Vitamin D Deficiency in Oncology Patients – an Ignored Condition: Impact on Hypocalcemia and Quality of Life

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ABSTRACT: **Background:** Vitamin D status is not evaluated routinely in cancer patients with bone metastasis who are treated with bisphosphonates.

Objectives: To assess the effect of vitamin D status on risk of hypocalcemia and quality of life in these patients.

Methods: We performed laboratory tests for routine serum biochemistry, 25(OH)D, plasma parathyroid hormone (PTH) and bone turnover markers (CTX, P1NP) in 54 patients aged 57.5 ± 13 years treated with intravenous bisphosphonates.

Results: Most of the patients (n=44, 77.8%) did not receive calcium and vitamin D supplementation. Their mean serum 25(OH)D levels (12.83 ± 6.86 ng/ml) correlated with vitamin D daily intake ($P = 0.002$). In 53 patients (98.1%) 25(OH) D levels were suboptimal (< 30 ng/ml). Albumin-corrected calcium levels correlated with plasma PTH ($P = 0.001$). No correlation was observed between daily calcium intake and serum calcium ($P = 0.45$). Hypocalcemia was observed in one patient. Mean plasma PTH was 88.5 ± 65 ng/L. Plasma PTH correlated negatively with 25(OH)D serum levels ($P = 0.003$) and positively with P1NP ($P = 0.004$). Albumin-corrected calcium correlated negatively with P1NP (mean 126.9 ± 191 ng/ml) but not with CTX levels (mean 0.265 ± 0.1 ng/ml) ($P < 0.001$). There was no correlation among quality of life parameters, yearly sun exposure and 25(OH)D levels ($P = 0.99$).

Conclusions: Vitamin D deficiency is frequent in oncology patients with bone metastasis treated with bisphosphonates and might increase bone damage. Our results indicate a minor risk for the development of severe hypocalcemia in vitamin D-deficient patients receiving bisphosphonate therapy. Although vitamin D deficiency might have some effect on the quality of life in these patients, it was not proven significant.

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For Editorial see page 637

Bisphosphonates are the standard of care for preventing skeletal morbidity and treating hypercalcemia of malignancy in patients with bone metastases. In oncology patients bisphosphonates are used mainly to reduce the overall risk of skeletal complications in patients with skeletal metastasis from breast and other cancers [1]. There is some evidence that bisphosphonates might have an additional anti-tumoral effect [2]. Intravenous administration of bisphosphonates to patients with skeletal metastases may lead to life-threatening hypocalcemia. Using calcium and vitamin D supplementation in patients receiving intravenous bisphosphonates was not included in standard care protocols in oncology departments in Israel. Suboptimal levels of vitamin D [25(OH)D < 30 ng/ml] is a common condition that can lead to secondary hyperparathyroidism. Lower levels of 25(OH)D can lead to severe hypocalcemia, which is considered one of the side effects of bisphosphonates, but it is usually a mild and transient phenomenon. However, administration of bisphosphonates in combination with poor vitamin D status may lead to life-threatening hypocalcemia. Oncology patients usually suffer from loss of appetite and reduced sun exposure and are therefore likely to have suboptimal levels of vitamin D. Apart from hypocalcemia, vitamin D deficiency correlates with muscle pain, decreased muscle strength, and mood changes. However, routine evaluation of vitamin D status and vitamin D supplementation is not included in the national or international guidelines for bisphosphonate treatment of metastatic bone diseases.

The aim of this work was to assess vitamin D status in oncology patients with bone metastasis treated by means of intravenous bisphosphonates, as well as the risk of these patients to develop hypocalcemia. In addition, an attempt was made to assess a possible impact of vitamin D deficiency on the quality of life in this population.

PATIENTS AND METHODS

Patients with various types of solid tumors and bone metastases who were treated in the Oncology Division of Rambam

Health Care Campus and received at least one dose of intravenous pamidronate 90 mg or zolendronate 4 mg every 3 or 4 weeks were enrolled in this cross-sectional study between September 2006 and June 2007. Exclusion criteria included prior hypercalcemia and ECOG performance status [3] grade 4. All patients with abnormal liver enzyme levels (aspartate aminotransferase and alanine aminotransferase > 50 IU/L) were excluded from the study.

