (obtained during the 2-h OGTT) were evaluated using repeated measures analysis of variance (ANOVA). All experimental data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 20; SPSS Inc., Chicago, IL, USA).

RESULTS

The present study was carried out between 20 March 2016 and 21 December 2016 on women with osteopenia and prediabetes states. A total of 20 participants, 10 patients from the placebo-treated group (poor compliance, $n = 10$; lost to follow up,

$n = 0$) and 10 patients from the 70 mg alendronate-treated group (poor compliance, $n = 5$; lost to follow up, $n = 5$) were excluded. Finally, 60 patients (placebo-treated group, $n = 30$; 70 mg alendronate-treated group, $n = 30$) completed the trial (Figure 1). The excluded participants were compared with those who completed the study on available data for HbA1c and FBS, and no significant differences were detected.

The baseline characteristics of patients are presented in Table 1. The participants of both groups were similar according to demographic and anthropometric characteristics, serum measurements and laboratory data including 25 hydroxyvitamin D_3 concentration ($P > 0.05$) at baseline.

A significant decrease was found in FPG and HbA1c, and an increase was found in the Matsuda Index ($P < 0.001$), and decrease in insulin of 120 min and HOMA-IR ($P < 0.05$) in the alendronate-treated group after intervention (Table 2). At the end of the study, the mean FPG and HbA1c were statistically different between the alendronate- and placebo-treated groups. The same outcomes were obtained between two groups after adjustment of baseline values for biochemical characteristics with ANCOVA. We also observed statistically significant reductions of FPG (−8.2 [8.63] mg/dL vs −2.5 [14.26] mg/dL, $P = 0.002$) and HbA1c (−0.2 [0.23]% vs −0.09 [0.26]%, $P = 0.015$) in the alendronate-treated group compared with the placebo-treated group during the course of the study.

The means (standard error) of plasma glucose and insulin levels during OGTT in the patients before and after intervention (administration of alendronate and placebo) are shown in Figures 2 and 3, respectively. The cubic trend was detected, and statistically significant differences in plasma glucose over time at all measured points (30, 60 and 120 min during the OGTT) were observed in 70 mg alendronate-treated group. These changes in alendronate-treated patients were significantly higher than the placebo-treated group ($F_{(1,58)} = 4.433$, P–value = 0.04). The changes in plasma insulin concentrations of alendronate-treated patients were statistically insignificant over the time-points of OGTT (30, 60 and 120 min). The mean of plasma glucose and insulin levels remained unchanged in the placebo-treated participants during OGTT.

Table 1 | Baseline characteristics of 70 mg alendronate- and placebo-treated patients

Characteristics	Alendronate treated ($n = 30$)	Placebo treated ($n = 30$)	P-value*
Age (years)	56.5 (6.3)	55.3 (4.0)	0.406
Height (cm)	160.33 (1.07)	161.80 (1.10)	0.344
Weight (kg)	68.5 (9.3)	68.3 (9.4)	0.912
Body mass index (kg/m^2)	26.6 (3.1)	26.0 (3.0)	0.449
Waist circumference (cm)	84.0 (9.5)	81.5 (10.9)	0.346
Systolic blood pressure (mmHg)	129.7 (14.0)	128.3 (15.8)	0.731
Diastolic blood pressure (mmHg)	69.4 (18.1)	71.0 (18.9)	0.728

*Resulted from independent samples *t*-test.

DISCUSSION

The primary aim of the present randomized controlled trial was to investigate the effect of alendronate on plasma glucose, insulin levels, sensitivity and resistance indices during an OGTT among osteopenic prediabetic postmenopausal women. We found an 8.2-mg/dL decrease in FPG and 0.2% in HbA1c among the alendronate-treated group, which remained statistically significant after adjustment for confounding variables in the intervention group, whereas the changes were not significant in the control group. These results suggest that 70 mg/week oral alendronate for 12 weeks can significantly improve FPG and HbA_1C levels of prediabetes postmenopausal women and might slow down the rate of progression to diabetes.

