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RESEARCH

Prevalence and clinical outcomes of vitamin D deficiency among Japanese multiple myeloma patients: a single-center observational study

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Abstract

Purpose Vitamin D plays a crucial role in skeletal metabolism and holds significant importance in the pathophysiology of multiple myeloma (MM). This study aimed to determine the prevalence of vitamin D deficiency among Japanese MM patients and its correlation with clinical outcomes.

Methods Serum 25-hydroxyvitamin D (25(OH)D) levels were assessed in 68 MM patients at a single institution in Japan, analyzing their association with clinical status, laboratory parameters including procollagen type 1 N-propeptide (P1NP) and tartrate-resistant acid phosphatase 5b (TRACP-5b), health-related quality of life (HR-QOL) scores, and overall survival. Additionally, patients with suboptimal 25(OH)D levels received cholecalciferol supplementation (1000 IU/day), and changes in laboratory parameters were monitored.

Results The median 25(OH)D level was 22 ng/ml, with 32% and 51% of patients exhibiting vitamin D deficiency (<20 ng/ml) and insufficiency (20–29 ng/ml), respectively. The 25(OH)D levels were unrelated to sex, age, MM stage, or bone lesions, but the vitamin D–deficient group showed a tendency towards lower HR-QOL scores. Among patients achieving complete remission, vitamin D supplementation increased P1NP, while TRACP-5b remained unchanged. Overall survivals from vitamin D measurement and from MM diagnosis were significantly worse in the vitamin D–deficient group compared to the vitamin D–insufficient/–sufficient group.

Conclusion The study identified a considerable number of Japanese MM patients with insufficient serum vitamin D levels, with one-third being deficient. Additionally, vitamin D deficiency predicted poor overall survival in Japanese MM patients. Further investigation is required to determine whether vitamin D supplementation can improve the frailty and survival of vitamin D–deficient MM patients.

Keywords Multiple myeloma · Vitamin D deficiency · Skeletal morbidity · Cholecalciferol · Japan

Introduction

Multiple myeloma (MM) is a malignant plasma cell neoplasm characterized by osteolytic bone lesions, anemia, renal failure, and hypercalcemia [1]. In particular, bone lesions develop in up to 90% of MM patients during the disease course [2], and pathological fractures adversely affect both quality of life (QOL) and overall survival (OS) [3, 4]. Recent studies have shown that osteoclasts promote an immunosuppressive microenvironment in the MM bone marrow and play an important role in the pathophysiology of MM and related bone diseases [5, 6]. The clinical utility of bisphosphonates and denosumab in MM bone complications is now well established [7, 8].

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However, advanced bone lesions rarely heal, even in MM patients who achieve complete remission.

Vitamin D was originally known as a steroid hormone that is essential in regulating calcium and bone homeostasis [9]. Vitamin D deficiency can result in secondary hyperparathyroidism, causing increased osteoclast activity, osteoporosis, and an increased risk of pathological fractures [10]. In addition to such classical skeletal roles, vitamin D is increasingly recognized as playing crucial roles in numerous physiological functions, showing immunomodulatory, anti-inflammatory, and anti-fibrotic properties [11, 12]. Most cells in the human body have a vitamin D receptor (VDR) and possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D), to the active form, 1,25-dihydroxyvitamin D (1,25(OH)2D). Indeed, vitamin D deficiency has been shown to be involved in the etiology of various cancers, autoimmune diseases, and infectious diseases [13]. In addition, vitamin D deficiency has been also suggested to be associated with peripheral neuropathy in MM patients [14, 15].

In humans, vitamin D comes mainly from cutaneous synthesis during sun exposure, limited food sources including fortified dairy products, and supplementary intake [16]. Serum vitamin D levels are thus greatly affected by season, latitude, skin color, nutrition condition, and genetic variations related to vitamin D metabolism [17]. The best method to estimate vitamin D status in the human body is to measure serum 25(OH)D concentrations [16]. However, screening for serum 25(OH)D levels is not currently a part of routine MM workups [18], and the significance of vitamin D deficiency among Japanese MM patients remains unclear.

In this study, we aimed to clarify the following three points: (1) the distribution of serum 25(OH)D levels in Japanese MM patients, (2) associations between vitamin D status and clinical outcomes such as skeletal morbidity and survival, and (3) the efficacy of vitamin D restitution on biochemical markers of bone turnover in MM patients lacking sufficient levels of vitamin D.

Materials and methods

Study design and objectives

This was a single-center observational study to evaluate the serum vitamin D status of Japanese MM patients and analyze the relationship between serum vitamin D levels and disease characteristics. We used a cohort of consecutive MM patients who visited Nishigunma Hospital from December 2015 through March 2016 (winter in the Northern Hemisphere). Patients taking dietary vitamin D supplements or vitamin D medications (alfacalcidol, calcitriol, or eldecalcitol) were excluded from the study.