The treatment policy and follow-up of these patients were not modified due to their inclusion in the study. The current instructions for the follow-up of these patients at the Rambam Health Care Campus oncology division were that before the first dose of bisphosphonate, serum calcium, magnesium, phosphate, albumin and creatinine levels be routinely checked. Serum creatinine was also routinely checked before each subsequent bisphosphonate dose. Serum calcium was corrected according to the albumin level [4]. All the tests were repeated according to clinical needs, and additional relevant measurements were performed. After each bisphosphonate dose and before discharging a patient, albumin-corrected calcium level was checked. In case of albumin-corrected serum calcium > 8 mg/dl no immediate action was taken. Patients with albumin-corrected serum calcium levels between 7.0 and 8 mg/dl and symptoms of hypocalcemia (parasthesias, Chvosteck and/or Trusseau symptoms positive) and those with levels < 7 mg/dl were hospitalized and treated accordingly. Hypocalcemia was treated according to standard guidelines. Oral calcium and vitamin D supplementation was not routinely recommended.

The study was approved by the local ethics committee, and all patients gave a written informed consent. Each patient completed a questionnaire on calcium and vitamin D consumption and sun exposure. Vitamin D and calcium intake were assessed using a food frequency questionnaire adjusted for local nutritional habits [5]. Oral calcium and/or vitamin D supplementation (200 IU of vitamin D and 600 mg calcium) were included in the assessment of the total intake. Sun exposure was assessed using the specially designed formula that is a product of:

- **Duration of sun exposure:** exposed body area was calculated according to a diagram depicting the relative percentage of the total body surface area of defined anatomic areas (used routinely to assess burn size)
- **Daily sun exposure:** every hour of sun exposure received a score of 1–3. For this measurement we used an ultraviolet index, which is an accepted measure of ultraviolet radiation. According to international data the average radiation intensity at noon is about three times higher than the rest of the day
- **Yearly sun exposure:** all data collected on sun exposure habits during the summer received a double weight compared to the corresponding figures during the winter. This is based on the assumption that the strength of summer sun UVB irradiation is at least twice that in the winter
- **Skin color of participants:** classified according to Fitzpatrick, with a score of -1 to 6 [6]. The formula is presented in Figure 1.

Figure 1. Formula for evaluation of sun exposure

[Sun exposure during winter {[(3-face exposure)*8+(3-neck exposure)*1+(3-cubits exposure)*3.5+(3-arms exposure)*4.5+(3-hands exposure)*1+(3-thighs exposure)*9+(3-cnemises exposure)*9]/72} * {daily sun exposure (minutes) in winter/750 (between 11 pm and 3 am the minutes are multiplied by 3)}*100/3 + 2 x Sun exposure during summer {[(3-face exposure)*8+(3-neck exposure)*1+(3-cubits exposure)*3.5+(3-arms exposure)*4.5+(3-hands exposure)*1+(3-thighs exposure)*9+(3-cnemises exposure)*9]/72} * {daily sun exposure (minutes) in summer/750 (between 11 pm and 3 am the minutes are multiplied by 3)}*100/3] x [use of sunscreen cream (1-2)] x[(7-grade of skin color)]

The patients were asked to answer questions related to four parameters relating to quality of life: physical performance, social life, mental health, and vitality. Coding was done according to the information found at the official internet site of SF-36. All the study procedures were performed during one visit.

LABORATORY ASSESSMENT

Serum calcium, inorganic phosphate, creatinine, albumin, and liver enzymes were assessed by standard laboratory techniques (Hitachi 747, Roche); 25(OH)D by ^{125}I-radioimmunoassay (DiaSorin, Stillwater, MN, USA), PTH (Intact) STAT (Roche Diagnostics GmbH, Mannheim, Germany), bone turnover markers: CTX (serum C-terminal telopeptide of type 1 collagen) and P1NP (pro-collagen type 1 nitrogenous propeptide) were measured using kits of Cobas E411 (Roche Diagnostics GmbH). Serum calcium levels were corrected for albumin: albumin-corrected calcium = [0.8 x (4-patient's albumin)] + serum Ca.

