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Original article

Changes in vitamin D after gastrectomy

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Abstract

Background. **We previously reported that the administration of 1α hydroxy vitamin D3 was effective for treating post-gastrectomy bone disorders. Accordingly, we performed the present study to obtain evidence supporting the effectiveness of 1α hydroxy vitamin D3 in post-gastrectomy patients.**

Methods. **The study involved 22 outpatients who had undergone gastrectomy for gastric cancer and had not been treated with 1α hydroxy vitamin D3 or calcium. They comprised 17 men and 5 women, with a mean age of 61.9 years. Laboratory tests were performed to examine the following parameters: $1,25(OH)_2$ vitamin D3; 25(OH) vitamin D3; $24,25(OH)_2$ vitamin D3; ionized calcium; calcium; phosphorus; alkaline phosphatase; N-parathyroid hormone; and osteocalcin.**

Results. **The level of $1,25(OH)_2$ vitamin D3, the most active of the vitamin D metabolites, was found to be normal in all of the patients. In contrast, the level of 25(OH) vitamin D3, which shows weak activity, was below the normal range in 7 of the 22 patients (31.8%). The mean serum level of 25(OH) vitamin D3 was significantly lower in patients at 1 year or more postoperatively than the level in those at less than 1 year postoperatively ($P = 0.041$), as well as being significantly lower in patients who had received total gastrectomy than in patients who underwent other gastrectomy procedures. The level of $24,25(OH)_2$ vitamin D3, a metabolite of 25(OH) vitamin D3 that shows weak activity, was below the normal range in 19 of the 22 patients (86.4%). On multivariate analyses, factors associated with the change in vitamin D metabolites did not remain.**

Conclusion. **The patients showed a decrease of 25(OH) vitamin D3 and $24,25(OH)_2$ vitamin D3, which are metabolites that show weak activity. This suggests that a homeostatic response maintains the normal level of $1,25(OH)_2$ vitamin D3, which is important for calcium regulation. Thus, it was suggested that gastrectomy had a moderate influence on the metabolism of vitamin D. However we could not detect any factor associated with the decrease of 25(OH) vitamin D3 and $24,25(OH)_2$ vitamin D3.**

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Key words Gastrectomy · Bone disorder · Vitamin D

Introduction

The occurrence of post-gastrectomy bone disorders has been explained in terms of impaired calcium (Ca) absorption, reduced milk intake, and decreased food intake [1]. As is done for patients with ordinary osteoporosis, Ca and vitamin supplements are administered to treat patients with post-gastrectomy bone disorders [2, 3]. As drugs that inhibit bone resorption by osteoclasts have also been developed recently [4, 5], a variety of treatment options is now available to manage bone disorders arising after gastrectomy for gastric cancer. It has been reported that the serum level of 25(OH) vitamin D3 is decreased and the serum level of $1,25(OH)_2$ vitamin D3 is increased in gastrectomy patients [6]. However, to the best of our knowledge, there have been no reports about changes in vitamin D3 (VD) metabolites. We previously reported that the administration of 1α hydroxy vitamin D3 (1α) was effective for treating post-gastrectomy bone disorders [7]. However, it has also been reported that the administration of such VD preparations has an adverse influence on bone metabolism [8]. Against this background, we performed the present study to obtain evidence to support the administration of 1α for treating post-gastrectomy bone disorders.

Patients and methods

The study involved 22 outpatients who had undergone gastrectomy for gastric cancer and had not been treated with 1α or Ca, and who gave informed consent for blood sampling for biochemistry tests. They comprised 17 men and 5 women, with a mean age of 61.9 years (range,

Table 1. Patient characteristics

Characteristic	Normal range	Mean ± SD (range)	No. of patients (*n*)
Male/female ratio			17/5
Age (years)		61.9 ± 12.7 (35–85)	
Surgical procedure	TG/B1/B2		4/13/5
Postoperative period (years)		3.4 ± 3.7 (0.2–13.8)	
$1,25(OH)_2VD$ (ng/ml)	20–76	50.0 ± 13.0 (21–75)	
25(OH)VD (ng/ml)	10–55	13.5 ± 5.1 (7–24)	
24,25(OH)2VD (ng/ml)	1.8–3.8	1.60 ± 1.13 (0.7–5.1)	
Ionized calcium (mEq/l)	2.21–2.52	2.51 ± 0.10 (2.30–2.70)	
Calcium (mEq/l)	4.25–4.90	4.58 ± 0.20 (4.05–4.90)	
P (mEq/l)	1.45–2.49	1.88 ± 0.32 (1.04–2.38)	
ALP (mU/ml)	79–224	243.1 ± 109.5 (139–650)	
N-PTH (pg/ml)	230–630	293.2 ± 173.6 (156–770)	
Osteocalcin (ng/ml)	1.5–6.5	10.1 ± 2.9 (7.3–18.0)	

