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Early Therapeutic Response of Bone Turnover Markers to Alendronate and Vitamin D3 in Older Women with High Fracture Risk: A Clinical Trial

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ABSTRACT

Background: Bone turnover markers are expected to decrease significantly after receiving anti-resorptive treatment in osteoporosis and they can be used to monitor the efficacy of the treatment.
Objectives: This study evaluated changes in serum procollagen type I N-propeptide (P1NP), a marker of bone formation, and serum cross-linked C-telopeptide of type I collagen (CTX), a marker of bone resorption, following treatment with alendronate (ALN) and vitamin D3 (VitD3) in postmenopausal women with high fracture risk.
Materials & Methods: Postmenopausal women with high fracture risk were recruited from the Galle area of Southern, Sri Lanka and randomly assigned into the treatment (n=30) and control (n=30) groups. Treatment group received oral ALN (70 mg/week) with oral VitD3 (1000 IU/day). Control group received VitD3 (1000 IU/day) along with a matching placebo (PLB). CTX and PINP were measured at baseline and after six months, and means were compared by paired t-test. CTX and PINP were measured by ELISA and body composition was measured by DXA.
Results: In the treatment group, mean CTX and PINP levels at baseline were 3.12 ng/mL and 262 pg/mL, respectively, while respective mean values for the control group were 2.66 ng/mL and 409 pg/mL. After six months, mean CTX and PINP levels in the treatment group were 1.24 ng/mL and 159 pg/mL, respectively, while in the control group, the respective mean values were 3.01 ng/mL and 412 pg/mL. In the treatment group, CTX and PINP levels were significantly decreased by 60% (p=0.001) and 39% (p=0.005), respectively, after six months compared to the baseline levels. Significant differences were not observed in the control group for mean CTX (p=0.43) and PINP (p=0.97) after six months compared to baseline.
Conclusion: A combination of alendronate and VitD3 treatment significantly reduces the bone turnover markers compared to VitD3 and placebo treatment.

INTRODUCTION

Prevention of fractures is the primary goal in treating women with a high fracture risk. Many classes of drugs have been used in osteoporosis such as bisphosphonates, selected oestrogen receptor modulators (SERMs), teriparatide and denosumab. Bisphosphonates are considered the first-line treatment for postmenopausal osteoporosis in standard management guidelines (Siris et al., 2014). It is evident that bisphosphonates increases bone mineral density (BMD) and decreases the rate of fractures (Maraka & Kennel, 2015). Thus, bisphosphonates such as alendronate (ALN) are used widely in the treatment of postmenopausal osteoporosis due to their efficacy as well as cost-effectiveness (Kanis et al., 2013). Vitamin D3 (VitD3) and its derivatives such as calcitriol and cholecalciferol have been shown to have anti-fracture efficacy. Japanese guidelines have recommended the use of vitamin D as a monotherapy since they are cheap and devoid of major side effects (Orimo et al., 2012). A meta-analysis examining the role of vitamin D in postmenopausal osteoporosis found that VitD3 daily dose of 700 to 800 IU reduces both vertebral and non-vertebral fractures (Bischoff-Ferrari et al., 2005). Bergman et al, also reported the use of VitD3 >800 IU daily reduces the incidence of non-vertebral and hip fractures in elderly women with osteoporosis (Bergman et al., 2010). Weekly oral ALN (70 mg) and VitD3 is a widely used drug combination in treating osteoporosis.

The most promising clinical application of bone turnover markers (BTMs) is utilizing them to monitor anti-resorptive therapy. Although BMD is commonly used to monitor the response to treatment, the use of BMD values is associated with certain limitations due to inefficiency in identifying persons at high risk of fractures, as osteoporotic fractures are not always associated with low BMD. Bone turnover markers, PINP and CTX, serve as markers of bone formation and resorption, respectively, and are useful for fracture risk prediction and monitoring osteoporosis treatment. Further, bone turnover markers are valuable for monitoring treatment response and assessing adherence (Harvey et al., 2025). Significant changes in BMD values are observed only after one to two years following the treatment strategy which is a fairly long period (Costa et al., 2013). Inconvenience, cost, and limited availability of Dual X-Ray Absorptiometry (DXA) are additional disadvantages associated with BMD assessment. Recent studies demonstrated that BTMs play an important role in fracture prediction and in monitoring and evaluating drug intervention during treatment according to the findings of clinical trials (Wheater et al., 2013). Among BTMs, PINP and CTX have been recommended internationally as the standard bone formation and bone resorption markers, respectively, for monitoring of treatment in osteoporosis (Li et al., 2014). The effect of ALN and VitD3 on both CTX and PINP in older women with high fracture risk has not been adequately studied. Therefore, this study aimed to evaluate the degree of response of CTX and PINP with alendronate and VitD3 treatment after six months, among a group of older women with high fracture risk.

