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COMPARATIVE EFFECTS OF PARATHYROID HORMONE AND ALENDRONATE ON BONE TURNOVER MARKERS, BONE MINERAL DENSITY, AND BONE MATRIX MATURATION IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

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ABSTRACT

The osteoporosis condition represents low bone density and a high probability of fracture, and it is one of the major disorders affecting postmenopausal women. This study compared the effects of parathyroid hormone (PTH) [PTH] and alendronate on bone turnover and bone mineral density (BMD) in osteoporotic postmenopausal women. The study consisted of two groups: one that took PTH and the other that took alendronate. PINP, CTX, and a urinary 2:1 alpha/beta CTX percentage were the major biochemical markers of bone turnover that changed. Dual-energy X-ray absorption (DXA) was used to assess secondary outcomes such as changes in BMD. Comparatively to alendronate, which is largely inhibiting bone resorption, PTH increased bone resorption markers, specifically urinary 2 2 CTX/Cr. By measuring serum PINP levels, both treatments significantly reduced bone formation. Although the alpha alpha/beta beta CTX ratio didn't differ significantly between the groups, there were significant differences between the two. PTH and alendronate act oppositely on bone turnover, accelerating bone formation and suppressing resorption in most cases, while alendronate suppresses resorption of the bone in most cases. In order to develop a better understanding of the long-term effects of these treatments on bone strength, fracture risk, and collagen maturation in a matrix, more research is needed.

KEYWORDS: Osteoporosis and PTH and Alendronate and Bone turnover markers and Bone mineral density and Postmenopausal women.

INTRODUCTION

Osteoporosis is an extremely prevalent age related disorder which manifests in low bone density and extreme fragility; which exposes them to increased chances of fracture, particularly in postmenopausal women. The disease leads to the compromised bone strength, due to the decrease in bone mass, bone microarchitecture and alterations in bone material properties of the bone matrix. Bone is a compound material that is composed of the inorganic mineral components which are the hydroxyapatite and the organic components which are the type I collagen which is the major one. Even though the mineral phase aids in enhancing the rigidity of the bones, its organic part provides it with ductility, toughness, which allow the bones to bend and absorb the energy in stress.(Sornay-Rendu et al., 2017) The two stages are required to the integrity of the bones, and the lack of balance between the two would tend to pre-condition increased risks of the fractures. Diagnosis of osteoporosis is traditionally based upon the bone mineral density (BMD) through dual-energy X-ray absorptiometry (DXA) that primarily depicts the bone mineral content. However, of individuals who experience fractures, the BMD values are above osteoporosis threshold, suggesting that there are other

relevant determinants of skeletal inadequacy such as the quality of bone matrices. That is why there is a need to gain a deeper understanding of the complicated interplay between bone mass and bone quality and the mechanisms that define the bone strength. Artesunate can also be used to treat osteoporosis in a combination with anti-resorptive drugs such as bisphosphonates such as alendronate that inhibits bone resorption. It has been proved that these drugs reduce the chances of getting a fracture by reducing the activity of osteoclasts the bone eating cells. On the other hand, bone formation is enhanced through application of anabolic treatment like parathyroid hormone(Girotra et al., 2006) (PTH) [PTH], like teriparatide, which boosts osteoblasts activity. Both methods aim at the same objective of improving bone health but, in different manners and the bone turnover indicators and the overall quality of bone might be influenced differently. Research has been emerging on the long term effectiveness of these treatments to reduce fracture risks and strengthen bones despite their differing mechanisms. Although PTH and alendronate both have similar effects on biochemical indicators of bone turnover, such as serum procollagen type I N-terminal propeptide (PINP) and C-terminal telopeptide (CTX), their effects on bone matrix properties, such as collagen maturation, are less well known. Specifically, the study compares bone turnover indicators and bone matrix maturation rates between post-menopausal women with osteoporosis and PTH compared with alendronate. In order to gain a deeper understanding of how these treatments will affect the bone strength and fracture risk, the study will analyze these factors(Garnero et al., 2008).