Blood examinations and QOL assessments

Blood samples for analysis were collected at the same point in time as the hospital visit, regardless of MM disease status and treatment. Serum 25(OH)D concentrations were measured by radioimmunoassay at a commercial laboratory (SRL Laboratory, Tokyo, Japan). Likewise, serum tartrate-resistant acid phosphatase 5b (TRACP-5b) concentrations were measured by enzyme immunoassay, and serum total procollagen type 1 N-propeptide (P1NP) and intact parathyroid hormone (PTH) concentrations were measured by electrochemiluminescent immunoassay at the same laboratory. Other laboratory data such as serum albumin, calcium, phosphorus, estimated glomerular filtration rate (eGFR), and complete blood count were collected from medical records. Health-related QOL (HR-QOL) scores were assessed using a Japanese version of EuroQol 5 dimensions 5 level (EQ-5D-5L). The EQ-5D-5L is a generic instrument for measuring HR-QOL based on a classification system that describes health status in five dimensions: mobility, personal care, usual activities, pain/discomfort, and anxiety/depression, where each of these dimensions has five levels of severity. Higher values indicate better QOL. The EQ-5D-5L also includes the Visual Analogue Scale (VAS), which is a vertical visual analogue scale used to record a patient's self-rated health. This scale ranges from 0 (representing the worst imaginable health status) to 100 (representing the best imaginable health status).

Definitions of staging, skeletal morbidity, and disease status of MM

The International Staging System (ISS) [19] and the Durie-Salmon staging system [20] were used for the staging of MM. In addition, a bone scale was employed to determine the status of bone lesions (skeletal morbidity) based on skeletal surveys using conventional whole-body skeletal radiography and computed tomography. The bone scale included the following categories: 0 for normal bones, 1 for osteoporosis, 2 for lytic bone lesions, and 3 for extensive skeletal destruction and major fractures [20]. According to the criteria established by the International Myeloma Working Group (IMWG) [21], the status of MM disease was classified into four categories: complete response (CR) (including stringent CR), partial response (PR) (including very good PR), stable disease (SD), and progressive disease (PD). Both ISS and Durie-Salmon stages were determined at the time of MM diagnosis, and the evaluation of skeletal morbidity and MM disease status were occurred before the first vitamin D measurement.

Definitions of vitamin D sufficiency, insufficiency, and deficiency

In accordance with the assessment criteria for vitamin D status in Japan [22], vitamin D deficiency was defined as serum 25(OH)D < 20 ng/ml, vitamin D insufficiency as serum 25(OH)D 20–29 ng/ml, and vitamin D sufficiency as serum 25(OH)D ≥ 30 ng/ml.

Supplementation of vitamin D for patients with suboptimal vitamin D levels

To clarify the effect of vitamin D supplementation on bone metabolism in MM patients, registered dietitians provided nutritional guidance to MM patients with suboptimal levels of vitamin D (serum 25(OH)D ≤ 25 ng/ml). The nutritional guidance included (1) active exposure of the arms and legs to sunlight, (2) selection of vitamin D–rich foods such as oily fish and mushrooms, and (3) intake of a dietary vitamin D supplement (cholecalciferol, 1000 IU/day) purchased from a local pharmacy. All patients who received the nutritional guidance were followed up by the same dietitians on each hospital visit for 3 months, after which serum levels of 25(OH)D, intact PTH, TRACP-5b, and total P1NP were re-measured. Continuation of vitamin D supplementation was recommended unless contraindicated.

Statistical analyses

We used EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [23], a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria) for analyses. The statistical significance of differences in categorical variables between groups was assessed using Fisher's exact test, while continuous variables were assessed using the Kruskal-Wallis test and Jonckheere-Terpstra test. Variables within groups and before and after receiving vitamin D nutritional guidance were compared using paired Student's *t*-test. Survival curves were plotted using the Kaplan-Meier methods, and survival analysis was assessed by log-rank testing. All statistical tests were two-sided, with values of $P < 0.05$ considered significant.

Results

Of the 79 patients initially screened, 11 patients were excluded from analysis because they were taking dietary vitamin D supplements or vitamin D medications. A total of 68 patients (29 men, 39 women) were included in the final analysis and all were identified as Japanese. Median age was 68 years (range, 48–93 years). Median duration from diagnosis of MM was 3.9 years (range, 0.3–15.3 years).

Distribution of serum 25(OH)D and intact PTH levels

Figure 1 shows the distribution of serum 25(OH)D levels in the cohort. Median serum 25(OH)D level for the total population was 22 ng/ml (interquartile range [IQR], 18.8–26.3 ng/ml). Only 16% of patients had sufficient levels of vitamin D (25(OH)D ≥ 30 ng/ml; vitamin D sufficiency), while 32% and 51% showed deficient levels (25(OH)D < 20 ng/ml; vitamin D deficiency) and insufficient levels (25(OH)D 20–29 ng/ml; vitamin D insufficiency), respectively. Figure 2 shows a correlation between serum intact PTH and serum 25(OH)D level. Mean (standard deviation) intact PTH level in vitamin D–deficient patients was 72.7 (51.9) pg/ml, compared to 53.0 (22.5) pg/ml in vitamin D–insufficient/sufficient patients.

Clinical characteristics

Table 1 details sex, age, duration from diagnosis of MM, ISS stage, Durie-Salmon stage, bone scale, and status of MM disease in vitamin D–deficient, –insufficient, and –sufficient groups. Subjects in the three groups generally displayed similar characteristics.

Laboratory parameters and HR-QOL scores

Figure 3 shows differences in laboratory parameters and HR-QOL scores between vitamin D–deficient, –insufficient, and –sufficient groups. No significant differences were seen in leukocyte count, lymphocyte count, hemoglobin, platelet count, eGFR, or albumin between the three groups. Likewise, with the exception of phosphorus, no significant difference in bone metabolism parameters such as intact PTH, total P1NP, and TRACP-5b, or calcium corrected for albumin level was seen between the three groups. Meanwhile, no significant difference in HR-QOL scores (EQ-5D-5L, VAS) was apparent between the three groups, whereas the vitamin D–deficient group included a higher proportion of subjects with low HR-QOL scores.

