Changes in Bone Mineral Density Following Conventional Oral Phosphonate Treatment of Hypophosphatemic Osteomalacia: a case-control study

Yue Guo

Second Xiangya Hospital

Xian-Ping Wu

Second Xiangya Hospital

Ying-Hui Zhou

Second Xiangya Hospital

Chen-Yi Tang

Second Xiangya Hospital

Min Wang

Central South University Xiangya School of Medicine

Zhao-Hui Mo

Central South University Third Xiangya Hospital

Jun Tang

Second Xiangya Hospital

John A Shepherd

University of California San Francisco

Bennett K Ng

University of California San Francisco

Bo Fan

University of California San Francisco

Yun-Zhi Feng

Second Xiangya Hospital

Hou-De Zhou (✉ houdeshou@csu.edu.cn)

Hunan provincial key laboratory of metabolic disease, National clinical research center for metabolic disease <https://orcid.org/0000-0001-9131-4141>

Research article

Keywords: Bone mineral density; Conventional treatment; Hypophosphatemic osteomalacia

Posted Date: July 31st, 2019

DOI: <https://doi.org/10.21203/rs.2.12284/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: There are limited clinical studies aimed at solving the problem of the efficiency of conventional treatment with oral phosphate and calcitriol in adults with hypophosphatemic osteomalacia (HO). In addition, there still had no good non-hazardous markers to evaluate the severity of bone loss of osteomalacia before and after treatment. Therefore, the purpose of this study was to assess the efficacy of conventional treatment with a self-blended phosphate supplementation and calcitriol on patients with HO and whether bone mineral density (BMD) can helpful for monitoring the efficacy. **Methods:** 21 HO patients and 105 healthy controls were enrolled. HO patients with calcium and calcitriol were divided into three phosphate treatment groups: Patients in group A (n=3) received continuous phosphate supplementation, patients in group B (n=5) received intermittent phosphate supplementation and patients in group C (n=3) received no phosphate supplementation. 11 of 21 HO patients were recalled for detection of BMD of the lumbar spine (L1–L4), femoral neck, and total left hip three years after the treatment. **Results:** The average initial serum phosphorus level of the patient group was approximately 50% lower than that of the control group. Lower BMD was significantly observed in the HO group than the control group at the lumbar spine and total hip. Continuous treatment with the phosphate supplement could increase BMD in the lumbar spine and total hip by 33.4–52.3% and the femoral neck increased by 43.2–79.3% compared with baseline, and the effect appears to be continued once treatment is discontinued. **Conclusions:** These findings suggest that conventional therapy can improve bone mineral defects in patients with HO, especially in the femoral neck. Detection of BMD in HO patients is a good tool to assess the extent of bone defects and the therapeutic effect.

Background

Phosphorus, which is ranked as the second most enriched mineral in human body, plays a very important role in a variety of biological processes. Chronic hypophosphatemia usually occurs due to increased renal phosphate loss (such as specific hereditary genetic mutations—X-linked hypophosphatemia, Fanconi syndrome and renal tubular acidosis), decreased intestinal phosphate absorption (such as malnourishment and short bowel syndrome) and extracellular phosphorus be migrated to cells or bone (such as vitamin D deficiency) [1]. This condition have decreased serum phosphorus (P) and calcium (Ca) concentrations [2, 3], and usually impaired mineralization of the bone matrix and results in abnormal growth and rickets in children, and osteomalacia in adults. It is recommended to use traditional medical treatment with oral phosphate and calcitriol for children. However, it is uncertain whether conventional medical treatment is continuously effective for adults and the efficacy has not yet been proved [4]. There are limited clinical studies showed that conventional therapy is effective for adults. Sullivan et al. conducted an open-label research which showed that the traditional medical treatment can reduce the severity of osteomalacia in symptomatic adults from the quantified data of pre- and posttreatment bone biopsies [5].