The comparison of the results of plasma glucose (OGTT) before and after intervention showed a statistically significant decrease in plasma glucose in the 70 mg alendronate-treated group at all intervals (30, 60 and 120 min during the OGTT), as well as a significant difference with the placebo group. These results are similar to the observational studies showing a lower incidence of type 2 diabetes mellitus in patients receiving bisphosphonates[17,18], and the present randomized controlled trial confirmed lower plasma glucose levels in OGTT by alendronate. A cohort study in Denmark[18] reported a reduced rate of developing type 2 diabetes mellitus in patients taking medications (alendronate, etidronate and raloxifene) for osteoporosis with non-diabetic control participants, and noted a dose–dependent risk reduction for alendronate. In individuals aged >60 years without diabetes at baseline, more than a year of exposure to bisphosphonates (including alendronate, risedronate, etidronate, zoledronate and ibandronate) reduced the risk of diabetes mellitus (odds ratio 0.52) compared with general matched unexposed individuals in a retrospective population-based study[17]. A significantly higher incidence of diabetes mellitus (odds ratio 1.21) was also reported in the control group compared with the alendronate-treated osteoporotic patients without diabetes mellitus in a retrospective cohort study[21]. This incidence rate was statistically significant among patients aged <65 years and those without hypertension or dyslipidemia[21]. Although the results of previous studies are in agreement with the present study, our group specifically included prediabetes and postmenopausal women. We measured FPG, HBA1C, HOMA-IR and the Matsuda Index, and compared two randomized groups with similar baseline characteristics, despite healthy individuals being chosen for the control groups in previous reports[17,18,21].

The present study is the first report on evaluating the effect of alendronate on serum glucose and insulin parameters (FPG, insulin, HOMA-IR, HOMA-B and Matsuda Index) of patients with osteopenia and prediabetes. Animal studies have shown that insulin signaling in osteoblasts promotes glucose metabolism in a bone resorption-dependent manner[19,20], prevents

Table 2 | Serum measurements before and 12 weeks after intervention in study groups

Variables	Alendronate treated (n = 30)			Mean difference (SE)	Placebo treated (n = 30)			Mean difference (SE)	P**
	Before	After	P*		Before	After	P*		
FPG (mg/dL)	102.4 (1.46) (101.5 [96.8–107.2])	94.2 (1.17) (95 [90.5–98.2])	<0.001	−8.2 (8.63)	106.4 (1.98) (105 [99–115.22])	103.9 (2.31) (102 [95–113])	0.345	−2.5 (14.26)	0.002
FPI (mU/L)	13.87 (1.60)	11.3 (1.05)	0.065	−2.56 (7.33)	15.33 (4.10)	15.63 (4.09)	0.949	0.3 (25.6)	0.327
HbA1c (%)	5.60 (0.06) (5.55 [5.4–5.8])	5.40 (0.05) (5.4 [5.25–5.5])	<0.001	−0.2 (0.23)	5.77 (0.07) (5.75 [5.48–5.03])	5.68 (0.08) (5.65 [5.3–6])	0.070	−0.09 (0.26)	0.015
25OH(D)$_3$ (ng/mL)	80.47 (9.06)	85.17 (7.46)	0.433	4.70 (32.39)	95.27 (12.18)	104.87 (11.73)	0.289	9.6 (48.7)	0.314
HOMA-IR	3.57 (0.45) (2.76 [1.87–4.4])	2.62 (0.24) (2.44 [1.54–3.19])	0.021	−0.95 (2.12)	4.19 (0.66) (3.12 [2.31–4.95])	4.11 (1.11) (2.79 [1.72–3.9])	0.951	−0.08 (7.26)	0.203
HOMA-B	124.30 (12.50)	136.3 (15.05)	0.353	12 (69.6)	122.96 (12.50)	139.23 (31.90)	0.632	16.27 (184.3)	0.920
AUC (glucose)	927.72 (47.49)	864.86 (28.64)	0.113	−62.86 (169)	1000.44 (39.40)	960.33 (45.47)	0.289	−40.11 (203.4)	0.165
AUC (insulin)	488.72 (75.6)	474.24 (2.7)	0.144	−14.48 (52.85)	489.54 (13.8)	475.88 (15.44)	0.403	−13.65 (88.1)	0.944
Matsuda index	7.7 (0.41) (7.67 [6.07–9.31])	9.2 (0.41) (8.71 [7.62–10.96])	<0.001	1.45 (2.3)	7.3 (45) (7.21 [5.77–8.37])	8.3 (41) (8.15 [6.74–10.39])	0.100	0.93 (2.9)	0.166

Values are shown as mean and standard error (SE) and (median [interquartile range]).*Obtained from paired samples test. **Obtained from ANCOVA after adjusting baseline values. 25OH(D)$_3$, 25 hydroxyvitamin D$_3$; AUC, area under curve; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA1c, hemoglobin A1c; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