Changes in bone metabolism parameters before and after vitamin D nutrition guidance

Figure 4 shows bone metabolism parameters before and after vitamin D nutritional guidance. Of the 49 patients with serum 25(OH)D levels ≤ 25 ng/ml at first examination, 15 subsequently received vitamin D nutritional guidance. After 3 months follow-up period, all 15 patients showed a significant increase in serum 25(OH)D levels ($p < 0.001$) and

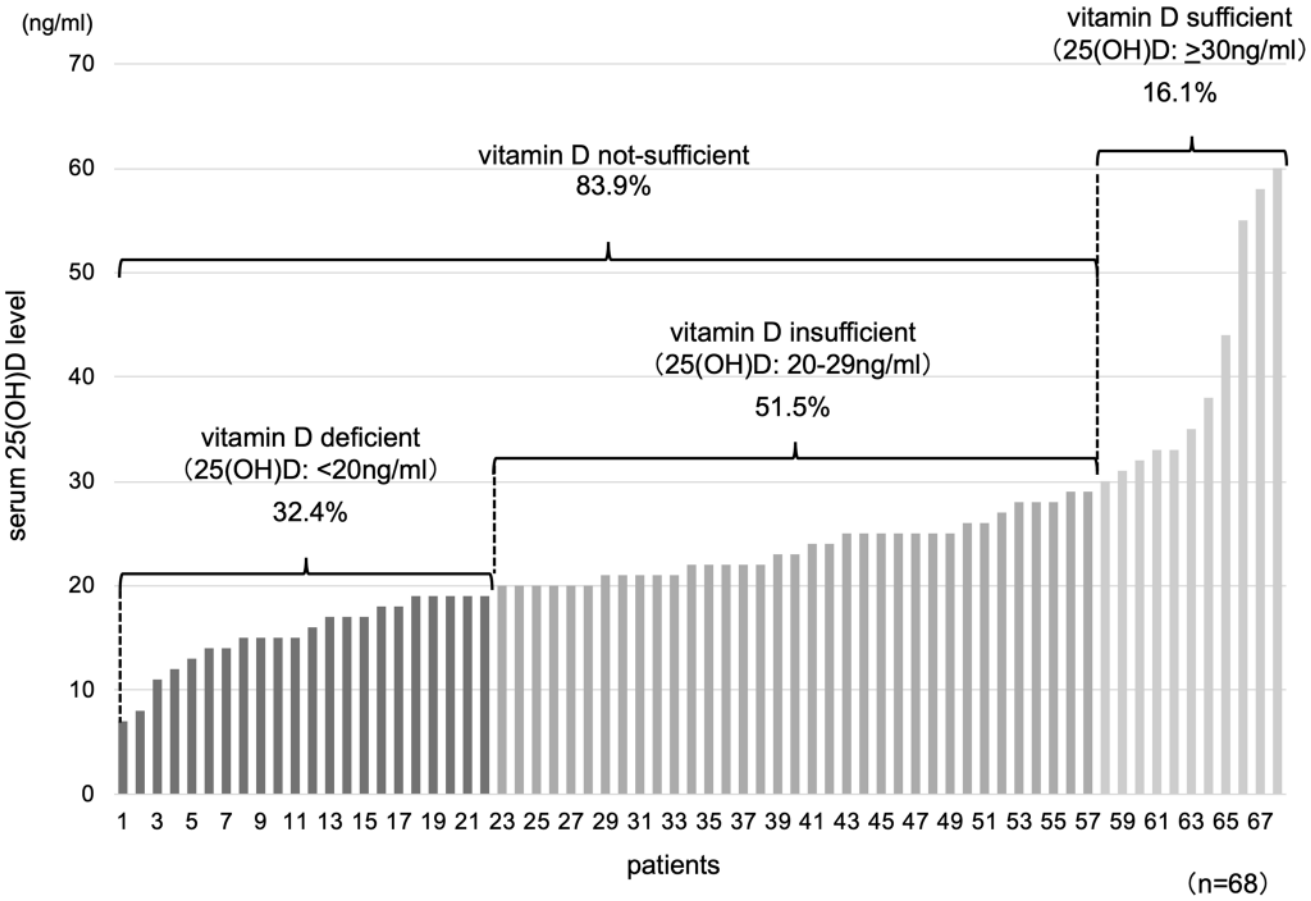

Fig. 1 Distribution of serum 25(OH)D levels in the cohort

a significant decrease in serum intact PTH levels ($p < 0.001$). Furthermore, in the six MM patients who achieved complete remission, serum total P1NP levels were significantly increased, whereas serum TRACP-5b levels were either unchanged or decreased. During follow-up, no adverse events related to vitamin D administration were encountered.

Overall survivals

Figure 5 shows OS in the vitamin D–deficient group (25(OH)D < 20 ng/ml) and vitamin D–insufficient/sufficient group (25(OH)D ≥ 20 ng/ml). Median durations of follow-up for all patients from vitamin D measurement and from diagnosis of MM were 4.8 years (range, 0.2–5.0 years) and 7.8 years (range, 1.1–20.0 years), respectively. OSs from both vitamin D measurement and diagnosis of MM were significantly worse in the vitamin D–deficient group than in the vitamin D–insufficient/sufficient group ($p = 0.03$). Conversely, no significant differences in OS from vitamin D measurement or diagnosis of MM were evident between groups with and without vitamin D supplementation (Fig. 6).

