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Effect of Bisphosphonate and Active Vitamin D Analog on Glucocorticoid-induced Osteoporosis in Patients with IgA Nephropathy: A Retrospective Observational Study

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Few studies on glucocorticoid (GC)-induced osteoporosis exist in IgA nephropathy (IgAN). Here we aimed to compare the effects of bisphosphonate (Bis) and active vitamin D analog (Vit. D) in maintaining bone mineral density (BMD) in patients with IgAN. This study is a retrospective observational one. Between April 2007 and December 2014, a total of 127 patients with IgAN received GC treatment at Kobe University Hospital. Among them, we measured the BMD of 48 patients with a mean age of approximately 30 years, before and after GC treatment. The %ΔBMD of the lumber spine increased in the Bis group (1.6% ± 2.3%), but decreased in the Vit. D group (−3.3% ± 3.6%). The %ΔBMD of the two groups differed significantly ($p < 0.05$). Although the %ΔBMD of the femoral neck showed the same tendency, the difference between two groups was not significant. Bis was significantly superior to Vit. D in maintaining the BMD of lumbar spine bones. Even in young patients with IgAN, Bis is recommended to prevent the reduction of BMD during GC treatment.

INTRODUCTION

IgA nephropathy (IgAN) is the most common chronic glomerulonephritis (CGN) in the world, with a peak onset age chiefly in the second and third decades of life (1, 2). Within 10–20 years of its onset, 15%–20% of patients with IgAN develop end-stage renal disease (ESRD) (3, 4). Many previous studies clarified the efficacy of glucocorticoid (GC) treatment and its essential role in inhibiting the progression of IgAN (5–9). Even in young patients with autoimmune diseases, bone fractures have been widely reported to occur after GC treatment (10–13). In general, patients with autoimmune diseases take high dose GC for many years (14–16). In contrast, GC is tapered and discontinued within one or two years in patients with IgAN. To date, to the best of our knowledge, only four studies have reported GC-induced osteoporosis in patients with CGN including nephrotic syndrome (17–20).

In previous randomized controlled trial on GC-induced osteoporosis, bisphosphonates (Bis) proved effective in preventing bone loss than active vitamin D analog (Vit. D) in patients with glomerular diseases (17). In Japanese guidelines for GC-induced osteoporosis, Bis is recommended as the first-line agent and Vit. D is the proposed alternative (21). Unfortunately, Bis has several side-effects—such as osteonecrosis of the jaw and gastrointestinal disorders—and some patients are thus forced to take Vit. D as an alternative in the clinical setting. Here we aim to compare the effects of Bis and Vit. D in maintaining bone mineral density (BMD) in patients with IgAN.

MATERIALS AND METHODS

Between April 2007 and December 2014, our institution treated 127 patients with IgAN using GC. The GC treatment schedule comprised three serial pulse therapies: one course consists of 500 mg/day of intravenous methylprednisolone (mPSL) infusion for three consecutive days and subsequent 30 mg/day of oral prednisolone (PSL) for four days. After the completion of three courses, alternate-day course of 30 mg/day of oral PSL starts, which is gradually tapered during one year and discontinued after one year. Of all 127 patients, we measured the BMD of 80 patients before and after GC treatment until December 2015. We excluded patients aged <18 years, postmenopausal women, those receiving hormone replacement treatment, those with a previous history of GC treatment, and those being administered Vit. D and/or Bis before the study enrollment. We also excluded patients who discontinued GC treatment and for whom we had insufficient data. Finally, we enrolled 48 patients with a mean age of 32.7 years in this study. We divided these patients into two groups based on their treatment with Bis or Vit. D as prophylactic agents for GC-induced osteoporosis (Bis group: n = 36; Vit. D group: n = 12). In 36

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patients of bisphosphonate users, only one used risedronate, the others used alendronate. In 12 patients of active vitamin D analog users, all of them used alfacalcidol (0.25 μg or 0.5 μg). Of the Bis and Vit. D groups, 31 (women: n = 22, men: n = 9) and 9 (women: n = 5; men: n = 4) patients, respectively, measured both lumber and femoral neck BMD. Ten patients were administered Vit. D due to dental caries treatment before the start of GC treatment; one patient planned to conceive and one suffered from skin rash due to Bis; in total, 12 patients were administered Vit. D.