STATISTICAL ANALYSIS

To examine the association between two quantitative variables, Pearson's linear correlation coefficient was calculated. Fisher's exact test and chi-square test were used to detect the association between categorical variables. Pearson's correlation was used to demonstrate a linear relation between quantitative variables. Homogeneity, normality and outlying observations were examined. The non-parametric Mann-Whitney U test and the Kruskal-Wallis test were applied to compare differences in quantitative variables between categorical variables. $P < 0.05$ was considered significant.

UVB = ultraviolet B

RESULTS

Fifty-four consecutive patients in Rambam's Department of Oncology were enrolled in the study. Patients' characteristics are presented in Table 1. The mean age was 57.5 ± 13 (range 32–85 years). Breast cancer was the most common diagnosis. Most of the patients had good ECOG performance status, and most received pamidronate.

Forty-four patients (77.8%) had not received calcium and/or vitamin D supplementation. Only one patient had severe but asymptomatic hypocalcemia (albumin-corrected calcium < 7 mg/dl). The hypocalcemia was promptly treated and there were no complications.

The range of 25(OH)D levels was -5 to 31 ng/ml, mean 12.83 ± 6.86. Fifty-three patients (98.1%) had suboptimal levels of vitamin D, 25(OH)D < 30 ng/ml: 25 patients (40.7%) had 25(OH)D levels < 10 ng/ml; 13 (24%) had levels between 10 and 15 ng/ml; only one patient (1.9%) had an adequate vitamin D level of 30 ng/ml. Among patients who received intravenous zoledronate, 25(OH)D < 10 ng/ml was observed less frequently, compared to pamidronate-treated patients, 1 (11%) vs. 18 (53%) respectively ($P = 0.002$).

Consumption of vitamin D ranged from 91 to 2037 IU daily, mean consumption of vitamin D (including vitamin D supplementation) was 491 ± 387 IU. Serum levels of 25(OH) D correlated positively with vitamin D supplementation ($P = 0.002$) and with vitamin D daily consumption (from food and oral supplements) ($P = 0.02$), and negatively with plasma PTH levels ($P = 0.003$). Patients' age, gender, primary tumor site, performance status, duration of the malignant disease, sun exposure, levels of serum inorganic phosphorus albumin-corrected calcium and total daily calcium consumption did not correlate with serum 25(OH)D levels. Mean albumin-corrected calcium was 9.2 ± 0.66 mg/dl (range 6.7–10.7 mg/dl, normal range 8.4–10.5 mg/dl). Only one patient had symptomatic severe hypocalcemia (albumin-corrected calcium 6.7 mg/dl). This patient was treated promptly, with correction of calcium levels. Albumin-corrected calcium correlated negatively with plasma PTH ($P = 0.001$, $r = -0.618$). No correlation was found between albumin-corrected calcium and 25(OH)D. Mean calcium consumption from food was 841 ± 708.7 mg; mean total calcium consumption (including calcium supplements) was 1033 ± 723 mg. Daily calcium consumption did not affect serum calcium level ($P = 0.45$). Mean plasma PTH was 88.5 ± 65 ng/L (range 23–289, normal range 12–65 ng/L). PTH was inversely related to serum 25(OH)D level ($P = 0.003$). There was a negative correlation between PTH and serum levels of inorganic phosphate ($P = 0.067$, $r = -0.251$). A positive correlation was also found between serum PTH levels and levels of P1NP ($r = 0.388$, $P = 0.004$) and serum alkaline phosphatase ($r = 0.316$, $P = 0.02$). The number of bisphosphonate treatments did not correlate with the PTH level ($P = 0.764$). Mean alkaline phosphatase was 155.8 ± 217 IU/L (range 11–1076, normal range 44–120). There was a negative correlation between albumin-corrected calcium levels and ALP ($r = -0.522$, $P = 0.002$).