Discussion

To the best of our knowledge, this is the first study in Japan to assess the distribution of serum vitamin D levels in MM patients. This study made three important clinical observations.

First, Japanese patients with MM showed a high prevalence of vitamin D deficiency. In our cohort, the majority of patients (84%) had less-than-sufficient levels of serum vitamin D (25(OH)D < 30 ng/ml), with one-third (32%) deficient in vitamin D (25(OH)D < 20 ng/ml) and an additional 52% with insufficient levels of vitamin D (25(OH)D 20–29 ng/ml). Median serum 25(OH)D level for the whole cohort was 22 ng/ml (IQR, 18.8–26.3 ng/ml). In a large cohort study of Japanese women over 50 years old (the JPOS study, $N = 1211$), only 10% of participants had sufficient levels of vitamin D (25(OH)D ≥ 30 ng/ml), while 52% and 38% had vitamin D deficiency (25(OH)D < 20 ng/ml) and insufficiency (25(OH)D 20–29 ng/ml), respectively [10]. Another Japanese general population–based cohort study (the ROAD study, $N = 1683$) showed that only 19% of the Japanese population had sufficient vitamin D levels

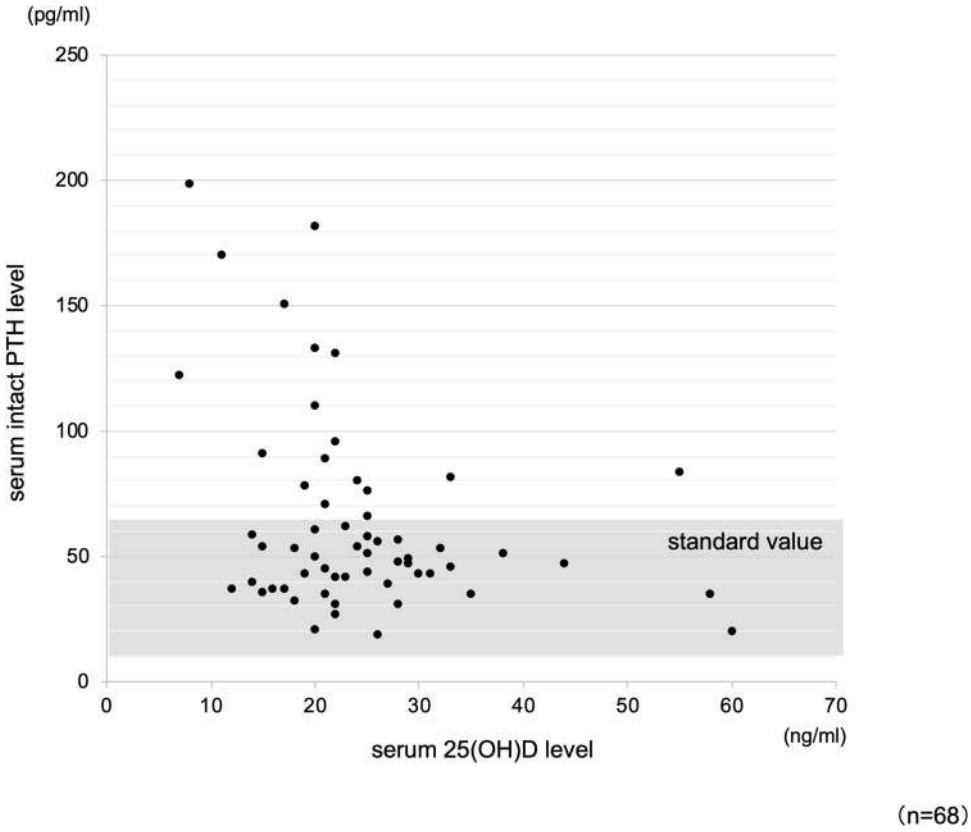

Fig. 2 Correlation between serum intact PTH and serum 25(OH)D levels. PTH, parathyroid hormone

(25(OH)D ≥ 30 ng/ml) and mean serum 25(OH)D level was 23.4 ng/ml [24]. On the other hand, several studies from Western countries have reported on serum vitamin D status in MM patients [25–30]. In those studies, although the criteria for vitamin D deficiency and insufficiency differed between studies, 25(OH)D levels < 20 ng/ml and < 30 ng/ml were reported in 24–31% and 72–87% of MM patients, respectively. Given such results, the distribution of serum 25(OH)D levels in Japanese MM patients seems similar to those in the general Japanese population and MM patients in Western countries.

Second, the present study found that serum vitamin D levels were not significantly associated with skeletal morbidity or bone turnover markers such as TRACP-5b or total P1NP. The relationship between vitamin D levels and bone complications in MM patients remains controversial. For example, Ng et al. reported that the prevalence of vitamin D deficiency increased in parallel with higher International Staging System (ISS) stage among newly diagnosed MM patients, whereas no significant correlation was identified between vitamin D status and bone disease [27]. Badros et al. also reported that vitamin D deficiency was independent of bone disease in patients with newly diagnosed or relapsed MM [25]. However, in that study, serum bone alkaline phosphatase (bALP), as a marker of bone formation, and intact PTH levels were higher in vitamin D–deficient patients than in vitamin D–sufficient patients. Furthermore, Diamond et al. demonstrated a significantly higher urinary deoxypyridinoline excretion rate and lower dual-energy X-ray absorptiometry *T*-score were observed in vitamin D–deficient MM patients [29]. The exact reasons for the discrepancies in results between the present study and previous investigations are unclear. However, one possible explanation may be that our study mainly included relapsed and/or refractory MM patients with different disease status and treatment schedules. In fact, many patients in our cohort had recently been treated with bortezomib and/or bone-targeted drugs such as bisphosphonates and denosumab.