We conducted this study in accordance with Declaration of Helsinki principles and the Ethics Committee of Kobe University Hospital approved the study protocol (No.1865). We collected study data from the medical history, physical examination, and laboratory finding of patients' medical records. All laboratory tests were measured by standard automated techniques, and estimated glomerular filtration rate (eGFR) was calculated according to the equation for Japanese people (22).

BMD of the lumbar spine (L2–L4) and femoral neck were measured by energy X-ray absorbiometry (DEXA) using a Hologic Discovery A (Hologic Inc, Bedford, MA, USA). For all patients, BMD was measured twice—just before the start of GC treatment, and after about one year from the start of GC treatment. We defined changes in BMD per year as %ΔBMD, according to the following equation:

%ΔBMD = [{(2nd BMD－1st BMD)/1stBMD}/ duration between 1st and 2nd BMD measurements (year)] × 100

We also used BMD percentage compared to young adult mean (%YAM; Lumber spine, 20–44 years old; Femoral neck, 20–29 years old) to evaluate BMD. T score is indicated as standard deviation from the mean peak BMD value of sex-matched, healthy, young adults (20–29 years old).

For all statistical analyses we used the software application IBM SPSS Statistics for Windows, version 28.0 (Chicago, IL, USA). We present values as means ± standard deviation. We analyzed the significance of differences between two groups by the Wilcoxon signed-rank test for continuous variables and the chi-squared test for categorical variables. We also used the Wilcoxon signed-rank test for comparison of data between the first and second BMD measurements. We performed multiple regression analysis to determine independent factors associated with %ΔBMD of the lumber spine. We selected age, eGFR, group (Bis or Vit. D), and baseline BMD as independent variables. We considered a p value less than 0.05 as statistically significant.

RESULTS

In Table I we show the baseline characteristics of Bis and Vit. D groups for whom it was possible to measure the BMD of the lumber spine before and after GC treatment (n = 48). The two groups did not differ significantly in terms of BMI, sex, diabetes mellitus, U-Pro/U-Cr, serum creatinine, eGFR, usage of RAS-I, thiazide, and cumulative dose of PSL. The average age of the Bis group was, however, significantly higher than that of the Vit. D group. In Table II we summarize BMD before and after GC treatment. After GC treatment, the BMD, %YAM and T score of the Bis group were significantly higher than those of the Vit. D group. In Figure 1 we show the %ΔBMD of both groups. The %ΔBMD of the Bis group was increased (1.6% ± 2.3%) while that of the Vit. D group decreased (−3.3% ± 3.6%) and the two groups differed significantly ($p < 0.05$). In multiple regression analysis, baseline factors, age, eGFR, and baseline BMD did not contribute significantly to %ΔBMD (Table III). The selection of Bis or Vit. D contributed significantly to %ΔBMD of lumbar spines.

Table I. Baseline characteristics of the cases who measured BMD of lumber spine

	Bis（n = 36）	Vit. D (n = 12)	p
Age (years old)	34.4 ± 9.1	27.8 ± 7.0	0.03
BMI (kg/m^2)	20.4 ± 2.8	21.5 ± 4.1	0.47
Male (%)	10 (27.8)	6 (50.0)	0.16
Diabetes (%)	1 (2.8)	2 (16.7)	0.09
U-Pro/ U-Cr (g/gCr)	1.1 ± 1.1	1.8 ± 2.7	0.73
S-Cr (mg/dL)	0.9 ± 0.3	0.9 ± 0.3	0.84
eGFR (mL/min/1.73m^2)	73.7 ± 25.5	84.0 ± 28.8	0.28
RAS-I (%)	29 (80.6)	10 (83.3)	0.83
Thiazide (%)	0 (0)	0 (0)	—
Cumulative dose of PSL (g)	9.8 ± 1.7	10.2 ± 1.1	0.08

