The effect of alendronate on lipid profile of postmenopausal women with osteopenia and prediabetes: A randomized triple-blind clinical trial

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Background: Prediabetes is a high-risk state for developing diabetes at an annual rate of 5%–10%. Early intervention can prevent further complications, including metabolic syndrome. Bisphosphonates are commonly used for osteoporotic postmenopausal women. The purpose of this study was to assess the effects of bisphosphonates on lipid profile including triglyceride (TG), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) of prediabetic postmenopausal women with osteopenia.

Materials and Methods: In this triple-blind randomized controlled trial, sixty prediabetic, postmenopausal women with sufficient Vitamin D and osteopenia, aged 45–60 years, were randomly enrolled in two groups of intervention (receiving 70-mg alendronate for 12 weeks [duration for maximum metabolic effect of bisphosphonates], n = 30) and control (receiving placebo, n = 30) according to a randomized block procedure of size 2 and 1:1 allocation ratio. The primary outcome of the study, the lipid profile, was evaluated before and after the interventions. The effect of the intervention was assessed using analysis of covariance.

Results: The lipid profiles showed no significant differences to the mean values at the baseline in both the groups (all \( P > 0.05 \)). At the end of the study, the differences between the groups were not significant for 25(OH) D₃ (mean difference: −11.09, 95% confidence interval: −32.43–10.25), T (4.19, −30.58–38.97), cholesterol (8.13, −13.07–29.33), LDL-cholesterol (5.07, −10.18–20.31), and HDL-cholesterol (−0.86, −6.04–4.31) when the baseline values and confounders were adjusted (all \( P > 0.05 \)).

Conclusion: No statistically significant difference was detected in the serum lipid profile of prediabetic postmenopausal women with osteopenia as a result of alendronate intervention. More studies with larger sample sizes and longer intervention periods are recommended.

Key words: Alendronate, bone diseases, lipid profile, menopause, metabolic, prediabetic

INTRODUCTION

Osteoporosis is a major concern in postmenopausal women, characterized by accelerated bone loss and increased bone fracture risk.¹⁻² It has several physical, emotional, and financial consequences that impair patients’ quality of life and increases morbidity and mortality rates.³ Considering the lifetime osteoporosis incidence of 16% among Iranian women,⁴ osteoporosis’s enormous economic burden is an important health issue in this population.⁵

Bisphosphonates are Food and Drug Administration-approved, well-tolerated, and safe compounds commonly used to prevent and treat osteoporosis. These medications inhibit bone resorption and significantly reduce the risk of fractures.⁶ On the
other hand, bisphosphonates have various mechanisms of action, including interactions with lipid metabolism enzymes. Nitrogen-containing bisphosphonates bind to farnesyl pyrophosphate synthase, obstruct the mevalonic acid pathway, and inhibit the production of cholesterol, other sterols, and isoprenoid lipids.\[^7\] Several studies have suggested that oral alendronate and intravenous alendronate decrease the total serum cholesterol level, triglyceride (TG), and low-density lipoprotein (LDL) and increase high-density lipoprotein (HDL).\[^8,9\] Other analogs of bisphosphonates, including etidronate, pamidronate, and clodronate, have shown no effect on serum lipid profile while prevented the development of atherosclerosis.\[^10\]

Diabetes is, on the other hand, a potentially debilitating disease with an estimated prevalence of about 8% among the Iranian population, half undiagnosed, with a prevalence of 19.4% in women aged 55–65 years.\[^11\] Prediabetic status is defined as high plasma glucose levels below the diabetes cutoff point.\[^12\] People with prediabetes indicate a high chance of progression to diabetes.\[^13\] Prediabetes is associated with several disorders, such as lipid metabolism disorders that predispose patients to cardiovascular diseases and metabolic syndrome. A randomized, triple-blind clinical trial\[^14\] demonstrated that alendronate improves fasting plasma glucose, hemoglobin A1c, and insulin indices in postmenopausal women. Alendronate is suggested to improve serum lipid profile, including total cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and TG in the osteoporotic population. Therefore, it might be a potential medication serving both purposes.\[^9,15\] Early therapeutic interventions in prediabetes prevent further complications considerably.\[^16\] Therefore, patients with prediabetes require further attention, especially metabolic syndrome associated with increased risk of cardiovascular morbidity and mortality.\[^17\] Despite the significance of osteoporosis and prediabetes in postmenopausal women and the high incidence rate of macro- and microvascular complications in the Iranian population,\[^18\] there is no report available to show the effect of alendronate on lipid profile among Iranian women. The risk of cardiovascular diseases increases in postmenopausal women, and thus, identifying a medication that can improve both bone density and atherosclerosis in these patients is of great significance. Human-based research is required to confirm the favorable and sufficient effect of bisphosphonates on preventing cardiovascular events in postmenopausal women.\[^19\] Moreover, the effectiveness of medications varies with races/ethnicities.\[^20\] The present study aimed to determine bisphosphonates’ effect on lipid profile of Iranian postmenopausal women with prediabetes and osteopenia.