In addition, we found that MM patients with suboptimal 25(OH)D levels who received vitamin D nutritional guidance, including cholecalciferol supplementation (1000 IU/day), subsequently showed elevated serum 25(OH)D levels with decreased serum levels of intact PTH. Notably, in patients who achieved complete remission of MM, serum levels of total P1NP, a marker of bone formation, increased significantly after vitamin D restitution, whereas TRACP-5b, a marker of bone resorption, decreased or remained unchanged. Lipe et al. have also demonstrated that, in patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM, oral calciferol supplementation (6000 IU/day for 8 weeks, followed by 2000 IU/day) improved bone metabolism markers such as

Table 1 Clinical characteristics of patients ($n=68$)

	Vitamin D deficient $n=22$	Vitamin D insufficient $n=35$	Vitamin D sufficient $n=11$	p value
Sex, *n* (%)				0.68
Male	11 (50.0)	13 (37.1)	5 (45.5)	
Female	11 (50.0)	22(62.9)	6 (54.5)	
Median age, years (range)	68 (55–83)	68 (48–93)	69 (57–77)	0.94
Duration from diagnosis of MM, years (range)	3.6 (0.4–15.3)	4.1 (0.3–15.1)	3.9 (0.9–9.2)	0.77
ISS stage, *n* (%)				0.41
1	7 (31.8)	11 (31.4)	5 (45.5)	
2	9 (40.9)	9 (25.7)	1 (9.0)	
3	4 (18.2)	12 (34.3)	5 (45.5)	
Unknown	2 (9.1)	3 (8.6)	0	
Durie-Salmon stage, *n* (%)				0.21
I	5 (22.7)	4 (11.4)	2 (18.2)	
II	10 (45.5)	8 (22.8)	2 (18.2)	
III	7 (31.8)	21 (60.0)	7 (63.6)	
Unknown	0	3 (8.6)	0	
Bone scale, *n* (%)				0.49
0	3 (13.6)	8 (22.8)	3 (27.3)	
1	4 (18.2)	5 (14.3)	0	
2	5 (22.7)	10 (28.6)	1 (9.1)	
3	10 (45.5)	12 (34.3)	7 (63.6)	
Status of MM disease, *n* (%)				0.78
CR	5 (22.7)	11 (31.4)	5 (45.5)	
PR	6 (27.3)	8 (22.8)	2 (18.2)	
SD	7 (31.8)	9(25.7)	1 (9.1)	
PD	4 (18.2)	7 (20.0)	3 (27.3)	

Vitamin D deficiency is defined as 25(OH) D < 20 ng/ml, insufficiency is defined as 25(OH) D 20–29 ng/ml, and sufficiency as 25(OH) D ≥ 30 ng/ml. *ISS*, International Staging System; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease

receptor activator of nuclear factor-kappa B ligand/osteoprotegerin, while reducing disease activity markers [31]. Meanwhile, in MM patients, several reports have indicated that serum bALP increased during bortezomib treatment and that the degree of increase was related to treatment response [32–34]. Importantly, Kaiser et al. revealed upregulation of VDR signaling as a mechanism for bortezomib-induced stimulation of osteoblastic differentiation [35]. In addition, serum 25(OH)D levels are reportedly associated with a sustained appropriate response to bisphosphonate treatment in postmenopausal osteoporotic women [36–38]. Taking these findings together, vitamin D supplementation could help achieve optimal bone formation in patients with plasma cell neoplasms. Further research is needed to clarify whether appropriate vitamin D replacement can reduce the residual risk of bone complications in MM patients.

The third important finding of this study was that in our Japanese MM cohort, patients with vitamin D deficiency (25(OH)D < 20 ng/ml) exhibited significantly worse OS compared to patients with insufficient/sufficient vitamin D levels (25(OH)D ≥ 20 ng/ml). Several retrospective studies in Western countries have shown associations between vitamin D status and prognosis in MM patients. For example, Rakhee et al. showed that low pre-transplant serum 25(OH) D levels (< 23 ng/ml) were related to inferior OS in MM patients undergoing high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) [39]. Eicher et al. also reported that MM patients with lower serum 25(OH)D levels (< 25 ng/ml) had inferior progression-free survival and OS in the HDC with ASCT setting [40]. More recently, Yellapragada et al. evaluated a large number of MM patients ($N=1889$) in the Veterans Affair's nationwide database and revealed that patients with lower serum 25(OH) D levels (< 20 ng/ml) experienced significantly worse OS than patients with normal levels [26]. Interestingly, such a survival effect of vitamin D levels was observed only in Caucasian Americans, not in African Americans. This observation indicates the presence of ethnicity-related disparities in the association between vitamin D levels and prognosis among MM patients. Although several in vitro studies have shown direct or indirect anti-myeloma effects of vitamin D [35, 41–43], the exact reasons for these survival differences according to serum vitamin D concentrations and ethnic backgrounds remain unclear. On the other hand, no reports