Table 1. Concomitant diseases, current oncological treatment and ECOG performance status in 54 patients with primary malignancies and bone metastases receiving intravenous bisphosphonates

Men/women	**19/35 (35.1/65.9%)**
Time interval from diagnosis of cancer to entering the study	2 mos–10 yrs, median 35 ± 30.6 mos
Time from the diagnosis of bone metastases	0–87 mos, mean ± SD 20 ± 19 mos
Type of primary tumor	No. (%)
Breast carcinoma	29 (53.7)
Lung (non-small and small) carcinoma	14 (25.9)
Prostate carcinoma	6 (11.1)
Gastrointestinal (n=2) carcinomas and carcinoids (n=2)	4 (7.4)
Renal cell carcinoma	1 (1.9)
All	54 (100)
Comorbidities	
None	13 (24)
Cardiovascular diseases	21 (38.8)
Osteoporosis	6 (11.1)
Diabetes mellitus	5 (9.25)
Other	25 (46.2)
Current oncological treatment	
Chemotherapy^	39 (72.2)
Radiotherapy	8 (14.8)
Hormonal therapy*	6 (11.1)
Best supportive care alone	1 (1.9)
All	54 (100)
ECOG performance status (grade)	
0–1	20 (37)
2	23 (42.5)
3	11 (20.5)
Bisphosphonate given#	
Pamidronate 90 mg every 3–4 wks	34 (62.9)
Zoledronate 5 mg every 3–4 mos	9 (16.7)
Zoledronate after pamodronate	9 (16.7)
Patients receiving calcium carbonate 1500 mg + vitamin D 200 IU daily	12 (22.2)

^ Five patients had chemotherapy + Herceptin®, 2 patients had radiotherapy+hormonal therapy
# For 2 patients (3.7%) it was not known which intravenous bisphosphonates had been given in other medical facilities before the patients came to our hospital
* Androgen deprivation treatment, SERMS

PTH = parathyroid

ALP = alkaline phosphatase

Mean plasma CTX level was 0.265 ± 0.1 ng/ml (range 0.01–1.8, within the premenopausal range of 0.14–0.299 ng/ml) and was not correlated with albumin-corrected calcium. Mean plasma P1NP level was 126.9 ± 191 ng/ml (range 6.1–1028, normal premenopausal range 20–100). There was a correlation between serum ALP and CTX levels ($r = 0.381$, $P = 0.01$), and between ALP and P1NP levels ($r = 0.82$, $P < 0.001$). A negative correlation was found between serum albumin-corrected calcium and P1NP ($r = -0.518$, $P < 0.001$). There was no correlation between yearly sun exposure and 25(OH)D levels ($P = 0.99$).

Patients who received pamidronate had a mean yearly sun exposure of 70.89 ± 99.15 (range 0.8–172.5). Patients who took zoledronic acid had a mean yearly sun exposure of 78.22 ± 64.48 (range 15.5–215.8); the difference between the groups was not significant.

Physical functioning, vitality, social functioning, and mental health scores were lower in the study patients than in the general population [Figures 2 and 3]. No correlations were found between quality of life parameters and 25(OH)D levels.

Figure 2. Quality of life parameters. Black line represents the general population mean, and the bars represent our patients' mean. PF = physical functioning, VT = vitality, SF = social functioning, MH = mental health

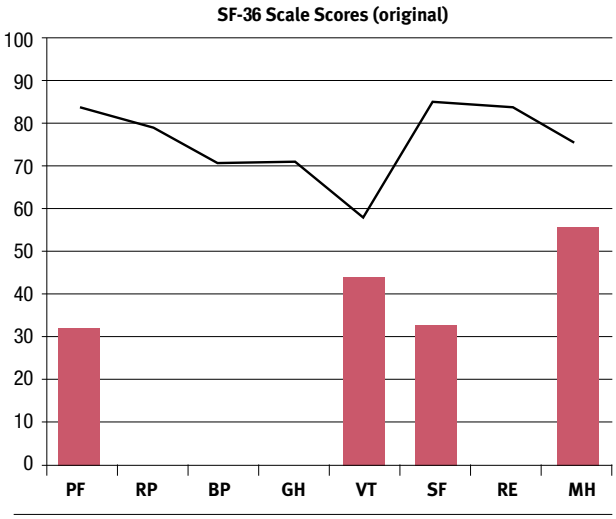
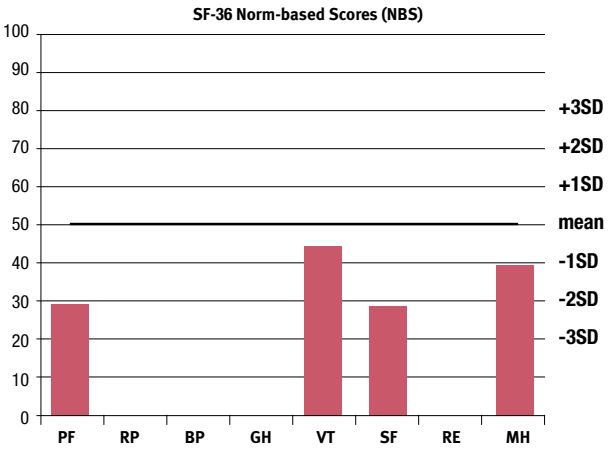