MATERIALS & METHODS

Study setting, study population and sample size calculation

The study sample was recruited from community-dwelling postmenopausal women residing in the Bope-Poddala Medical Officer of Health (MOH) area, Galle district, Southern Province, Sri Lanka. Sample size (n) was calculated using the standard formula recommended for comparison of two independent means: $n = (u + v)^2 \ (\sigma_1^2 + \sigma_2^2)/ (\mu_1 - \mu_2)^2$, where σ represents the population standard deviation, $\mu_1 - \mu_2$ denotes the expected difference in mean values between the treatment and control groups, u corresponds to the standard normal deviate for a two-sided significance level of 5%, and v corresponds to the standard normal deviate for 80% statistical power which was appropriate for clinical trials. The data published by Madar et al., Olmos et al., and Yoshimura et al., were considered for

the sample size calculation as there were no local publications on BTMs (Madar et al., 2015; Olmos et al., 2012; Yoshimura et al., 2011). Based on the calculation, 30 individuals were considered for treatment and control groups separately.

Study design and sampling technique

This study was a double-blind, randomized, controlled trial conducted from 2017 to 2020. Postmenopausal women were randomly recruited and the women with a high fracture risk were considered for the trial. Fracture risk was assessed by the FRAX (Fracture Risk Assessment Tool;

https://www.sheffield.ac.uk/FRAX/tool.aspx?country=45) following the DXA scans. Women with major fracture risk >9% and/or hip fracture risk >3% were considered to have a high fracture risk (Lekamwasam, 2013). Women with endocrine disorders, chronic liver disease, chronic kidney disease stage 4 or 5 (eGFR <30 mL min-1/1.73 m2), metabolic or inherited bone diseases, malignancies, on treatment which could alter the bone metabolism and who had a fracture during the last 1 year, were excluded from the study. A total of 171 women were screened for the eligibility and 60 of them were eligible for the study.

Randomization, masking, and group assignment

The patients were randomly assigned into the treatment group (n=30) and control group (n=30) using a computer-generated random number table. Patient and all the investigators were blinded to the randomization, group assignment and for the type of treatment.

Treatment administration

Treatment group received 70 mg/week dose of oral ALN with 1000 IU/day dose of oral VitD3 as recommended by the European guidance for the diagnosis and management of osteoporosis in postmenopausal women in 2012 (Kanis et al., 2013). Control group received a placebo (PLB) with VitD3 of 1000 IU per day. Patients were informed and counselled regarding the adverse reactions related to ALN prior to the intervention. They were advised to take the ALN or PLB 60 minutes before breakfast (fasting) with a glass of water. Further, they were advised to stay upright at least 30 minutes after taking the ALN or PLB to minimize the gastrointestinal (GI) tract-related adverse effects (AEs).

Patient care and follow–up (six months)

Patients were followed up for a period of six months. A caregiver at home was assigned to supervise the treatment to ensure the compliance and a diary was provided to record the usage of drugs. The first visit was scheduled after two weeks of the commencement of treatment to enquire about AEs. Then three more visits were scheduled. The remaining pills were counted at the end of each visit to assess the treatment adherence and patients were considered adherent to the treatment, if they had consumed ≥80% of the previous provision of the treatments (Brown et al., 2009). After the follow-up period, patients in the treatment group were advised to continue the treatment and they were referred to the physician for further treatment. Patients in the control group were also referred to the physician after the follow-up period to start the proper treatment.