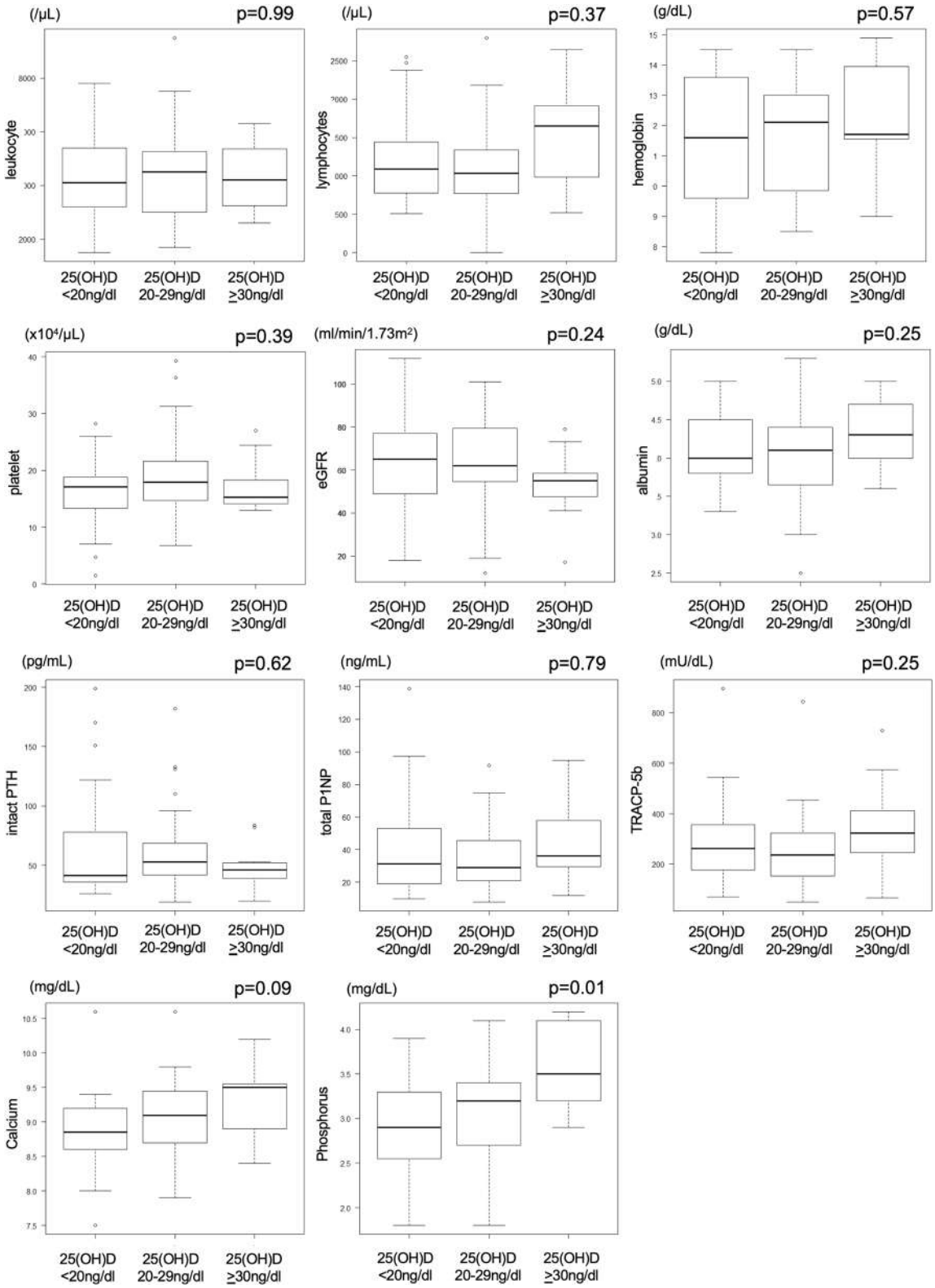

Fig. 3 Differences in laboratory parameters and HR-QOL scores between vitamin D–deficient, –insufficient, and –sufficient groups. HR-QOL, health-related quality of life; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; P1NP, procollagen type 1 N-propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b; EQ-5D-5L, EuroQol 5 dimensions 5 level; VAS, visual analogue scale

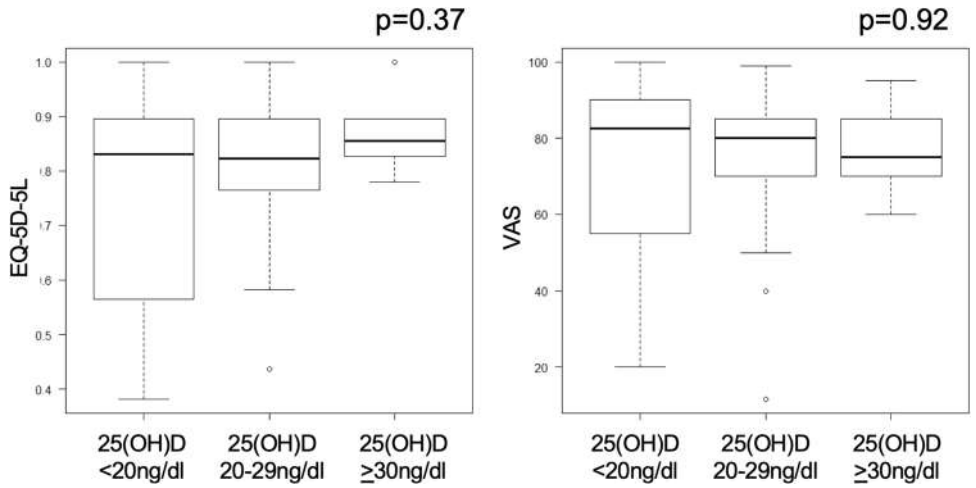

Fig. 3 (continued)