Figure 3. Quality of life parameters. Horizontal line represents the general population mean, and the bars represent our patients' mean. PF = physical functioning, VT = vitality, SF = social functioning, MH = mental health



DISCUSSION

In the current study bisphosphonates were given to reduce the risk of skeletal metastasis-related events. Although oral calcium and vitamin D supplementation has been recommended for cancer patients treated with intravenous bisphosphonates [7], only 12 patients (22.2%) received daily supplementation with 600 mg of calcium carbonate and 200 IU of vitamin D. We found a very high proportion of patients with low 25(OH)D serum levels. In fact, all the patients but one (98%) had suboptimal levels of vitamin D, while about 40% were vitamin D deficient. A high prevalence of vitamin D deficiency in cancer patients has been reported. In a study [8] of 7437 patients and another study [9] of 1536 patients, 87% and 52% of patients respectively had 25(OH)D levels < 30 ng/ml. In the first-mentioned study [8] 15.5% of the patients were vitamin D deficient. In another study [10] 82% of patients were found to be vitamin D insufficient with 25(OH)D levels < 30 ng/ml, while 50% had vitamin D deficiency (25(OH)D levels < 20 ng/ml). One possible explanation for the frequent finding of vitamin D deficiency in the current series is that cancer patients suffering from a metastatic disease and who have a poor quality of life are less exposed to sun.

The role of vitamin D concentration and cancer risk is poorly understood and the data are conflicting. A significant inverse association was found [11] between serum 25(OH)D concentration and post-menopausal breast cancer risk; the relationship was non-linear, suggesting a stronger effect in women with low 25(OH)D concentrations as compared to women with higher concentrations. Based on these data, supplementation with vitamin D seems logical and useful, especially for patients with high risk for both breast cancer and vitamin D deficiency. Noteworthy is a report from the Women's Health Initiative [12], which failed to identify a beneficial effect of vitamin D supplementation (at a lower dose of 400 IU/day) on breast cancer risk compared to a placebo. Since cancer patients are often prescribed numerous medications they may try to avoid additional medication or supplement use, including vitamin D. Our patients consumed less than 500 IU of 25(OH)D daily, while the recommended daily consumption of vitamin D to prevent osteoporosis is 800–1000 IU [13] and 600–800 IU daily according to the recent Institute of Medicine recommendation [14]. According to Heaney [15], at low calcium intakes the net

calcium absorption is low, irrespective of vitamin D status, and can even be negative when endogenous secretion is greater than gross absorption. To correct for the impaired calcium absorption, in the state of vitamin D deficiency plasma PTH levels rise and secondary hyperparathyroidism develops [9,16,17], leading to an increase in 1,25(OH)2D3 serum levels to compensate for the calcium deficit caused by low vitamin D levels, but this increases bone loss and bone fragility and may impair mineralization of the newly formed bone [18]. Development of secondary hyperparathyroidism might explain the fact that of our 54 bisphosphonate-treated patients only 1 presented with significant hypocalcemia. The only parameter that was negatively correlated with serum calcium level in our study was PTH level ($P < 0.001$, $r = -0.618$). Neither 25(OH)D serum levels nor daily calcium consumption and calcium supplementation were correlated with albumin-corrected serum calcium levels. In patients with bone metastases any additional factor leading to bone deterioration could be extremely important. It is now generally accepted that vitamin D deficiency is associated with poor muscle function [19] as well as with depressive mood [20]. Our cross-sectional small study dealt with an oncology population heterogenic in age, disease stage, general health condition and concomitant diseases. In this situation it was impossible to assess the isolated influence of vitamin D status. However, vitamin D deficiency and insufficiency could, at least partly, be reflected by a poor quality of life in our patients, despite the absence of a significant link between 25(OH)D levels and quality of life parameters. Vitamin D deficiency was also found to be related to a poorer prognosis in lymphoma patients [21].