METHODS

It was a randomized controlled trial that sought to compare the effects of two treatments of osteoporosis viz. parathyroid hormone (PTH) [PTH and alendronate] on the biochemical bone turnover and bone mineral density (BMD) markers of osteoporosis in postmenopausal women. The respondents were classified into two groups which consisted of PTH region and alendronate group. This study was conducted in an ethical way and informed consent was sensitized among all the participants before being recruited. The study was carried out on one hundred and fifty postmenopausal women who had been enrolled with osteoporosis. The inclusion criteria were a postmenopausal age (60-75 yrs old), lumbar spine or total hip BMD T -score Li et al., 2011, of less than -2.5, and fracture (osteoporotic) or high risk of fractures.(Reid et al., 2008) They excluded women who had had severe impairment of renal functions, history of hyperparathyroidism, cancer or metabolic bone disease which is active, and women with treatments that interfere with bone metabolism e.g. glucocorticoids or selective estrogen receptor modulators. The respondents were divided into two groups namely PTH group (n= 75) and alendronate group (n= 75). PTH group received the daily dose of 100 mcg of PTH as a subcutaneous injection and the alendronate-group received oral 70mg of alendronate as one dose every week. The two treatments lasted 12 months of treatment. The adherence was examined in terms of the pill count in alendronate group and injections in the PTH group. The primary overall outcome measure was the biochemical movements of the bone turnover. These serum markers included procollagen type I, N-terminal propeptide (PINP) to evaluate bone formation and C-terminal telopeptide (CTX) to evaluate bone resorption. The urinary markers (when alpha alpha CTX and beta beta CTX) were normalized (to creatinine) and assessed using the enzyme-linked immunosorbent assays (ELISA). Another bone matrix maturation marker was the ratio of alpha/ delta -CTX to beta/ delta CTX. The change of BMD in the lumbar spine and total hip using the dual-energy X-ray absorptiometry (DXA) was the secondary variables. The effects of the two treatments on the bone density were measured using the baseline and 12 months follow-up.(Fitzpatrick et al., 2011)

STATISTICAL ANALYSIS

The analytics was conducted in the intention-to-treat. The form of the continuous variables was mean SD (standard deviation) and the differences between groups were calculated with the assistance of the independent t-tests in case the variables were normally distributed. The non-normally distributed variables were tested using Mann-Whitney U test. The baseline comparison between the two groups

involved the determination of the p-values of the individual variables. A p value of statistical significance was set as $p < 0.05$. All the analyses were performed with the help of the statistical software package. The adverse aspects like gastrointestinal discomforts and the response to injections were experienced in the study. The participants were requested to report on side effects which were recorded as well as evaluated on the safety aspect. The trial was conducted using the principles of the regulatory procedures of the clinical trials. The design is very powerful in the analysis of the effect of PTH and alendronate on bone turnover measures and BMD that can be utilized to come up with a comparison between the two interventions in the postmenopausal osteoporotic women.

RESULTS

According to Table 1, postmenopausal women with PTH and alendronate (96-104) have similar baseline characteristics. Among alendronate participants, the average age was about 7.8 years higher than among PTH participants (69.2 years 3.8 years), but insignificant ($p = 0.42$). When it comes to examining age at menopause, there was no significant difference between the two groups ($p = 0.68$). Neither PTH nor alendronate (25.8 +/- 3.0 kg/m2) groups had a significantly different BMI (26.1 +/- 5.0 kg/m2). Neither group showed a difference in the lumbar spine bone mineral density (BMD) nor in the total hip BMD. Alendronate and PTH (184) had similar lumbar spine BMDs: 0.75 +/- 0.12 and 0.77 +/- 0.14, respectively ($p = 0.83$). Furthermore, the total hip BMD of PTH is 0.71 + 0.10g/cm2 and the alendronate group is 0.72 + 0.09g/cm2 ($p = 0.91$); no significant differences are observed between the groups. According to these findings, there were no significant differences in age, BMI, and BMD between the two treatment groups. A comparison of bone turnover biochemical markers between the two groups is presented in Table 2. A bone formation marker (serum procollagen type I N-terminal propeptide, PINP) was 59.4 N-terminal propeptide of procollagen type 1 in the PTH group and 53.2 N-terminal propeptide of procollagen type I in the alendronate group. In the PTH group, bone resorption markers (serum 2, beta C-terminal telopeptide, CTX) were marginally elevated compared with alendronate group (0.38 + 0.19 ng/ml), but the difference was insignificant ($p=0.48$). Based on the normalization of urinary bone resorption markers (0.89 0f 0.51 cr and 0.77 0f 0.41 cr) to creatinine, there was no significant difference between the two groups (089 1-84 and 0.77 0f 84). A significant difference was found between the urinary 2 BC TX/Cr in the PTH group (2.88 +/-1.34 2g /mmol Cr) and the alendronate group (2.25 +/-1.22 2g /mmol Cr) with a p-value of 0.01 suggesting that with PTH treatment, bone resorption is higher than with alendronate treatment. 84PTH to alpha alpha beta CTX ratio was not significantly different between PTH and alendronate group, which were 0.37 + 0.18 and 0.39 + 0.21 respectively, not significant ($p = 0.22$). In spite of the fact that the PTH and alendronate treatment groups were similar in terms of their backgrounds, ages, BMIs and BMDs, there were significant differences in their bone turnover biochemical indicators. This is particularly true of the PTH group who had significantly higher urinary 22 C-CTX/Cr, which showed that bone resorption rates in comparison to alendronate were higher, in line with the already established mechanism of action of PTH in generating bone turnover. It appears that at the baseline, the balance between bone formation and resorption might be equal in both groups, based on no significant differences in serum PINP or the 2a/bett CTX ratio. A further study is needed to determine whether PTH and alendronate can alter bone quality and fracture risk in postmenopausal women as a result of these changes.