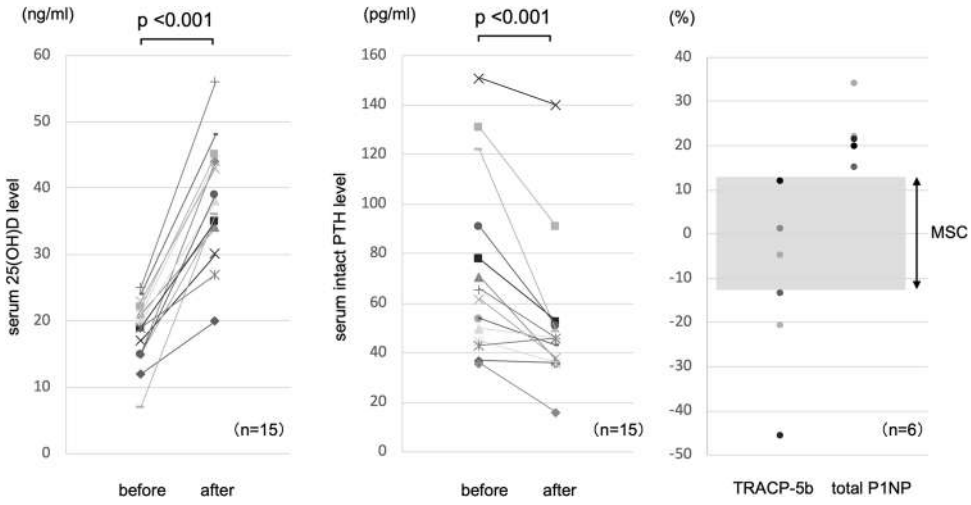

Fig. 4 Changes in bone metabolism parameters before and after vitamin D nutrition guidance. PTH, parathyroid hormone; P1NP, procollagen type 1 N-propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b; MSC, minimum significant change

to date (including the present study) have shown that vitamin D supplementation actually improves the prognosis of MM patients. Since serum vitamin D levels are primarily affected by exposure to both ultraviolet radiation and dietary sources, low serum levels of vitamin D may simply reflect reduced outdoor activity and malnutrition, which are likely surrogate markers associated with "frailty" in MM patients. Indeed, in our cohort, some vitamin D–deficient MM patients had lower HR-QOL scores on questionnaires, although the difference was not statistically significant. Whether vitamin D supplementation can overcome the poor survival and frailty of MM patients with vitamin D deficiency should be investigated in further prospective studies.

Some limitations of this study need to be recognized. First, our study was limited by the relatively small cohort from a single-center referral population (Gunma Prefecture, located in the northern part of the Kanto region in Japan). The hours of sunshine in Gunma prefecture are relatively long in Japan (approximately 2400 h/year). Therefore, the results of this study may not be fully generalizable to the entire Japanese population. Second, serum 25(OH)D levels in this study were measured only once in each patient during the winter season, so whether seasonal changes in vitamin D levels were associated with bone disease or prognosis remains unclear. Third, the present data were collected from patients with relapsed and/or refractory MM, and serum 25(OH)D levels were measured during or after MM treatment. The clinical setting thus differed from those of previous studies described above [26, 39, 40]. Meanwhile, our results indicate that serum vitamin D levels are associated with the prognosis of MM patients, regardless of the time of measurement. Additional studies with a larger number of uniformly treated patients are warranted to confirm and expand on these preliminary findings.