**METHODS**

**Study design and participants**

We designed a triple-blind randomized controlled trial (RCT) to investigate the effect of bisphosphonate on the lipid profile of postmenopausal women with prediabetes and osteopenia. The study was carried out at the Isfahan Endocrine and Metabolism Research Center. All patients were informed about the potential adverse effects, and informed consent was obtained from all participants. We selected osteopenic patients for the current study because it is unethical to deprive osteoporotic women of taking alendronate. The trial registration number is IRCT2016101530309N1.

**Eligibility criteria**

The participants were recruited based on the inclusion criteria from all eligible prediabetic, postmenopausal patients with osteopenia who visited the Isfahan Endocrine and Metabolism Research Center from 20 March 2016 to 21 December 2016. Inclusion criteria consisted of postmenopausal states, aged 45–60 years, diagnosed prediabetes based on American Diabetes Association criteria 2017,\[^12\] and osteopenia, based on T score between −1.5 and −2.4 bone density, measured by Hologic device model 2008.\[^11\] Those patients taking medication that could affect lipid metabolism or those who had renal failure, Vitamin D deficiency (serum concentration of 25OHD3 <30 ng/ml), or unattended follow-up visits were excluded from the study.

**Study size**

The study’s sample size was calculated as thirty patients for each group, considering the type I error rate (α = 0.05), a power of $\beta = 80\%$, and detecting a standardized effect size of 0.7.\[^21\] The proposed study primary outcomes, the lipid profile. To compensate for the possible dropout rate of about 30% in participants due to the medication’s adverse effects, the sample size increased to 40 patients. Eventually, at the end of the study period, 30 patients were assessed in each group. All analyses were conducted according to a per-protocol approach (Figure 1).

**Randomization**

Patients who attended the Isfahan Endocrine Research Center were subjected to initial assessments based on the inclusion/exclusion criteria. The eligible patients were randomly assigned to treatment arms to receive alendronate or placebo according to a randomized block procedure of size 2 and 1:1 allocation ratio. The random sequence of the allocation was generated by the study statistician utilizing random allocation software and was given to the administration team sequentially to preserve
the allocation concealment. The patients who recorded the data, the physician who visited patients, the person who administered two medications (labeled with code A and B), and the statistician who analyzed the data were all blinded to the group allocations (triple-blind).

**Intervention**

The intervention group received a 70-mg weekly dose of alendronate (Dr. Abidi Company, Tehran, Iran), and the control group received a placebo, prepared in the same size and color of alendronate tablet without any therapeutic substance (produced by the Pharmaceutical Faculty of the Isfahan University of Medical Sciences). The Pharmaceutical Faculty allocated A and B codes to these medications and revealed codes to the research team after completing the study. Medications were taken weekly for 12 weeks. Both the groups were asked to take one tablet in the morning while fasting with a glass of water and avoid a supine position for at least an hour after taking the tablet.

**Primary and secondary outcomes**

The participants’ recorded basic characteristics included age, height, weight, body mass index (BMI), and abdominal circumference. Patients’ weight was measured by light clothing without footwear. BMI was calculated by dividing weight in kilogram to squared height in meter (kg/m²). The systolic and diastolic blood pressure was measured from the right arm while the patient was rested for 5 min. Waist circumference was measured in a standing position at the top of the iliac crest in the horizontal plane. Fasting blood samples were taken from participants at the baseline and after 12 weeks of follow-up. For this purpose, a 5 ml vein blood sample was taken from patients’ left arm in a sitting position. It was sent to the laboratory to measure serum lipid profile, including TG, total cholesterol, LDL, HDL, and 25(OH)2D3. The photometric technique measured the lipid profile. Inter-assay coefficients of variations (CVs) were 1.23, 1.09, 1.37, and 1.8 for TG, cholesterol, LDL-C, and HDL-C, respectively. The corresponding intra-assay CVs were 1.6, 0.95, 0.65, and 0.78, respectively. The concentration of 25OHD3 was assessed by direct competitive chemiluminescent immunoassay (IDS, Boldon, UK).