The main purposes of therapy for hypophosphatemic osteomalacia (HO) in adults are to relieve pain and the severity of osteomalacia and/or to promote fracture healing or surgical recovery [6]. Bone biopsies

and serum levels of alkaline phosphatase, P, Ca are often used to assess the therapeutic response of osteomalacia. However, it is too invasive to use bone biopsies routinely and it is also not enough to use biochemical parameters to evaluate the endpoints of treatment due to the time course and eventual extent of recovery in bone mineral defects are various at different skeletal sites[7]. There still has no good non-hazardous markers to evaluate the extent of the osteomalacia before and after therapy. Although bone mineral density (BMD) detected by dual-energy X-ray absorptiometry (DXA) is not necessary for the diagnosis of osteomalacia, many studies showed that osteomalacia may lead to decreased BMD [7-13], which in turn leads to increased risk of fracture. In addition, it has been illustrated that the BMD of the spine and femur is significantly correlated with quantitative histological measurement in patients with a variety of metabolic bone diseases including osteomalacia [14]. Thus, the measurement of BMD in patients with HO is important and maybe also beneficial for evaluation of the extent of bone defects and the following management.

In the present study, we, therefore, performed a self-blended oral phosphate supplement and calcitriol on patients with HO and measured the BMD of pre- and posttreatment to access the efficacy of conventional therapy and whether BMD can helpful for monitoring the efficacy.

Methods

Participants

126 participants were identified for this study through medical record review at three affiliated hospitals of Central South University (Xiang-Ya Hospital, the Second Xiang-Ya Hospital, the third Xiang-Ya Hospital) from January 1, 2006 to September 1, 2013. 21 patients (13 males and 8 females) diagnosed with HO were selected as the case group. 105 age, sex, height, and weight matched participants with normal blood biochemical and BMD measurements and no systemic disease were selected as the control group. The study was approved by the Ethics Committee of The Second Xiang-Ya Hospital of Central South University and informed consent was obtained from the subjects before all measurements. Our study adheres to CONSORT guidelines of clinical trials.

The diagnoses of 21 HO patients were as follows: hereditary hypophosphatemic rickets by genetic testing ($n=5$, one of the patients had a pathogenic PHEX mutation, the remaining four patients who refused genetic testing was diagnosed according to the biochemical characteristics [4]), Fanconi syndrome with the features of renal tubular acidosis and vitamin D deficiency ($n=4$), and hereditary vitamin D abnormality ($n=12$). Patients with underlying phosphorus imbalance stemming from chronic disease and/or tumors were excluded. Additionally, patients who were suffering from hyperparathyroidism were also excluded.

All measurements were collected using standard laboratory methods. During an initial clinical visit, age, sex, height, weight, current medications, clinical diagnosis, serum P levels, serum Ca levels, serum alkaline phosphatase (ALP) and parathyroid hormone (PTH) levels were measured. X-rays was used to

confirm any reported bone deformities. Blood samples (second morning void) were obtained between 08:00 and 09:00 after an overnight fast.

Bone area, mineral content and density

Bone area (BA, cm²), bone mineral content (BMC, g) and BMD of participants were measured using dual-energy X-ray absorptiometry (DXA) (Prodigy, GE Lunar, Madison, WI, USA). BMD of the projected bone area was calculated as BMC / BA (g cm⁻²). Skeletal sites included the lumbar spine (L1–L4), the femoral neck and total left hip were also examined. Depending on body thickness and the area scanned, scanning times ranged from 3 to 20 min. Total radiation dose for each participant was less than 1 µSv.

Follow-up

11 Patients with HO were recalled for clinical assessment approximately three years following their initial visits. The protocol for the formulation of the phosphorus solutions was described as follows: First of all, the patients need to weigh 253 grams of Na₂HPO₄ and 126 grams of KH₂PO₄ respectively, and then mix them together. The next step is to adjust the PH to 7.2 after adding 1000 ml drinking water to the mixture. Most importantly, we suggest the participants to administer the phosphate solution from 3-4 ml on, and take it every 5 hours. However, the does will be adjusted according to the participants' serum phosphorus level, and usually the administration is to take the phosphate solution 6 ml each time and four times a day.