Supplementation with vitamin D is a major factor influencing serum 25(OH)D levels. Consumption of every 100 IU of vitamin D from supplements may raise serum 25(OH)D levels by 1 ng/ml, which means that relatively high doses of vitamin D are needed to substantially increase serum levels in vitamin D-deficient and insufficient patients. The unpredictable relationship between vitamin D intake and blood levels [12] (likely reflecting individual variability in diet, absorption, metabolism and adiposity, and in sun exposure as an alternate source of vitamin D) makes it difficult to recommend a standard supplement dose and supports incorporating serum level measurement in the recommendations [22].

Like others [23], we found hypocalcemia to be a rare complication of treatment with bisphosphonates. We can only speculate that the negative correlation between serum albumin-corrected calcium levels and ALP and P1NP levels may be due in part to the stimulating PTH effect on the osteoblasts, which might deposit a poorly mineralized matrix that may correspond to an increase in osteoblastic bone turnover markers (ALP and P1NP) in a situation of decreased serum calcium level due to poor calcium absorption. Additional studies are needed to confirm this finding and to find possible mechanisms for this relationship.

In conclusion, deficient to suboptimal 25(OH)D serum levels were found in almost all the study participants. Vitamin D deficiency might further increase bone damage in these patients due to consequent sustained elevation of plasma PTH level. Although supplementation with vitamin D significantly increased serum 25(OH)D levels, the supplementation dose was insufficient to insure the vitamin D sufficiency state. Therefore, adequate vitamin D supplementation in this population is extremely important. Our results do not indicate a frequent and high risk for developing severe hypocalcemia in vitamin D-insufficient patients on bisphosphonate therapy. However, this possibility could not be ruled out with certainty due to the limitations of the design of this study. Vitamin D deficiency might have some influence on the quality of life in these patients, but in our study the correlation between them was not statistically significant.

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Capsule

Cytomegalovirus and tumor stress surveillance by binding of a human γδ T cell antigen receptor to endothelial protein C receptor

T cells bearing γδ T cell antigen receptors (TCRs) function in lymphoid stress surveillance. However, the contribution of γδ TCRs to such responses is unclear. Willcox et al. found that the TCR of a human Vγ4Vδ5 clone directly bound endothelial protein C receptor (EPCR), which allowed γδ T cells to recognize both endothelial cells targeted by cytomegalovirus and epithelial tumors. EPCR is a major histocompatibility complex-like molecule that binds lipids analogously to the antigen-presenting molecule CD1d. However, the Vγ4Vδ5 TCR bound EPCR independently of lipids, in an antibody-like way. Moreover, the recognition of target cells by γδ T cells required a multimolecular stress signature composed of EPCR and costimulatory ligand(s). These results demonstrate how a γδ TCR mediates recognition of broadly stressed human cells by engaging a stress-regulated self-antigen.

Nature Immunol 2012; 13: 872
Eitan Israeli

Capsule

Crucial cerebellar glial cells

The role of glial cells and their interaction with neurons in normal behavior is unclear. To address this question, Saab and associates studied a special type of glial cell in the cerebellum. Conditional mutant mice were produced in which the two glutamate receptor subunits normally present in Bergmann glial cells were efficiently ablated in a temporally controlled manner. Glutamate signaling of the glial cells contributed to the structural and functional integrity of the cerebellar network. Bergmann glial cells also played a role in the "fine-tuning" of neuronal processing, which is crucial for the fast and precise control of complex motor behavior.

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Capsule

Bio-inspired drug delivery

Noting that platelets naturally migrate to narrowed blood vessels characterized by high fluid shear stress, Korin et al. developed a nanoparticle-based therapeutic that uses a similar targeting mechanism to deliver a drug to vessels obstructed by blood clots. Aggregates of nanoparticles coated with the clot-dissolving drug tPA (tissue plasminogen activator) were designed to fall apart and release the drug only when encountering high fluid shear stress. In preclinical models, the bio-inspired therapeutic dissolved clots and restored normal blood flow at lower doses than free tPA, suggesting that this localized delivery system may help reduce the risk of side effects such as excessive bleeding.

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