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Original article

Determination of serum bone-related minerals during denosumab treatment in osteoporosis patients with rheumatoid arthritis Mineral change by denosumab in osteoporosis with rheumatoid arthritis

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SUMMARY

Objectives: This study included 51 osteoporosis patients with rheumatoid arthritis (RA) who were treated with anti-resorption drug, denosumab. To date, there has been no report on the changes of bone-related minerals after anti-resorption drug therapy.

Methods: Fifty one osteoporotic patients with RA were retrospectively enrolled. Serum Zinc (Zn), Magnesium (Mg), Iron (Fe), and Copper (Cu) were examined at 1 week, 1, 2, 4, 6, 8, 10, 12 months. Lumbar spine (L1-4) bone mineral density (L-BMD), and bilateral total hip BMD (H-BMD) were examined before and at 6 and 12 months after treatment commencement.

Results: Serum Fe gradually increased except at 4 and 10 months, and significantly increased at 12 months. Serum Mg slightly decreased at 1 week and 1 month, then increased up to 4 months, then gradually decreased to 8 months, then increased thereafter. Serum Zn significantly increased at every time point except at 1 week during the period. Serum Cu increased during the period but slightly decreased at 2, 8, and 12 months. L-BMD as well as H-BMD significantly increased at 12 months (5.1% and 5.1%, respectively).

Conclusions: Denosumab might be a good option to improve bone-related minerals in OP patients with RA even without dietary supplement. Serum Fe and Mg values became approximately within normal range after the therapy. On the other hand, serum Zn significantly increased for 12 months, however, the Zn values showed still low status after the treatment. Thus, Zn supplementation and/or nutrition education are basically required for OP patients with RA, even though denosumab increases serum Zn level.

1. Introduction

The pathophysiology of osteoporosis (OP) accompanying with rheumatoid arthritis (RA) is complex and multi-factorial while there have been several reports on it [1]. Thus, it is required to reveal the relevant pathogenic factors, such as bone minerals, hormone changes, in those patients.

Denosumab is a fully human monoclonal antibody that inhibits receptor activator of nuclear factor kappa-β ligand (RANKL), which selectively inhibits osteoclastogenesis. Denosumab prevents fractures and increases bone mineral density (BMD) in OP [2,3], while bisphosphonates (BPs), which are anti-resorption drugs, are the first-line OP therapy [4]. To the best of our knowledge, there has been no report on the bone-related minerals in OP with RA after denosumab treatment to date. We therefore examined the baseline values in those patients during denosumab therapy.

Minerals, such as magnesium (Mg), zinc (Zn), copper (Cu), and Iron (Fe) are all essential for health, which accelerates strong bones. There have been some reports that Mg and Zn are essential for organic bone matrix synthesis [5], and Mg deficiency could affect the quality of bone by decreasing bone formation [6]. Zn plays a physiological role in mineralization of bone tissue [7], while its deficiency is a global health problem [8,9]. Several studies have

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demonstrated that in bone, Cu deficiency decreased the mechanical strength [10,11]. Thus, due to the key role of those minerals on bone health, supplementation with Mg, Zn, Fe, and perhaps Cu is recommended in OP.

In this study, we examined the changes of bone-related minerals and BMD in OP with RA after denosumab treatment for 12 months.

2. Materials and methods

2.1. Patient characteristics

We collected data for 51 female OP patients with RA who received denosumab treatment between April 2016 and March 2017. The average data of age was 68.0 ± 1.1 years and body mass index (BMI) was 20.1 ± 0.4 (kg/m^2). All of patients had taken BPs (alendronate: 19 cases, risedronate: 32 case). The average period of BP therapy was 7.4 ± 0.6 years (Table 1).

Table 1
Patient characteristics prior to the denosumab therapy.