Each patient received continuous calcitriol (0.25µg, qd), calcium treatment (CaCO₃ 0.3g bid) and three treatment levels of a self-blended neutral phosphate solution (0.8 M Na₂HPO₄, 0.6 M KH₂PO₄, pH = 7.2):

- Patients in group A (*n*=3) received 6 mL phosphate solution doses at a frequency dependent upon measured serum phosphorus. If serum phosphorus was below 0.7 mmol L⁻¹, phosphate solution was administered four times a day; daily dose count was reduced by one for each 0.1 mmol L⁻¹ increase in serum phosphorus.
- Patients in group B (*n*=5) received phosphate solution doses only every three to four days.
- Patients in group C (*n*=3) received no phosphate solution. Patients in this group chose not to take the phosphate solution due to difficulties in preparing the solution in low-resource environments.

BA, BMC, and BMD of each follow-up participant were measured by the same licensed doctor from department of endocrinology using the same DXA scanner as during the initial visit. Each participant's fracture history and medication history were recorded.

Statistical analysis

Data analyses were carried out using SPSS version 17.0 for Windows (IBM Corp., Armonk, NY, USA). Student's *t*-test was used to compare BA, BMC and BMD levels in the different body sites between the case and control groups. Changes between the initial-visit and follow-up serum P, Ca, and ALP

concentrations, as well as BMD in the different body sites were analyzed using paired sample t-test. All tests were two-tailed and $P < 0.05$ was considered significant.

Results

Participants

21 patients (13 males and 8 females) in case group were diagnosed with HO. The duration of illness averaged 24 ± 13 (mean $\pm$ standard deviation) years. All HO patients had some bone pain history. 16 of them had some bone deformity: vertebral deformities (62.5 %), lower limb deformities (25.0%), and rib-sternal deformities (12.5 %). 6 patients had a history of bone fracture: 3 with vertebra fractures, 2 with femur fractures, and 1 with a rib-sternal fracture.

Table 1 showed the demographic and biochemical data for all participants by gender. Ages of 21 HO patients ranged from 13 to 50 years with an average of 37 ± 10 years. No significant difference in serum P, Ca and PTH was observed between sexes, but serum ALP of females was significantly higher than that of males. Average baseline serum P level of case group ($0.59 \pm 0.18 \text{ mmol L}^{-1}$) was about 25% lower than that of control group. The case group average baseline serum ALP and PTH levels were $238.95 \pm 74.08 \text{ u L}^{-1}$ and $11.04 \pm 5.71 \text{ pmol L}^{-1}$, respectively, which were significantly higher than those of control group.

Table 1 Distribution of demographic and biochemical data of patients according to sex

Sex	n	Height (cm)	Weight (kg)	Serum P (mmol L^{-1})	Serum Ca (mmol L^{-1})	Serum ALP (u L^{-1})	PTH (pmol L^{-1})
Patients							
Males	13	161.1 ± 8.7	60.4 ± 8.6	0.59 ± 0.18	2.02 ± 0.32	235.83 ± 83.56	9.94 ± 5.82
Females	8	140.8 ± 18.2	52.7 ± 22.0	0.60 ± 0.22	2.10 ± 0.29	244.43 ± 65.31	14.68 ± 4.13
Total	21	153.0 ± 16.4	57.3 ± 15.4	0.59 ± 0.18	2.05 ± 0.30	238.95 ± 74.08^b	11.04 ± 5.71^b
Controls							
Males	65	163.8 ± 4.5	62.7 ± 6.5	1.16 ± 0.11	2.18 ± 0.09	75.99 ± 19.60	3.88 ± 1.38
Females	40	152.5 ± 5.6	52.1 ± 9.0	1.12 ± 0.13	2.22 ± 0.11	72.31 ± 26.98	3.86 ± 1.26
Total	105	159.5 ± 7.4	58.7 ± 9.1	1.14 ± 0.12	2.20 ± 0.10	74.08 ± 23.34	3.87 ± 1.30