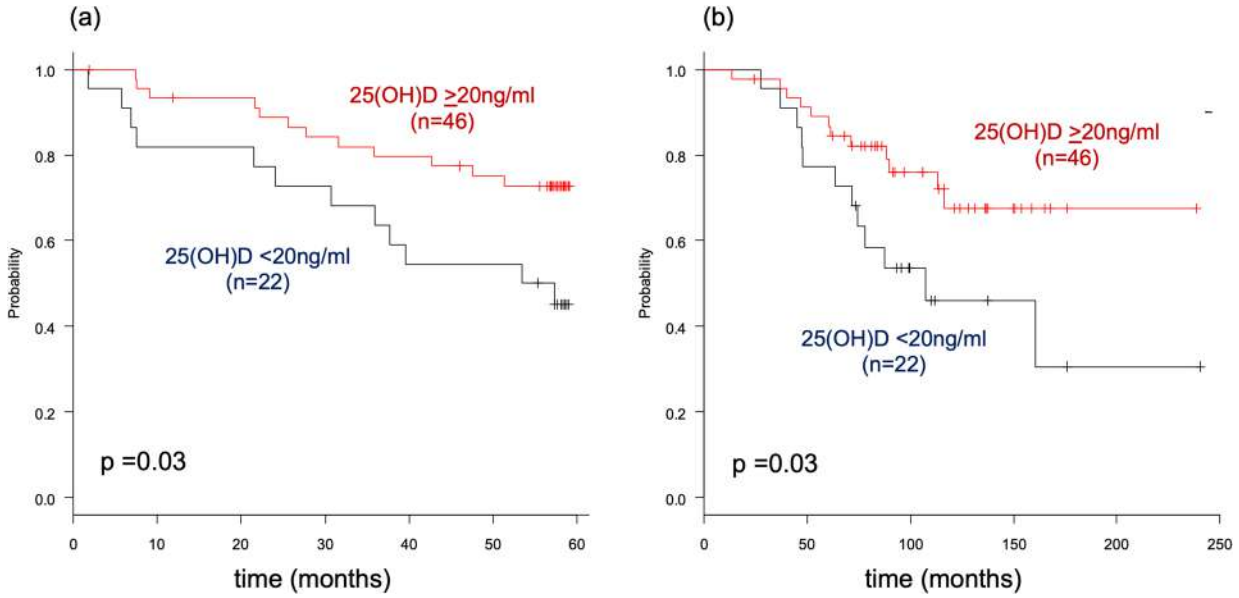

Fig. 5 Overall survival in vitamin D–deficient group (25(OH)D < 20 ng/ml) and vitamin D–insufficient/–sufficient group (25(OH)D ≥ 20 ng/ml). Overall survival from 25(OH)D measurement (**a**) and overall survival from MM diagnosis (**b**). MM, multiple myeloma

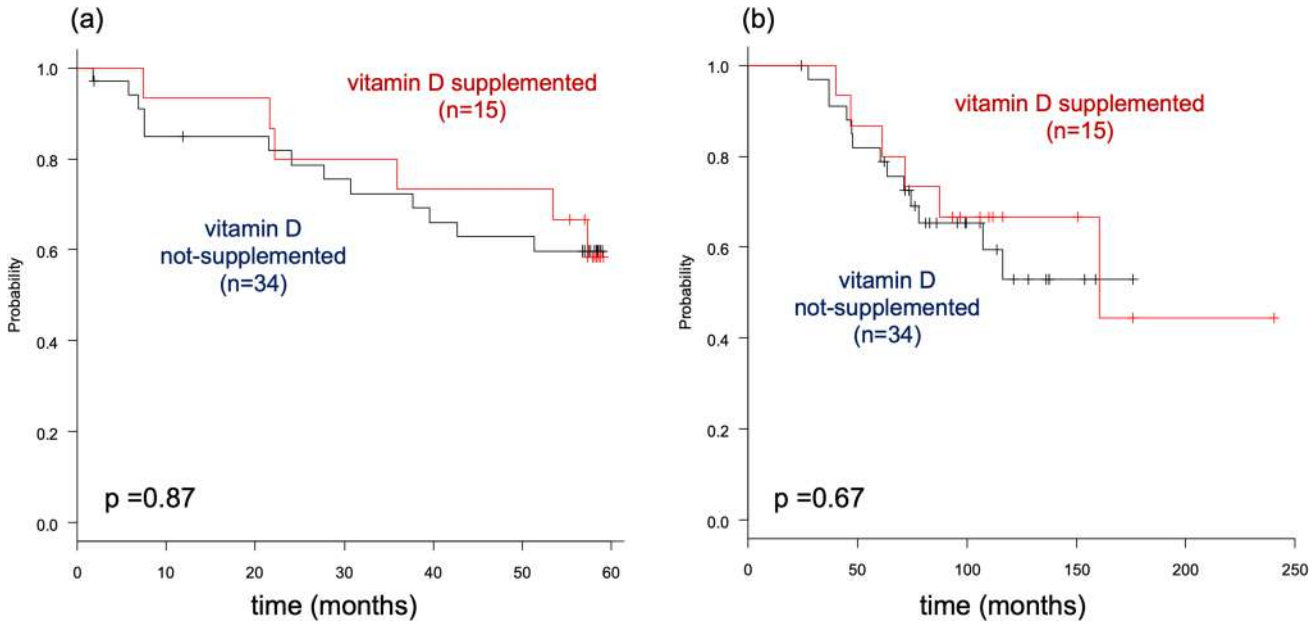

Fig. 6 Overall survival in vitamin D–supplemented group and vitamin D–not-supplemented group. Overall survival from 25(OH)D measurement (**a**) and overall survival from MM diagnosis (**b**). MM, multiple myeloma

Conclusion

Our study revealed that most (84%) Japanese MM patients had less-than-sufficient levels of serum vitamin D (25(OH)D < 30 ng/ml) and one-third (32%) had outright deficiency (25(OH)D < 20 ng/ml). Serum vitamin D levels were not significantly associated with skeletal morbidity or bone turnover markers, but vitamin D–deficient MM patients experienced significantly worse OS than vitamin D–insufficient/sufficient MM patients. Serum 25(OH)D levels could therefore offer a useful prognostic marker in Japanese MM patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-023-08021-w.

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Author contribution A. Isoda designed the research study and analyzed data. All authors enrolled patients and performed the research. The first draft of the manuscript was written by A. Isoda and all authors commented on previous versions of manuscript. All authors read and approved the final manuscript.

Data availability The datasets generated and/or analyzed during the current study are available upon request to the corresponding author and after appropriate ethical approval.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. All study protocols were reviewed and approved by the ethics review board at Nishigunma Hospital (approval nos. 15-11-04, 16-01-03) and the study was registered to the University Hospital Medical Information Network Clinical Trials Registry (UMIN000042804).

Consent to participate All participants provided written informed consent prior to participation.

Consent for publication N/A.

Competing interests M. Matsumoto received an honorarium from Janssen Pharmaceutical and Sanofi K.K.

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