Assays for bone turnover markers

Fasting blood samples were collected between 8 AM to 9 AM at baseline and after six months. Serum concentrations of PINP (Elabscience®, USA_Catalog No: E-EL-H0185) and CTX (Elabscience®, USA_Catalog No:E-EL-H0835) were estimated at baseline and after follow-up in both groups using ELISA. The manufacturer's quality control (QC) serum (high and low) was used during the assays to maintain the accuracy of the test results. Sensitivity of the CTX and PINP test kits was 0.1 ng/mL and 9.38 pg/mL respectively. Respective detection ranges were 0.16–10 ng/mL and 15.63–1000 pg/mL. Percentage reduction of serum concentration of BTMs was used as an indicator of response to treatment.

Estimation of serum creatinine and GFR

Serum creatinine was measured using a test kit based on spectrophotometry (Biorex Diagnostics, UK) and GFR was estimated based on the MDRD equation (Mula-Abed et al., 2012).

Measurement of BMD and anthropometric parameters

BMD (g/cm^2) of the whole body (TBBMD), lumbar spine: L1-L4 (LSBMD) and left proximal femur including the total hip (THBMD), femoral neck (FNBMD), total body fat mass (TBFM) and total body lean mass (TBLM) were measured using DXA (Dual X-ray absorptiometry) scanner (Hologic Discovery, Bedford, MA, USA) adhering to the manufacturer's protocols. Trabecular bone score (TBS) was estimated using TBS iNsight® software by the same DXA machine. The DXA scanner was calibrated with quality control daily, before the measurements. A trained technical officer performed all DXA scans and analysed all scans to avoid inter-personal variability. Weight and height were measured, and body mass index (BMI) was calculated.

Ethical approval and clinical trial registration

This study was conducted in accordance with the ethical standards of the Helsinki Declaration 1975. Ethical approval for the study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Ruhuna. The clinical trial was approved by the Sri Lanka Clinical Trial Registry (SLCTR/ 2018/ 038). Written informed consent was received from patients prior to inclusion for the study.

Data analysis

The data on serum concentration of CTX and PINP were not normally distributed, and they were log-transformed before statistical analysis. Therefore, CTX and PINP levels were presented as geometric means (GM) with 95% confidence interval (95% CI). Independent sample t-test was used to compare the means between treatment and control groups. BTM levels before and after treatment were compared by paired t-test. Significant level was defined as p values <0.05.

RESULTS

Comparison of descriptive data of the study sample is presented in Table 1. The baseline characteristics examined were not significantly different between the treatment and control groups.

Significant reductions of mean CTX and PINP from the baseline values were observed in the treatment group after six months of treatment with ALN and VitD3. No significant mean differences were observed in CTX or PINP before and after treatment in the control group (Table 2). Between-group differences (treatment versus control groups) of CTX ($p=0.36$) and PINP ($p=0.06$) were not significant.

AEs were seen in 15 (50%) members of the treatment group (unpublished data). Of them, the majority (87%) had musculoskeletal AEs followed by gastro-intestinal (27%) AEs and nervous system (20%) AEs. A total of 11 (37%) had two or more symptoms of the above. All the symptoms observed in the treatment group were present within the first 3 days of starting the first dose of oral alendronate. None of the patients discontinued the treatment due to AEs and AEs were well tolerated. One dropout from each group was reported due to other reasons. No cases of the osteonecrosis of the jaw, deaths or fractures were reported during the period of intervention. More than 95% prescribed drugs were used by the patients.

Table 1. Comparison of baseline characteristics between the treatment and control groups