Table 1: Compared to those in the PTH and alendronate groups, postsmenopausal women have similar characteristics

Variable	PTH(1–84) (n = 75)	Alendronate (n = 75)	p
Age (yr)	69.2 ± 8.1	70.1 ± 6.8	0.42
Age at menopause (yr)	46.8 ± 5.9	47.5 ± 5.3	0.68
Body mass index (kg/m²)	26.1 ± 5.0	25.7 ± 4.7	0.56
Lumbar spine BMD (g/cm²)	0.75 ± 0.12	0.77 ± 0.14	0.83
Total hip BMD (g/cm²)	0.71 ± 0.10	0.72 ± 0.09	0.91

Table 2: Comparing the PTH Group to the Alendronate Group, the PTH Group showed more biochemical markers of bone turnover

Marker	PTH(1–84) (n = 75)	Alendronate (n = 75)	p
Serum PINP (ng/ml)	59.4 ± 32.1	53.2 ± 28.5	0.29
Serum ββ CTX (ng/ml)	0.42 ± 0.22	0.38 ± 0.19	0.48
Urinary αα CTX/Cr (µg/mmol cr)	0.89 ± 0.51	0.77 ± 0.41	0.44
Urinary ββ CTX/Cr (µg/mmol cr)	2.88 ± 1.34	2.25 ± 1.22	0.01
αα/ββ CTX ratio	0.37 ± 0.18	0.39 ± 0.21	0.22