**Statistical analysis**

Numeric variables were reported as the mean (standard deviation [SD]) and categorical data using frequency (percent). Normality of data was evaluated and confirmed using the Kolmogorov–Smirnov test and distribution measures, the skewness (within ±1.5) and kurtosis (within ±2). Independent samples t- and Chi-squared tests were used to compare numeric variables and categorical variables between the two groups, respectively. The paired-samples t-test was used to detect within-group differences of lipid profiles per group. The analysis of covariance (ANCOVA) was carried out to determine the differences between the two groups, adjusted by baseline values and potential confounders, age, sex, baseline BMI, and waist circumference. Two-way ANOVAs with repeated measures ANOVA were used to test the measurement effect, group effect, and possible interactions. The Mauchly test tested the underlying assumption of sphericity, and proper Greenhouse–Geisser correction was chosen when the assumption was not met. All data were analyzed using the IBM SPSS Statistics, version 26 (IBM SPSS Statistics, Armonk, NY, USA), at a significance level of 0.05.

Furthermore, a power analysis was carried out for primary outcomes in the ANCOVA context, considering the adjusted mean (SD) of after intervention in each group, a sample size equal to 30, an alpha = 0.05, five covariates (baseline values, age, sex, baseline BMI, and waist circumference), and the R² obtained from the analysis. The PASS 15 (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.) gave the analysis results.

**RESULTS**

**Participants’ recruitment**

Five hundred prediabetic women with osteopenia were screened to select the eligible participants, and eventually, eighty women who met the inclusion criteria were recruited in this study. A total of ten patients from the placebo-treated group (ten for poor compliance and zero for loss to follow-up) and ten patients from the alendronate-treated group (five for poor compliance and five for loss to
follow-up) were excluded, leading to a 25% dropout rate in each group. Finally, the data for sixty postmenopausal osteopenic prediabetic women were analyzed, thirty women in each group [Figure 1].

**Participants’ profile**

Table 1 shows the background characteristics of the patients. No significant differences were observed between the alendronate- and placebo-treated groups for demographic, anthropometric measurements, and systolic and diastolic blood pressure (all $P > 0.05$).

### Table 1: Participants’ profile in background characteristics ($n=30$)

| Characteristics          | Alendronate treated | Placebo treated | $P^a$ |
|--------------------------|---------------------|-----------------|-------|
| Age (years)              | 56.5 (63)           | 55.3 (40)       | 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 |
| BMI (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 |

Data are expressed as mean (SD). $^a$Based on independent $t$-test for between-group comparisons. SD=Standard deviation; BMI=Body mass index.

Comparing primary outcomes at baseline

Participants in the two groups show no significant differences in terms of $25(OH)_3 D_3$ ($P = 0.435$) and serum lipids, TG ($P = 0.906$), cholesterol ($P = 0.813$), LDL-C ($P = 0.347$), and HDL-C ($P = 0.650$) concentration.

**The effect of the intervention on primary outcomes**

Figure 2 shows the results of $25(OH)_3 D_3$ and serum lipids. According to the Greenhouse–Geisser test, the interaction effect was not significant, so the changes were not significantly different across groups for $25(OH)_3 D_3$ concentration ($P = 0.567$), serum lipids, TG ($P = 0.826$), cholesterol ($P = 0.415$), LDL-C ($P = 0.268$), and HDL-C ($P = 0.794$) concentration [Figure 2].

Table 2 shows the mean (SD) levels of serum lipids for patients before and after the placebo and alendronate administration. No significant changes were detected within each group in terms of $25(OH)_3 D_3$ and lipid profile concentration ($P > 0.05$).

At the end of the study, mean levels of lipid profiles were not significantly different between the alendronate- and placebo-treated groups when their baseline values (all $P > 0.05$), as well as the potential confounders (age, sex, BMI, and waist circumferences), were adjusted [Table 2].

**Power analyses**

The results of the power analysis indicated that considering the sample size of the study, the power were calculated for $25(OH)_3 D_3$ concentration (0.75), TG (0.63), Cholesterol (0.59), LDL-C (0.55), HDL-C (0.68) indicating that for some variables, the study has not enough power.

**DISCUSSION**

The present RCT study assessed 70-mg oral alendronate on patients’ lipid profile compared to a control group with similar demographic characteristics, including age and anthropometric measurements. No statistically significant differences were detected in TG, cholesterol, HDL-C, and LDL-C within and between the groups at the baseline and after 12 weeks of treatment [Table 2].