^b $P < 0.01$

Bone area, mineral content, and density

Table 2 suggested that there were no significant differences in BA between the HO and control groups ($P > 0.05$); while the BMC measurements of L1–L4 and femur neck region in patients with HO were significantly lower than those of control group ($P < 0.05$). BMD in the L1–L4 regions was 10.4% ($P < 0.01$) lower in the HO group than in the control group. Meanwhile, the average BMD of the femur neck was 22.4% decreased in case group than that in control group. The average BMD of the total hip was 21.2 % lower in HO group than the control group. Our results indicated that BMD of the femur neck showed the greatest difference ($P < 0.05$) between the HO and control groups.

Table 2 Distribution of BA, BMC and BMD data in different sites for patient and control groups

Measurements	Patient ($n=21$)	Controls ($n=105$)	P value
L1-L4			
BA (cm ²)	57.22 ± 5.29	58.15 ± 7.46	0.200
BMC (g)	47.07 ± 15.48	52.86 ± 11.85	0.048 ^a
BMD (g cm ⁻²)	0.807 ± 0.256	0.901 ± 0.126	0.000 ^b
Femur Neck			
BA (cm ²)	5.07 ± 0.58	5.04 ± 0.46	0.459
BMC (g)	3.07 ± 1.04	3.84 ± 0.73	0.041 ^a
BMD (g cm ⁻²)	0.589 ± 0.173	0.759 ± 0.117	0.031 ^a
Total Hip			
BA (cm ²)	37.78 ± 5.55	35.79 ± 5.17	0.774
BMC (g)	25.57 ± 8.69	31.87 ± 7.59	0.796
BMD (g cm ⁻²)	0.673 ± 0.184	0.854 ± 0.129	0.014 ^a

^a $P < 0.05$; ^b $P < 0.01$

Serum biomarkers

Correlations between serum biochemical indices (P, Ca, and ALP) and BMD at various sites were presented in Table 3 (patient group, $n = 21$). Serum P level was positively correlated with baseline femur neck BMD ($r = 0.575$, $P < 0.05$), but no significant correlations were observed between serum P and BMD at the other tested sites.

Correlations between the first-visit serum Ca and ALP levels and BMD of the different sites were not significant, suggesting that first-visit serum Ca and ALP levels may not directly influence BMD.

Table 3 Correlation between serum P, Ca and ALP levels and BMD at different anatomical sites

	L1–L4		Femur Neck		Total	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Serum P	0.135	0.605	0.575	0.044 ^a	0.109	0.699
Serum Ca	–0.207	0.425	–0.392	0.120	–0.415	0.124
Serum ALP	0.478	0.137	0.665	0.175	0.469	0.203

^a $P < 0.05$

Follow-up

11 of 21 HO patients returned for follow-up. Figure 1 showed the measured BMD changes during the treatment period at the different anatomical sites. Compared with the initial pre-treatment measurement, the BMD of patients who were prescribed phosphate supplementation was noted to increase after treatment. Patients in group A showed total BMD increased between 37.9% and 52.3%. In particular, an increase of 43.2–79.3% was noted for the femoral neck. One participant in group B ($n = 5$) had previously received phosphate therapy but discontinued the treatment upon relief of pain, and phosphate supplementation was accepted again when the bone pain subsequently intensified. The rest of 4 patients in group B were initially treated consistently with a neutral phosphate solution, followed by a period of intermittent supplementation. The BMD of these patients was noted to increase between 4.9% and 33.5% in the total hip, and between 17.7% and 33.4% in the femoral neck. However, BMD measurements of group C were noted to decrease in the femoral neck (–41.7% to –22.5%). During treatment, one participant in group C had fractures of the right ribs 8-10 and the left ribs 7-9 caused by a turbulent bus ride. No other follow-up patients in any of the three groups had fractures during the treatment period (Fig 1).