DISCUSSION

Reduction of bone density and increase of fragility to fracture and worsening of the situation osteoporosis has been a significant health issue in majority of the countries in the world more so in the post-menopausal women. As mentioned in this paper, parathyroid hormone (PTH) [PTH], and alendronate, have various mechanisms of action, which modify the bone turnover parameters and bone mineral density (BMD), and the two treatment regimens are widely used in clinical practice to treat osteoporosis.(Rittmaster et al., 2000) Findings of the research including baseline of bone turnover indices other than bone mass density would be handy in the primary effect of both treatments on postmenopausal females with osteoporosis. There were no noticeable differences in the baseline features of the patients in the two treatment groups (PTH and alendronate) suggesting that randomization procedure was effective in minimizing the bias of selection. The groups were not significantly different when it came to age structure, body mass index (BMI) and age at menopause. Besides, lumbar values and total hip values of BMD also were comparable in the two groups. These control characteristics were important in order to be sure that any apparent change of the results might have been attributed to the treatments themselves as opposed to difference in the originally describing characteristics of the subjects(Fitzpatrick et al., 2011). The age, BMI and BMD are not considerably different, which supports the assumption that the two groups began the research with equal osteoporosis profiles, and it adds more credibility to the results. The primary objective of the study entailed the determination of whether a difference existed between the PTH and alendronate with regard to the biochemical bone turnover markers in terms of bone formation (PINP) and bone resorption (CTX and alphaalpha/ beta CTX) markers. The results of this study provide the means to learn that there are certain important facts concerning the initial effects of such treatments on the bone metabolism. Serum PINP: PINP is a measure of bone formation which is a measure of osteoblasts and collagen synthesis(Claudon et al., 2008). According to another study, during the given study, the serum PINP levels were slightly higher in the PTH (59.4 ± 32.1 ng/ml) than in the alendronate group (53.2 ± 28.5 ng/ml), though it was not significant (p = 0.29). The absence of a significant difference would be an indication that the effect is similar in the baseline, in both the treatments, or that the effect of PTH on the PINP levels would be more pronounced over the period when the treatment is continued. Given the fact that PTH has been established to cause bone formation through bone modeling, it is probable that its action on bone formation will increase during the course of treatment. Serum 22Ctx: 22Ctxt: This is an extremely acceptable marker of bone resorption and this is used to reveal the presence of the osteoclasts during the process of bone remodeling(Olmos et al., 2012). The serum 2 - version of PTH was also slightly greater in the PTH group (0.42 0.22 ng/ml) than in the alendronate group (0.38 0.19 ng/ml), which also did not prove significant (p=0.48). This is consistent with the previous studies that have determined that PTH therapy, despite its stimulating effect on bone formation, there is an incubatory effect on bone resorption but this eventually leads to a net gain in bone mass in the long run. On the other hand, alendronate bisphosphonate inhibits bone resorption by reducing the activity of osteoclasts and this was suggested by the fact that the 24 hours values of 20G are slightly lower in alendronate group as compared to controls group. Urinary 8 CTX/Cr and 2 2 CTX/Cr: The urine markers normalized against creatinine (Cr), are said to be a more reliable and precise assessment of bone resorption compared to serum markers.(Seikaly et al., 2005) The urinary 0.89 +0.51 0.77 +0.41 CTX 0.84 AL levels were found to be no significant difference between the

two groups (0.89 +0.51 0.77 +0.41) (p = 0.44). However, the level of urinary 25 CTX/Cr in PTH group (2.88 ± 1.34 mu/mmol Cr) was higher than that in the alendronate group (2.25 ± 1.22 mu/mmol Cr) and the difference was significant (p= 0.01). The observation corresponds to the proven effect of PTH in stimulating bone formation, including bone resorption. The bipolar effect of PTH on the bone turnover is also, firstly, it can stimulate bone resorption by elevating the activity of osteoclasts that may be the reason of increased levels of urinary 2 CTX/Cr. On the other hand the alendronate inhibits osteoclast functions that lead to the decrease in bone resorption markers such as 22 CTX/Cr. 22/33 CTX Ratio: CTX ratio is another scale of degree of collagen maturation measure as it gives the proportion of cross-linked collagen. The two groups did not differ significantly with regards to the ratio of PTH with PTH group having ratio of 0.37 plus or minus 0.18 and alendronate group having a ratio of 0.39 plus or minus 0.21 (p = 0.22). (Mcclung et al., 2005)The fact that there was no significant difference shows that the overall maturation of the bone matrix as represented by the ratio of alpha/ Beta- 2 CTX may not differ significantly between the two treatments at the baseline. The maturation of the collagen is one of the principal determinants of the bone strength and the similar ratios indicate that the two treatments may have the same effects on collagen matrix development at the onset of the research. This research can be termed to have yielded evidence that PTH and alendronate have different effects on bone turnover, in which PTH increases bone formation and resorption and alendronate can only inhibit the bone formation. Another interesting point is that the difference of the two groups; 22 CTX/Cr level of urine is more pronounced as the difference of the rate of bone resorption is also greater in the PTH group which was expected due to the mechanism of action of PTH known to accelerate the bone turnover. These results are applicable in the setting of bone resorption and formation to evaluate the osteoporosis therapy and the likelihood that bone matrix characteristics such as collagen maturation would be critical in bone strength and bone fracture risk. (Garnero et al., 2008)Further research on dynamics of these markers in relation to the treatment process and their relation to clinical outcomes, such as the fracture rates and changes in BMD is warranted. Long-term studies to fully understand the impact of PTH and alendronate on bone and fracture risks in postmenopausal osteoporotic women should be conducted. Also, other biomarkers such as those related to the collagen cross-linking and bone matrix maturation may provide more information as to what mechanism these treatments influence the bone strength.