35–85 years). Four patients had been treated by total gastrectomy, 13 had undergone subtotal Billroth-I gastrectomy, and 5 had received subtotal Billroth-II gastrectomy. The postoperative period until the beginning of the study ranged from 2 months to 14 years (Table 1). Because of the VD pathway, we performed laboratory tests to examine the following parameters: $1,25(OH)_2VD$ (normal range, 20–76 ng/ml); 25(OH)VD (normal range, 10–55 ng/ml); $24,25(OH)_2VD$ (normal range, 1.8–3.8 ng/ml); ionized Ca (normal range, 2.21–2.52 mEq/l); Ca (normal range, 4.25–4.90 mEq/l); phosphorus (P; normal range, 1.45–2.49 mEq/l); alkaline phosphatase (ALP; normal range, 79–224 mU/ml); N-parathyroid hormone (N-PTH; normal range, 230–630 pg/ml); and osteocalcin (normal range, 1.5–6.5 ng/ml).

Statistical analyses were performed using the χ^2 test, Student's *t*-test, and multivariate analysis. Statistical significance was defined as $P < 0.05$.

Results

The level of $1,25(OH)_2VD$, the most active of the VD metabolites, was found to be normal in all of the patients. That is, serum $1,25(OH)_2VD$ did not decrease over time after gastrectomy and was not affected by the type of gastrectomy procedure. In contrast, the level of 25(OH)VD, which shows weak activity, was below the normal range in 7 of the 22 patients (32%). One of the 6 patients (17%) tested at less than 1 year postoperatively had a 25(OH)VD below the normal range, versus 6 of the 16 patients (38%) tested at 1 year or more postoperatively, although the difference between the two groups was not statistically significant (Fig. 1). However, the mean serum level of 25(OH)VD was significantly lower in patients at 1 year or more postoperatively than in those at less than 1 year postoperatively ($P = 0.041$), as well as being significantly lower in patients