Discussion

The aim of our study is to investigate the changes in BMD in HO patients before and after treatment. Many investigators have shown that BMD is markedly reduced in osteomalacic bone [7-13]. It has been reported that up to 70% osteomalacia patients had BMD with osteoporosis in their lumbar spine, and up to 60% osteomalacia patients had BMD with osteoporosis in their femoral neck by a study from Iran [9]. The results from this study also showed that the BMD of HO patients is markedly reduced before treatment and increased after conventional treatment with oral phosphate and calcitriol. This indicated that BMD is decreased in most osteomalacia and it may help in assessing the bone status before and after treatment.

In our study, BMD in the L1–L4, total hip and femur neck regions in HO patients were significantly lower than that in healthy individuals before treatment with the BMD in femur neck decreased the most obvious. These results are equal to the previous research in which BMD measurements both at the lumbar spine and the femoral neck are in the osteoporotic range in a Caucasian patient with HO [11]. After treatment with neutral phosphate solution concurrent with calcitriol and calcium, both the BMD in L1-L4 and total hip showed an improvement in which the femoral neck BMD increased the most (43.2–79.3%). These results indicated that BMD, especially femoral neck BMD appeared to be better markers to monitor therapy. The study of Bhambri et. al discovered that within the first few months treatment, there was a huge improvement in clinical syndrome and biochemical markers in osteomalacia patients, but the bone mineral defects take much longer to repair and the ultimate extent of recovery at different skeletal sites is various [7]. Therefore, it is of vital importance to continue treatment until bone mineral defects are satisfactorily improved.

Although bone biopsy is the most reliable test for bone mineral deficits monitoring in osteomalacia patients, its clinical routine application is limited due to the invasive nature. Compared with bone biopsy, BMD measured by DXA is a non-invasive method with minimal radiation exposure. Based on the fact that BMD of the lumbar spine and femur significantly correlated with quantitative histological measurement in patients with a variety of metabolic bone diseases including osteomalacia [14], our study demonstrated that BMD may contribute to the retrospective confirmation of the bone mineral deficits and also contribute to the evaluation of the therapeutic efficacy in HO. Thus, BMD could be used for clinicians to determine when to reduce phosphate supplementation so as to avoid overtreatment and maintain serum phosphate levels close to the lower limit of normal.

Treatment is recommended in hypophosphatemia adults with symptoms including osteomalacia. However, there are limited clinical studies demonstrated the efficacy of conventional therapy with oral phosphate and calcitriol in adults with HO [5, 11]. Therefore, our study performed conventional therapy on patients with HO and evaluated its efficiency. Because commercialized oral phosphate supplements are unavailable in developing areas such as in rural China, a self-blended phosphate solution according to the recommended daily elemental phosphorus (750 to 1000 mg/d in 3 to 4 divided dosages) [6] for HO was used for the treatment so that patients themselves prepared the oral phosphate solution at home. Femur neck BMD was found to significantly positive correlate with serum P levels before treatment. Reduced serum phosphorous leads to activation of PTH and 1, 25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$), and consequently causes a reduction of serum Ca [15]. Reduction of serum Ca further increases the synthesis and secretion of PTH, which results in receptor activation for nuclear factor- κB ligand (RANKL) by osteoblast cells, thus enhancing osteoblast formation and bone resorption [16]. Increasing serum P levels, then, is an important component of treatment plans to increase and maintain BMD in patients with HO. Therefore, self-blended neutral phosphate solution used for the treatment was adjusted according to measured serum P levels. After treatment, we found that patients who received calcitriol and calcium without neutral phosphate solution showed decreases in BMD, and in one case, multiple fragility fractures. While consistent supplementation with neutral phosphate solution, calcitriol and calcium could