BMD, bone mineral density; Bis, bisphosphonate; Vit. D, active vitamin D analog; BMI, body mass index; U-Pro, urinary protein; U-Cr, urinary creatinine; S-Cr, serum creatinine; eGFR, estimated glomerular filtration rate; RAS-I, renin-angiotensin system inhibitor; PSL, prednisolone

Table II. BMD of lumber spine at baselines and after GC treatment

	Baseline			After GC		
	Bis (n = 36)	Vit. D (n = 12)	p	Bis (n = 36)	Vit. D (n = 12)	p
BMD	1.05 ± 0.14	0.99 ± 0.09	0.23	1.08 ± 0.15	0.96 ± 0.12	<0.05
%YAM	104.03 ± 14.24	96.33 ± 9.43	0.12	105.47 ± 14.44	92.83 ± 12.58	<0.05
T score	0.28 ± 1.30	−0.33 ± 0.85	0.20	0.42 ± 1.22	−0.45 ± 1.01	<0.05

BMD, bone mineral density; GC, glucocorticoid; Bis, bisphosphonate; Vit. D, active vitamin D analog;
%YAM, percentage compared to young adult mean

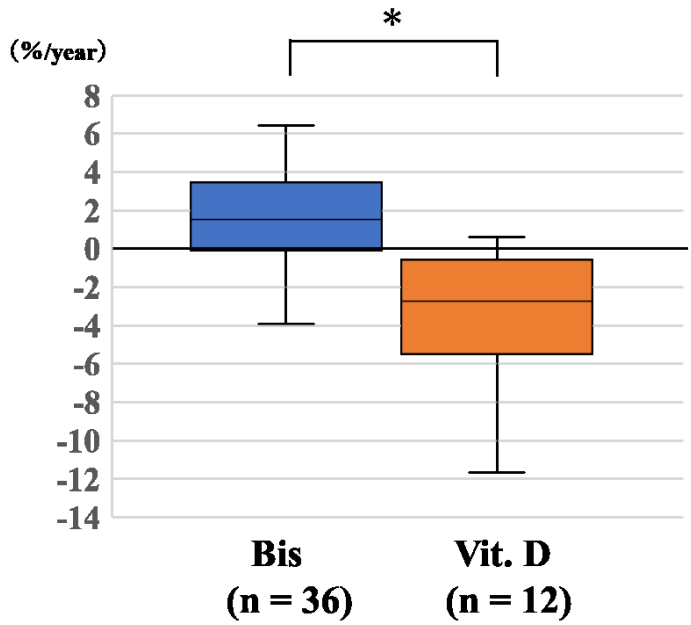

Figure 1. %Δ BMD of the lumbar spine in Bis and Vit. D groups.
The %ΔBMD in the Bis group was increased while that in the Vit. D group decreased, and we confirmed a significant difference between the two groups.
*: $p < 0.05$

Table III. Multiple regression analysis for %ΔBMD of lumber spine (n = 48)

	β	p
Age	−0.093	0.581
Group (Bis, Vit. D)	0.648	<0.001
eGFR	0.026	0.872
Baseline BMD	0.104	0.409

BMD, bone mineral density; Bis, bisphosphonate; Vit. D, active vitamin D analog;
eGFR, estimated glomerular filtration rate; β, standardized partial regression coefficient

In Table IV we document the baseline characteristics of the Bis and Vit. D groups for whom it was possible to measure the BMD of the femoral neck. The two groups did not differ significantly apart from their rates of diabetes complication. In Table V we summarize BMD before and after GC treatment. The two groups did not differ significantly before and after GC treatment. In the %ΔBMD of the femoral neck, it was also increased in Bis group (1.7% ± 5.2%), and decreased in Vit. D group (−1.6% ± 3.8%), but the two groups did not differ significantly.