Variable	Treatment group (n=30)	Control group (n=30)	*P* value
	Mean (SD)	Mean (SD)	
Age (years)	66 ± 6	65 ± 7	0.51
Menopause age (years)	50 (47-51)	50 (45-52)	0.97
Menopause years	16 (13-21)	15 (10-19)	0.35
HT (cm)	148.1 ± 4.9	146.3 ± 5.3	0.17
WT (kg)	50.0 ± 7.4	51.1 ± 7.9	0.55
BMD and body composition			
THBMD (g/cm^2)	0.739 ± 0.085	0.748 ± 0.080	0.67
FNBMD (g/cm^2)	0.581 ± 0.074	0.581 ± 0.072	0.99
LSBMD (g/cm^2)	0.628 ± 0.097	0.643 ± 0.073	0.50
TBBMD (g/cm^2)	0.838 ± 0.066	0.862 ± 0.065	0.17
TBBMC (g)	1217.6 ± 166.7	1231.2 ± 159.6	0.75
TBFM (g)	18588.2 ± 4949.8	20093.8 ± 5165.2	0.25
TBLM (g)	28796.4 ±3603.0	28801.0 ± 3378.7	0.99
Fracture risk			
MFR (%)	8.4 (6.1-9.9)	7.5 (5.3-9.4)	0.39
HFR (%)	2.6 (1.3-3.8)	2.6 (2.6-3.6)	0.78
Biochemical parameters			
CTX (ng/mL) †	3.09 (1.8-5.15)	2.79 (1.58-4.92)	0.78
PINP (pg/mL) †	273 (141-535)	424 (313-567)	0.22
eGFR (mL $min^{-1}/1.73\ m^2$)	76 (66-85)	78 (69-88)	0.74

HT= Height, WT= Weight, BMI= Body mass index, THBMD= Total hip bone mineral density, FNBMD= Femoral neck bone mineral density, LSBMD= Lumbar spine bone mineral density, TBBMD= Total body bone mineral density, TBBMC= Total body bone mineral content, TBFM= Total body fat mass, TBLM= Total body lean mass, MFR= Major fracture risk, HFR= Hip fracture risk, CTX= C-terminal cross-linking telopeptides of type I collagen, PINP= Procollagen type I N-propeptide

† Geometric mean (95% Confidence Interval)

Table 2. Percentage reduction of BTMs during the six-month intervention

	Treatment group n=29				Control group n=29			
	Baseline	**6 months**	**Mean difference (% difference)**	***p***	**Baseline**	**6 months**	**Mean difference (% difference)**	***p***
CTX (ng/mL)†	3.12 (1.84-5.3)	1.24 (0.60-2.56)	-1.88 (-60%)	0.001	2.66 (1.49-4.75)	3.01 (1.82-4.96)	0.34 (13%)	0.43
PINP (pg/mL)†	262 (133-518)	159 (076-336)	-103 (-39%)	0.005	409 (303-554)	412 (302-560)	003 (0.01%)	0.97

CTX= Cross linked C-telopeptide of type I collagen, PINP= Procollagen type I N-propeptide

†Geometric mean (95% Confidence Interval)

DISCUSSION

This study investigated the effects of ALN and VitD3 combination and ViD3 alone on BTMs among Sri Lankan postmenopausal women with osteoporosis and high fracture risk. ALN together with VitD3 is a standard and well-established treatment for postmenopausal osteoporosis. Since the use of BMD in treatment monitoring is associated with several disadvantages, it is important to explore alternative methods such as BTMs. According to the findings of this study, a combination of ALN and VitD3 significantly reduced the mean levels of bone turnover markers, CTX and PINP after six months compared to the baseline. VitD3 alone showed no significant effects on mean CTX and PINP levels. Despite the minor AEs, ALN together with VitD3 was continued by this group of women and non-adherence was not reported.

The findings of the present study are consistent with the existing evidence. ALN decreases bone resorption by inhibiting osteoclast action without affecting bone mineralization (Maraka & Kennel, 2015). Current guidelines recommend using Vitamin D and/or calcium along with ALN in postmenopausal osteoporosis (Kanis et al., 2013). However, studies conducted in Asia on the effect of ALN and VitD3 on BTMs in postmenopausal women with osteoporosis and high fracture risk are rare. Olmos et al reported that ALN treatment withVitD3 decreased the CTX by 61% and PINP by 50% over 3 months of treatment in Spanish postmenopausal women with osteoporosis (Olmos et al., 2012). Sakai et al, showed a significant reduction in BTMs after ALN and VitD3 therapy in Japanese men and women with osteoporosis, where CTX and PINP decreased by 63% and 71% respectively after six months (Sakai et al., 2015). It is evident that VitD3 supplementation improves BMD and reduces the fracture risk in postmenopausal osteoporosis (Lips et al., 2010). Yet, it is unclear whether the effect of VitD3 supplementation on BTMs. In the present study there was no significant change in CTX and PINP with VitD3 and PLB supplementation. Therefore, VitD3 supplementation does not appear to have a major impact on changes in CTX and PINP. Grimnes et al, reported that VitD3 supplementation was not effective in reducing CTX and PINP in Norwegian postmenopausal women with low bone mass (Grimnes et al., 2012). Similarly, Madar et al found that there was no significant change in CTX and PINP in healthy adult men and women of African and Asian origins after VitD supplementation (Madar et al., 2015).