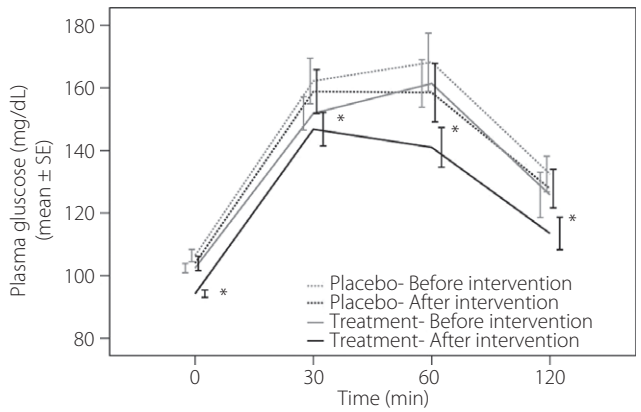

Figure 2 | The effect of alendronate and the placebo on plasma glucose during an oral glucose tolerance test before and after intervention in both groups. *P-value <0.05 in comparison between before and after treatment by 70 mg alendronate (cubic trend) at all measured time-points. SE, standard error.

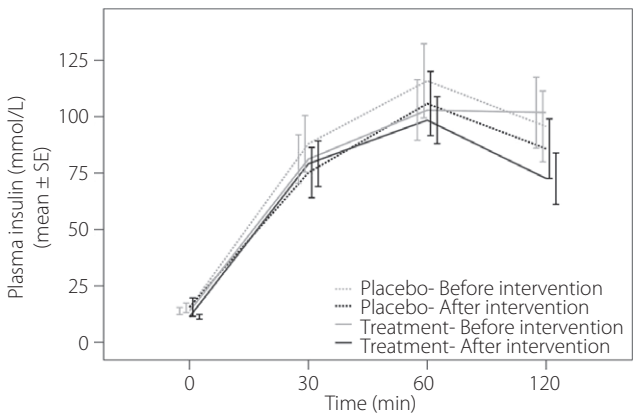

Figure 3 | Effect of alendronate and the placebo on plasma insulin levels during an oral glucose tolerance test before and after intervention in both groups.

insulin resistance and diabetes, and regulates glucose metabolism through alterations in bone metabolism and fat mass[24], suggesting bone as an endocrine regulator for glucose metabolism[24,25]. In addition, the effect of bisphosphonates on early diabetes-associated bone loss has been confirmed in rodent models[26,27]. Decarboxylation of osteocalcin produced by osteoblasts due to unknown factors results in its activation. Osteocalcin interacts with the insulin receptor of the pancreatic β-cells, leading to altered glucose metabolism[19], and regulates the expression of the insulin genes and cell proliferation markers in rat models[24]. We anticipate that alendronate influences glucose metabolism through the above-mentioned mechanisms, as well as disruption of prenylation of small molecular mass G-proteins and pro-inflammatory cytokines or mutations in gastric inhibitory polypeptide receptors[17,28]. Further evidence in humans reported improved bone health by bisphosphonates in postmenopausal women with type 2 diabetes mellitus[29,30], but could not confirm the effect of bisphosphonates on osteocalcin and insulin metabolism[31], which is in agreement with the present study, indicating no significant difference in plasma insulin

levels between the 70 mg alendronate-treated group and the control group. We have shown that bisphosphonates might prevent progression of prediabetes to diabetes mellitus in postmenopausal patients.

The major strength of the present study was designing a well-controlled triple-blind clinical trial, which compared two randomized groups with parallel baseline characteristics, whereas previous studies mainly evaluated participants using a retrospective design. We also investigated the serum variables to assess diabetes-related indices (FPG, insulin, HOMA-IR, HOMA-B, Matsuda Index) among postmenopausal prediabetic women with a high risk of developing diabetes mellitus and osteoporosis, whereas previous reports studied the general population.

In contrast, the present study had some limitations, including the small sample size in each group, which could explain the non-significant differences between groups. We detected no significant differences between available characteristics of excluded patients compared with those who completed the study; however, this comparison was made based on limited data. Although 30 participants is statistically sufficient to achieve reliable results, it is suggested that future multicentric studies address the same population with a larger sample size.

Administration of 70 mg/week alendronate significantly reduced FPG, HbA1c and HOMA-IR, and increased the Matsuda Index in postmenopausal women with prediabetes and osteopenia, whereas there was a significant difference only in terms of FPG and HbA1c between the two groups at the end of study. This indicates a positive effect of alendronate on diabetes-related indices, specifically FPG and HbA1c.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 | Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist of information to include when reporting a randomized trial.