Table IV. Baseline characteristics of the cases who measured BMD of femoral neck

	Bis (n = 31)	Vit. D (n = 9)	p
Age (years old)	33.0 ± 9.1	28.2 ± 8.1	0.15
BMI (kg/m^2)	20.3 ± 2.8	21.4 ± 4.7	0.68
Male (%)	9 (29.0%)	4 (44.4%)	0.39
Diabetes (%)	0 (0.0%)	2 (22.2%)	0.01
U-Pro/ U-Cr (g/gCr)	1.0 ± 1.1	2.0 ± 3.0	0.55
S-Cr (mg/dL)	0.9 ± 0.3	0.9 ± 0.3	0.43
eGFR (mL/min/1.73m^2)	76.7 ± 25.6	80.8 ± 32.6	0.98
RAS-I (%)	24 (77.4%)	8 (88.9%)	0.45
Thiazide (%)	0 (0)	0 (0)	—
Cumulative dose of PSL (g)	9.7 ± 1.7	10.0 ± 1.1	0.26

BMD, bone mineral density; Bis, bisphosphonate; Vit. D, active vitamin D analog;
BMI, body mass index; U-Pro, urinary protein; U-Cr, urinary creatinine; S-Cr, serum creatinine;
eGFR, estimated glomerular filtration rate; RAS-I, renin-angiotensin system inhibitor; PSL, prednisolone

Table V. BMD of femoral neck at baseline and after GC treatment

	Baseline		p	After GC		p
	Bis (n = 31)	Vit. D (n = 9)		Bis (n = 31)	Vit. D (n = 9)	
BMD	0.82 ± 0.15	0.80 ± 0.21	0.52	0.84 ± 0.14	0.78 ± 0.19	0.29
%YAM	101.48 ± 17.15	97.33 ± 24.23	0.35	103.30 ± 16.77	95.33 ± 22.32	0.20
T score	0.07 ± 1.26	−0.19 ± 1.70	0.40	0.25 ± 1.19	−0.31 ± 1.56	0.21

BMD, bone mineral density; GC, glucocorticoid; Bis, bisphosphonate; Vit. D, active vitamin D analog;
%YAM, percentage compared to young adult mean

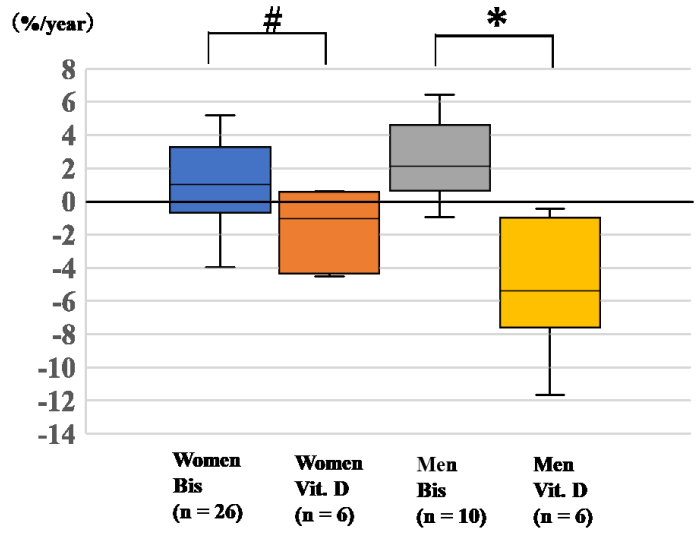

Figure 2. %Δ BMD of the lumber spine in men and women.
%ΔBMD in the Bis group was increased while that in the Vit. D group decreased in both women and men. Differences were significant.
#: $p < 0.05$, *: $p < 0.05$

On the basis of sex, we confirmed significant declines in the %ΔBMD of the lumbar spine in both women and men of the Vit. D group. (Figure 2 women: $p < 0.05$; men: $p < 0.05$). Although the %ΔBMD of the femoral neck showed the same tendency, the differences between two groups were not significant in both women and men (women: $p = 0.485$; men: $p = 0.148$).