Bisphosphonates such as ALN causes GI and musculoskeletal AEs, since it activates the acute phase reaction mediated via acute phase proteins, namely TNF and IL-6 (Hewitt et al., 2005). In the present study, half of the women who received ALN had transient AEs (unpublished data). This value is lower when compared with the percentage reported by Brown et al, and Sakai et al, where more than 80% of the participants had ALN-related AEs (Brown et al., 2009; Sakai et al., 2015). In the present study most frequently reported AEs were musculoskeletal-related symptoms. Patients did not report discontinuation of treatment due to minor AEs in the current study. However, in other studies, adherence to oral ALN is reported to be low and significant number of patients discontinue the treatment due to GI-related AEs (Kanis et al., 2012). Swedish Adherence Register Analysis (SARA) reported that nearly 50% of patients on ALN treatment discontinued the drug within the first year of treatment (Landfeldt et al., 2012). A systematic review by Fatoye et al, revealed that bisphosphonates such as ALN causes poor compliance (Fatoye et al., 2019). Nevertheless, non-adherence was not observed among participants of the current study. This is probably due to the shorter duration of the study and the frequent reinforcement of the need for continuation of the drugs.

This study has several strengths and limitations. Study participants were from a suburban community and long-term residents of the Southern region of the country. Those with diseases or on medications that could affect

bone metabolism were excluded to maintain the accuracy of results. The participants of the study had never smoked and were not users of alcohol. Women who had a fracture within one year by the time of data collection were excluded since serum BTM levels are influenced by the fracture (Ivaska et al., 2007). Central-type DXA was used in measuring BMD and TBS after daily in vitro calibrations and the measurements were done by a single technician with nearly 10 years of experience in DXA measurements. ELISA test kits with CV less than 5% were used to measure the BTMs by using a semi-automated ELISA reader. All the biochemical assays were performed adhering to the manufacturer's protocols and QC (High and Low) were used to maintain the accuracy of each assay. Fasting blood samples were obtained in the morning to minimise the effects of diet and diurnal variation which are known to be associated with BTM levels in serum (Redmond et al., 2016). Women who had eGFR less than <30 mL min-1/1.73 m2 were excluded as advanced chronic kidney disease significantly alters the serum CTX and PINP levels (Delanaye et al., 2014). The patients were given standard instructions to follow when taking the ALN tablet which facilitates the maximum absorption of the drug and they were informed to stay upright at least 30 minutes after taking the tablet to reduce the risk of acid reflux, esophagitis, gastritis and ulcers. Patient, principal investigator and supervisors were blinded to the treatment to minimise the bias. Adequate supportive care was given to patients during the intervention period. For the acute phase reactions and AEs, patients were treated with analgesics. A six-month follow-up period was selected as serum levels of P1NP and CTX are known to change significantly to anti-resorptive therapy within 3-6 months, according to the previous studies and recommendations (Park et al., 2019). TBMDs were not measured at the end of the trial because the duration (6 months) of the trial was not sufficient for a significant change in BMD over and above the least significant change of the DXA machine (Burnett-Bowie et al., 2009). Although, the shorter follow-up period is adequate for assessing early changes in P1NP and CTX, it does not allow evaluation of longer-term outcomes such as fracture risk. In addition, relatively small sample size may limit the generalizability of the findings.

CONCLUSION

Serum CTX and PINP levels are significantly reduced with the treatment of ALN combined with VitD3, while VitD3 along with PLB showed no significant effect on serum BTMs levels in this group of women. CTX and PINP can be used to monitor early therapeutic response of this treatment combination among postmenopausal women with high fracture risk. This would allow clinicians to recognize patients with inadequate response to treatment and look for possible causes such as poor adherence and the existence of unidentified underlying secondary causes.

CONFLICT OF INTEREST

Rathnayake H, Lekamwasam S, Wickramatilake C and Lenora J declare that they have no conflicts of interest.

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