Previous studies reported the effect of bisphosphonate on postmenopausal women. However, none had targeted prediabetic women.$^{[23,24]}$ Prediabetic patients have insulin resistance,$^{[25]}$ which is associated with impaired bone density.$^{[24,25]}$

The administration of alendronate for 12 weeks improved insulin resistance in these women$^{[14]}$ however, it had no
It appears that alendronate
1 33.1 5 (53.22)

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0.55 (−4.28-5.38), 0.81 7

2: Serum lipid level measures in alendronate- and placebo-treated groups

Before
1 39.93 (77.79)

Although the national lipid association
49.67 (12.35)

−1 2.27 (−43.55-19.02), 0.435

−10.31 (−30.95-10.34), 0.321

−11 6.28 (18.05)

Reduced total cholesterol, TG, and
8.13 (−13.07-29.33), 0.444

after 6-month intake of 10 mg/day
1 41.96 (81.45)

reported the positive
1 44.33 (63.46)

1 3.07 (−6.39-32.52),

−2.59 (−24.52-19.33), 0.813

−10.34 (−23.92-3.25), 0.130

−2.59 (−19.81-7.08), 0.347

−1.43 (−6.63-3.77), 0.584

−0.86 (−6.04-4.31), 0.739

Consequently, the effect of insulin resistance can decrease the proportion of small dense lipoprotein and lower atherogenic lipid, although there are no changes in lipid profile.

No statistically significant differences were observed in the TG or lipid profile of osteoporotic women who took 70 mg/week of alendronate after 6 and 12 months. These results are consistent with the current study regarding the lipid profile. However, we have studied only prediabetic women with osteopenia. A total of 15 patients were excluded from the intervention group in our study due to gastrointestinal (GI) and musculoskeletal complications. A previous report suggested that this complication was caused by the patients’ GI background rather than alendronate. We have detected no severe adverse effects in any of the patients, including jaw necrosis, reported as a rare adverse effect. It appears that alendronate is a safe medication with limited side effects on serum lipid profile.

Contrary to the present study, favorable effects of alendronate on serum lipid profile are reported. 10 mg/day oral intake of alendronate for 2 years in Korean postmenopausal women older than 50 years has shown declined TG and cholesterol and increased HDL-C, while the total cholesterol and TG were increased in the control group. Although the national lipid association recommended a minimum 3-month period to assess the intervention’s effect on serum lipid profiles, the previous study was performed for over 2 years, which was longer than their control group study. The changes in participants’ lifestyle, diet, and physical activity might have influenced their lipid profile. Reduced total cholesterol, TG, and LDL-C levels among osteoporosis and hyperlipidemia patients were reported after 6-month intake of 10 mg/day oral alendronate, when patients with osteoporosis state were included in the study and no control group was studied. We have selected osteopenic women who received no treatment for their bone density and excluded patients with Vitamin D deficiency to eliminate the possible effects of this deficiency on bone resorption.

Three 60-mg cycles of intravenous pamidronate in patients with Paget’s bone disease have shown no significant changes in the control group’s lipid profile. In contrast, in the pamidronate-treated patients, HDL-C and LDL-C were significantly increased, and a slight decrease was observed in the total cholesterol.

In general, previous studies reported the positive effect of alendronate on serum lipid profile, used nonrandomized individuals, performed retrospective analysis, and targeted different populations than the present report. Therefore, the possible effect of insulin resistance and other prediabetic mechanisms on bone density and the differences between patients with osteopenia and osteoporosis might cause discrepancies between our results and previous reports.
Study strengths and limitations

The present study had several strengths, including the assessment of osteopenic prediabetic postmenopausal women for the first time in a triple-blind RCT. We have controlled the possible confounders, including Vitamin D deficiency and renal failure, to overcome previous studies’ limitations in this field. Moreover, a triple blind RCT was adopted to increase the reliability of the results, we have also measured all anthropometric variables. In contrast, previous reports have retrospectively obtained the data from medical records or patients’ reports. However, the short duration of the study was our limitation. Therefore, studies with longer duration are suggested. The results of power analyses showed that this study was under-power for all primary outcomes, therefore, multicentric studies with a larger sample size are recommended. Besides, the present study is RCT with a comparison group on prediabetic and osteopenic cases, affecting the findings’ imprecise estimation. The lack of comparable groups in the literature resulted in presenting the findings without a more detailed comparison. The population study was heterogeneous as our cases had a long duration of osteopenia; this, in turn, led to more imprecise findings.

CONCLUSIONS

This study showed no statistically significant differences between serum lipid profiles of prediabetic postmenopausal women with osteopenia before and after 12-week intake of 70-mg oral alendronate per week. A positive effect of oral alendronate intake on serum lipid profile (TG, cholesterol, HDL-C, and LDL-C) was suggested in previous studies, where either no control group was recruited or the duration of the study was varied between the groups, nonrandomized individuals were studied, and patients with osteoporosis were also included in the studies. This suggests that patients in prediabetic osteopenic status have different physical conditions than other studied groups.

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Conflicts of interest

There are no conflicts of interest.

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