increase the BMD of HO patients, especially in the femoral neck, and the effect appears to be partially maintained once treatment is discontinued. This is consistent with the study by Sullivan et al. and Harrell et. al, who showed that calcitriol and phosphorus supplements could reverse the extent of mineralization defect detected by bone biopsy in HO [5, 17]. Meanwhile, none of the previously reported side-effects such as hyperparathyroidism, nephrocalcinosis, or other diseases [18, 19] were observed during therapy. These results indicated that conventional therapy combined calcitriol and phosphate could improve bone mineralization in both the lumbar spine and hip bone in HO.

This study had a few notable limitations. The duration of illness and time for follow-up were uncontrolled and only 11 of 21 HO patients returned for follow-up. Small sample sizes, especially in the HO subgroups limit the statistical power of our results, and preclude adjustment for sex, age and menopause status. Further research with a larger sample size is needed to better understand the efficacy of phosphate supplementation and optimize treatment regimens for HO patients of various demographics.

Conclusions

In conclusion, the results from this study suggest that BMD measured by DXA may be a good noninvasive marker to assess the severity of bone mineral defects before and after treatment. Furthermore, evaluating changes in BMD with combined self-blended neutral phosphate solution and calcitriol therapy in HO patients show that conventional medical therapy is beneficial in the treatment of mineralization defects in patients with HO in China, as proved by the improvement of BMD in the lumbar spine, hip and femoral neck. Therefore, we suggest that BMD changes should be monitored in patients with HO at regular intervals to evaluate the therapeutic effect and treatment should be continued until BMD is satisfactorily improved .

List Of Abbreviations

HO: hypophosphatemic osteomalacia; BMD: bone mineral density ; P: phosphorus; Ca: calcium; DXA: dual-energy X-ray absorptiometry; ALP: alkaline phosphatase; PTH: parathyroid hormone; BA: Bone area; BMC:bone mineral content; L1–L4: lumbar spine; 1,25(OH)2D: 1, 25-dihydroxyvitamin D; RANKL: receptor activation for nuclear factor- κ B ligand.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Second Xiang-Ya Hospital of Central South University. Written informed consent was obtained from the subjects before all measurements.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are available in the ResMan repository, <http://www.medresman.org/pub/cn/proj/projectshow.aspx?proj=2108>.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by grants from the National Natural Scientific Foundation of China [grant numbers 81370975, 81070278, 81401835, 81800788 and 81770880], the Science & Technology Department of Hunan Province [grant numbers 2015JC3012, 100JJ1007, 2018SK52511]. The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' Contributions

HDZ designed the study; YG, XPW, CYT, MW, ZHM and JT collected data; YG, YHZ and YZF analyzed and interpreted the data; YG and YHZ drafted the manuscript. BF, JAS analyzed the data and revised the paper. BKN revised the paper. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

- 1 Kinoshita Y, Fukumoto S. X-linked hypophosphatemia and fgf23-related hypophosphatemic diseases: Prospect for new treatment. *Endocr Rev.* 2018;39(3):274-91.
- 2 Bockenhauer D, Bokenkamp A, van't Hoff W, Levtchenko E, Kist-van Holthe JE, Tasic V, et al. Renal phenotype in lowe syndrome: A selective proximal tubular dysfunction. *Clin J Am Soc Nephrol.* 2008;3(5):1430-6.
- 3 Bergwitz C, Roslin NM, Tieder M, Loredó-Osti JC, Bastepe M, Abu-Zahra H, et al. Slc34a3 mutations in patients with hereditary hypophosphatemic rickets with hypercalciuria predict a key role for the sodium-phosphate cotransporter npi-ii in maintaining phosphate homeostasis. *Am J Hum Genet.* 2006;78(2):179-92.
- 4 Shanbhogue VV, Hansen S, Jorgensen NR, Beck-Nielsen SS. Impact of conventional medical therapy on bone mineral density and bone turnover in adult patients with x-linked hypophosphatemia: A 6-year prospective cohort study. *Calcif Tissue Int.* 2018;102(3):321-8.