DISCUSSION

Patients with autoimmune diseases such as rheumatic arthritis and systemic lupus erythematosus usually receive GC treatment for several years (14–16). GC suppresses bone formation and activates bone resorption, leading to BMD decreases (23). However, whether short term GC treatment affects BMD in young IgAN patients, and whether Bis or Vit. D can prevent the reduction of BMD in short term GC treatment of about one year, has not been evaluated in depth.

In our GC treatment for IgAN, the lumber spine %ΔBMD of the groups differed significantly: that of the Bis group increased (1.6% ± 2.3%) and that of the Vit. D group decreased (−3.3% ± 3.6%) over one year. Bis proved effective in maintaining the BMD of the lumber spine, whereas Vit. D failed to maintain the BMD even in young IgA patients with a mean age of approximately 30 years.

Guidelines on the management and treatment of glucocorticoid-induced osteoporosis (GIO) of the Japanese Society for Bone and Mineral Research: 2014 update (21) recommend Bis as a first selective agent for the prevention of GIO. In this guideline, the recommendation was derived from the control or observational studies evaluating patients with autoimmune diseases, with a mean age of approximately 50 years. The American College of Rheumatology Guideline for the Prevention and Treatment of GIO published in 2017 recommends Vit. D as a first selective agent in patients <40 years without osteoporosis risk factors such as malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, and history of heavy alcohol use or smoking (24).

Many previous reports have clarified the relationships between GC treatment and bone fracture. The risk of fracture appeared within 3–6 months after the start of GC treatment (25) and was higher particularly in cases using more than 5 mg of daily prednisolone (25). The correlation between daily GC dose and risk of fracture was strong (26). Even after the discontinuation of GC, its prior use significantly increased the risk of fragility fracture (27, 28). The intravenous pulse treatment with methylprednisolone contributed to higher rates of bone loss (29). Even in young patients with normal levels of BMD, high dose GC treatment for one year could cause bone fracture (10–13).

GIO in CGN patients with proteinuria was evaluated in some previous reports. Fujii et al. noted that lumber spine BMD increased by 2.1% ± 1.0% from baseline in Bis groups but decreased by 1.2% ± 0.6% from baseline in Vit. D groups during one year of GC treatment. The age of enrolled cases was 42.5 ± 16.6 years and the mean GC dose at baseline was 9.8 mg/day in a PRIUS-CKD study (17). Kikuchi et al. showed in their study that the BMD at 12 months in Bis group did not show a significant change compared with that at the baseline, the BMD in Vit. D group was significantly decreased (−5.6%). In combination group of Bis+Vit. D, the BMD was significantly increased from baseline (+2.0%). They felt that the decrease of BMD in the patients treated with Vit. D alone was remarkable. In this study, the age of enrolled cases was 42 ± 16 years (18). Considering this evidence, precautions against GIO might be necessary even in young IgAN patients after intravenous pulse treatment with methylprednisolone and subsequent oral prednisolone treatment for one year.

In the present study, the %ΔBMD of the lumber spine of the Bis and Vit. D groups differed significantly. In the %BMD of femoral neck, the two groups showed the same tendency, but the difference was not significant. In addition, we divided the Bis and Vit. D groups on the basis of sex respectively, the results were the same. In terms of BMD retention Bis was superior to Vit. D in our present study. This fact might come from cortical bone is less sensitive to bisphosphonate than trabecular bone (30).

There are some limitations in this study. First, our sample size was small and our follow-up period was short. More patients are necessary for a precise comparison between the Bis and Vit. D groups. Second, the prescription dose of Vit. D was smaller than those of previous studies and the allocation into Bis and Vit. D groups was non-randomized. The selection of Vit. D depended on the necessity for immediate invasive dental treatment and the consequent precaution against bisphosphonate-related osteonecrosis of the jaw (31). Fortunately, the baseline characters were almost comparable in excluding age and diabetes in the present study.

In conclusion, even in young IgAN patients, in terms of the prevention of GIO, administering Bis is preferable when they receive steroid pulse therapy and subsequent GC treatment for one year. Vit. D is not effective in maintaining BMD.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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