Characteristic	
Age (years)	68.0 ± 1.1
Gender (F: M)	51: 0
BMI (kg/m^2)	20.1 ± 0.4
BP use, n (%)	51 (100)
Alendronate, n	19
Risedronate, n	32
Vitamin D, n	24
Denotas Chewable, n	24
Period of BP use (year)	7.4 ± 0.6
L-BMD (g/cm^2)	0.704 ± 0.01
H-BMD (g/cm^2)	0.466 ± 0.01
MTX, n (mg/week)	37 (7.5 ± 0.5)
PSL, n (mg/day)	6 (3.5 ± 0.8)
MMP-3 (ng/ml)	90.5 ± 9.0
Disease duration (years)	18.3 ± 1.5
DAS28-CRP	2.4 ± 0.1
SDAI	5.6 ± 0.7
HAQ-DI	0.3 ± 0.1

The inclusion criteria for the study were OP patients with low L-BMD and/or H-BMD (T score: less than −2.5 standard deviation) and RA. The exclusion criteria were patients with chronic renal failure (estimated glomerular filtration rate <40 ml/min/1.73 m^2), bone metabolic disorder, or diabetes mellitus, which affect OP, and fracture within 1 year prior to the study. The diagnosis of OP was made in accordance with the revised criteria established by the Japanese Society of Bone and Mineral Research [12]. Each patient received denosumab (60 mg, s.c.) once every 6 months.

The diagnosis and treatment of RA were conducted in accordance with the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification system [13]. All serologic analyses were conducted just prior to denosumab commencement using cryogenically stored samples by commercially available kits in accordance with each manufacturer's instructions, including matrix metalloproteinase-3 (MMP-3; Kyowa Pharma Chemicals, Toyama, Japan). We also examined the values of disease activity score (DAS) 28-C-reactive protein (CRP), simplified disease activity index (SDAI), and patient-reported health assessment questionnaire-disability index (HAQ-DI) as indicators of RA status for all patients prior to denosumab. All data are expressed as the mean ± standard error (S.E.). All of the patients were in remission of RA before, during, and after the denosumab treatment.

Table 2
Baseline values prior to treatment.

Zinc (μg/dL)	53.5 ± 1.2
Copper (μg/dL)	126.0 ± 3.1
Iron (μg/dL)	70.8 ± 5.2
Magnesium (μg/dL)	2.1 ± 0.02

Table 3
Values at 12 months after treatment.

Zinc (μg/dL)	61.1 ± 1.8
Copper (μg/dL)	132.7 ± 3.6
Iron (μg/dL)	77.6 ± 5.5
Magnesium (μg/dL)	2.1 ± 0.03

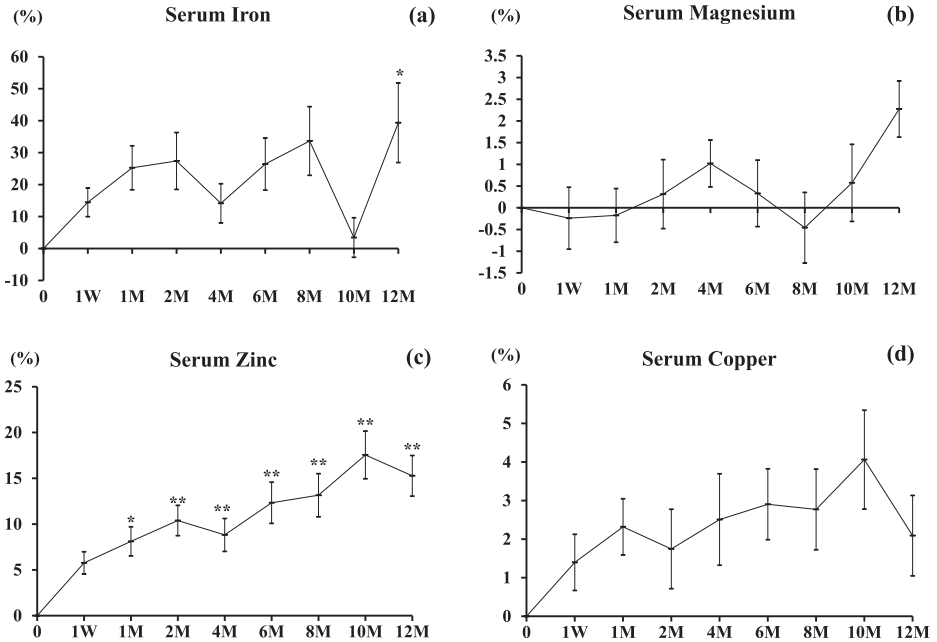

Fig. 1. Percent changes in serum Iron (a), serum Magnesium (b), serum Zinc (c), and serum Cupper (d) were examined at 1 week (W), 1, 2, 4, 6, 8, 10, 12 months (M) after denosumab treatment. Results are expressed as mean ± standard error. *P < 0.05, significant difference compared with pretreatment. **P < 0.01, significant difference compared with pretreatment levels.