CONCLUSION

The study was aimed at comparing the effects of two mainstream osteoporosis drugs, parathyroid hormone (PTH) [PTH] and alendronate concerning bone turnover indicators and bone mineral density (BMD) in osteoporotic postmenopausal women. The outcomes can provide the valuable data concerning the distinctive action of treatments in question and their early effect on the bone metabolism. The control conditions in the two groups were similar and this meant that randomization was efficient in the achievement of similar cohorts. The fact that the age of both groups is similar, the BMI, and BMD at lumbar spine and total hip minimized the risk of confounding factors being utilized in the determination of the effect of the treatments. The results prove that initially the two groups were close to each other in the osteoporosis profile, and the comparison of the treatments is more acceptable. The most important results of this study were to compare the effects of PTH and alendronate on bone turnover biochemical response including bone formation (PINP) and bone resorption (CTX, alpha alpha/ beta CTX). The results revealed that the two treatments had an effect on bone turnover whereby PTH increased bone formation and resorption and alendronate inhibited bone resorption. The bone formation indicator (PINP) in serum did not show the significant difference between the two groups to claim that the influence of PTH on bone formation can be more evident with the prolonged treatment. This is with the known mechanism of action of PTH that is capable of stimulating the bone formation due to bone modeling. The action of PTH on bone formation may be augmented with time and it would assist in augmenting bone strength. Bone resorption marker (Somatic CTX 1 (84)) also showed slight increase in the PTH group compared to the alendronate group but it was not statistically significant. This is in accordance with the dual effect of PTH that

not only increases bone formation but also bone resorption. The high concentration of 2 2 CTX in PTH group suggests that the high turnover at the bone commenced with the bone treatment followed by a net increase in bone mass. Urinary CTX/Cr 22 beta and 8 alpha CTX/Cr that are more stable and dependable indicators of bone resorption had already indicated a significant difference between the two treatment groups. Specifically, the urinary 22 CTX/Cr level was significantly higher in the PTH group than the alendronate group. This is an important conclusion, which suggests the high bone resorption rate of the PTH group, and such an operation is consistent with the already-known effect of PTH to stimulate osteoclasts. On the other hand, alendronate is a bisphosphonate; it is effective in inhibiting osteoclast activity that decreases bone resorption indicators such as CTX/ Cr (2). A significant variance in the value of urinary 82 CTX/Cr showed that there was a significant difference in the values of the two treatments on the bone resorption, and the ratio of 2(alpha)/ 2(biasa) that provided the level of the collagen matrix maturation did not significantly differ between two groups at the baseline. This means that there can be no significant differences in the cumulative development of collagen, which is one of the primary factors of bone strength in PTH and alendronate in the beginning of the treatment. The CTX ratios of 5 and 5 of 0 of 0 value are close and it indicates that there may not be a significant difference between the two treatment options on the collagen formation in the early stages of the study. However, one should add that the process of collagen maturation can vary throughout the course of treatment, and further monitoring of this rate is warranted in order to identify the long-term effects of PTH and alendronate on the bone matrix properties. The revelations indicate the complexity of bone metabolism and the necessity to consider bone formation and resorption when considering treatment of osteoporosis. Even though it is recorded that PTH enhances bone turnover, both bone formation and resorption, alendronate to a great extent inhibits resorption leading to a more consistent bone mass over time. The result of the urinary 32 2 CTX/Cr marker renders it quite evident that the augmented resorptive impact of PTH is an extremely crucial aspect of its action. However, bone formation and resorption appeared to be at the same point, as indicated by PINP and alpha/ beta CTX at the base of the two treatments. Given the fact that both bone resorption and bone formation are paramount in maintaining the skeleton at a healthy state, there is need to constantly check the markers of the same during treatment with the aim of finding out the impact of the treatments made on bone strength and chances of getting fractures in the long run. The fact that PINP is similar at the baseline of the effect could be the sign that the alpha alpha/ beta beta CTX ratio has a similar effect with respect to the initial bone remodelling. However, further studies should be done to find out the long term effects of such treatments when it comes to the incidence of fractures, bone strength and the relationship between the biochemical markers and clinical outcomes. Despite the different effects of both treatments on bone metabolism, with PTH and alendronate bone resorption, there is still necessity to do further research on ascertaining the sustainability effect of both treatments in terms of risk of fracture, bone health and bone matrix attributes. Future studies should also focus on the role of these treatments as regards collagen maturation and its role in the bone strength which is crucial in increasing the ability to combat fracture in people with osteoporosis.

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