- 5 Sullivan W, Carpenter T, Glorieux F, Travers R, Insogna K. A prospective trial of phosphate and 1,25-dihydroxyvitamin d3 therapy in symptomatic adults with x-linked hypophosphatemic rickets. *J Clin Endocrinol Metab.* 1992;75:879-85.
- 6 Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to x-linked hypophosphatemia. *J Clin Endocrinol Metab.* 1992;75(3):879-85.
- 7 Bhambri R, Naik V, Malhotra N, Taneja S, Rastogi S, Ravishanker U, et al. Changes in bone mineral density following treatment of osteomalacia. *J Clin Densitom.* 2006;9(1):120-7.
- 8 Jeong HJ, Lee JM, Lee TH, Lee JY, Kim HB, Heo MH, et al. Two cases of hypophosphatemic osteomalacia after long-term low dose adefovir therapy in chronic hepatitis b and literature review. *J Bone Metab.* 2014;21(1):76-83.
- 9 Saghafi M, Azarian A, Hashemzadeh K, Sahebari M, Rezaieyazdi Z. Bone densitometry in patients with osteomalacia: Is it valuable? *Clin Cases Miner Bone Metab.* 2013;10(3):180-2.
- 10 Arthur S, Chopra A. Familial hypophosphatemia: an unusual presentation with low back ache, heel pain, and a limp in a young man, and literature review. *Clin Rheumatol.* 2011;30(4):585-9.
- 11 Negri AL, Bogado CE, Zanchetta JR. Bone densitometry in a patient with hypophosphatemic osteomalacia. *J Bone Miner Metab.* 2004;22(5):514-7.
- 12 El-Desouki MI, Othman SM, Fouda MA. Bone mineral density and bone scintigraphy in adult saudi female patients with osteomalacia. *Saudi Med J.* 2004;25(3):355-8.
- 13 El-Desouki M, Al-Jurayyan N. Bone mineral density and bone scintigraphy in children and adolescents with osteomalacia. *Eur J Nucl Med.* 1997;24(2):202-5.
- 14 Cosman F, Schnitzer MB, McCann PD, Parisien MV, Dempster DW, Lindsay R. Relationships between quantitative histological measurements and noninvasive assessments of bone mass. *Bone.* 1992;13(3):237-42.
- 15 Fukumoto S. The role of bone in phosphate metabolism. *Mol Cell Endocrinol.* 2009;310(1-2):63-70.
- 16 Martin A, David V, Quarles LD. Regulation and function of the fgf23/klotho endocrine pathways. *Physiol Rev.* 2012;92(1):131-55.
- 17 Harrell RM, Lyles KW, Harrelson JM, Friedman NE, Drezner MK. Healing of bone disease in x-linked hypophosphatemic rickets/osteomalacia. Induction and maintenance with phosphorus and calcitriol. *J Clin Invest.* 1985;75(6):1858-68.
- 18 Imel EA, DiMeglio LA, Hui SL, Carpenter TO, Econs MJ. Treatment of x-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations. *J Clin*

19 Faul C, Amaral AP, Oskoueï B, Hu MC, Sloan A, Isakova T, et al. Fgf23 induces left ventricular hypertrophy. J Clin Invest. 2011;121(11):4393-408.

Figures

Figure 1

Figure 1

Observed BMD changes of HO patients after different treatments. BMD of L1–L4, the femoral neck and the total hip significantly increased ($P < 0.01$) after continuous treatment with a neutral phosphate solution (group A). There was no significant improvement in the BMD after intermittent treatment with a neutral phosphate solution (group B, $P > 0.05$). Patients not treated with a neutral phosphate solution showed decreased BMD (group C, $P < 0.05$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CONSORT2010Checklist.pdf](#)
- [renamedadb4.pdf](#)