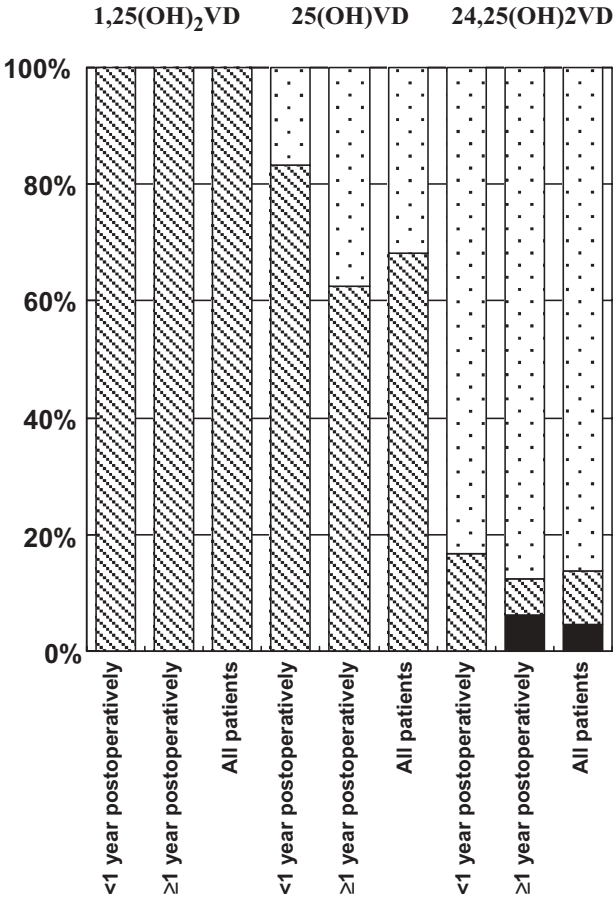

Fig. 1. Percentages of patients with low, normal, and high serum levels of $1,25(OH)_2$ vitamin D3 (VD), 25(OH)VD, and $24,25(OH)_2VD$. The serum level of $1,25(OH)_2VD$ was normal in all of the patients. The serum level of 25(OH)VD was lower than the normal range in 32% of the patients, including 17% of those at less than 1 year postoperatively and 38% of those at 1 year or more postoperatively. There was no significant difference between these two subgroups. The serum level of $24,25(OH)_2VD$ was lower than the normal range in 86% of the patients, including 83% of those at less than 1 year postoperatively and 88% of those at 1 year or more postoperatively. *White dotted bars*, low level; *striped bars*, normal level; *black bars*, high level

Table 2. Relation between vitamin D and surgery

Clinical factors	25(OH)VD	24,25$(OH)_2$VD	1,25$(OH)_2$VD	1,25$(OH)_2$VD/25(OH)VD	1,25$(OH)_2$VD/ 24,25$(OH)_2$VD	25(OH)VD/ 24,25$(OH)_2$VD
Surgical procedure						
TG	8.3 ± 1.3	0.98 ± 0.21	51.8 ± 9.2	6.5 ± 1.8	63.5 ± 25.1	9.6 ± 1.5
SG	14.6 ± 4.9	1.40 ± 1.07	49.6 ± 13.9	3.8 ± 1.7	48.2 ± 16.5	12.6 ± 4.3
	$P = 0.019$	NS	NS	$P = 0.010$	NS	NS
Duodenal passage						
Yes	14.9 ± 4.4	1.20 ± 0.57	47.8 ± 15.1	3.5 ± 1.5	48.0 ± 24.8	13.7 ± 4.1
No	11.3 ± 5.4	1.46 ± 1.42	53.2 ± 9.1	5.4 ± 2.0	55.4 ± 29.5	9.7 ± 2.7
	NS	NS	NS	$P = 0.020$	NS	$P = 0.018$
Postoperative period (years)						
<1	17.0 ± 5.8	1.92 ± 1.61	45.3 ± 16.8	2.9 ± 1.4	33.2 ± 19.4	11.6 ± 5.3
>=1	12.1 ± 4.2	1.08 ± 0.53	51.8 ± 11.4	4.8 ± 1.9	57.7 ± 26.0	12.2 ± 3.7
	$P = 0.041$	NS	NS	$P = 0.045$	NS	NS

who had received a total gastrectomy than in patients who had undergone the other gastrectomy procedures (Table 2). The level of 24,25$(OH)_2$VD, a metabolite of 25(OH)VD that shows weak activity, was below the normal range in 19 of the 22 patients (86%). The level of 24,25$(OH)_2$VD was below normal in 5 of the 6 patients (83%) at less than 1 year postoperatively, versus 14 out of 16 patients (88%) at 1 year or more. Although difference between the groups was not significant, one of the patients at 1 year or more postoperatively had a 24,25$(OH)_2$VD level above the normal range (Fig. 1). The mean 24,25$(OH)_2$VD level was lower, although not significantly so, in patients at 1 year or more postoperatively than in patients at less than 1 year postoperatively, as was the case for 25(OH)VD. The mean 24,25$(OH)_2$VD level was also lower, although not significantly so, in patients who had received a total gastrectomy (Table 2).

From a comparison of these three VD metabolites, the following results were obtained: the 1,25$(OH)_2$VD/25(OH)VD ratio was significantly higher after a total gastrectomy, after gastrectomy procedures avoiding the duodenal passage of food, and at 1 year or more postoperatively, while the 25(OH)VD/24,25$(OH)_2$VD ratio was significantly lower after gastrectomy procedures avoiding the duodenal passage of food (Table 2).

The ionized Ca level was above the normal range in 9 of the 22 patients (41%), and was not below the normal range in any of the patients. Calcium was below the normal range in 1 of the 22 patients (5%). Phosphorus was also below the normal range in 1 of the 22 patients (5%). The ALP level was above the normal range in 12 of the 22 patients (55%). N-PTH was above the normal range in 1 of the 22 patients (5%), but was below the normal range in 11 patients (50%; Fig 2).

The levels of ionized Ca, Ca, P, ALP, and N-PTH did not differ in relation to the postoperative period or the type of gastrectomy procedure. The osteocalcin level was above the normal range in all of the patients.

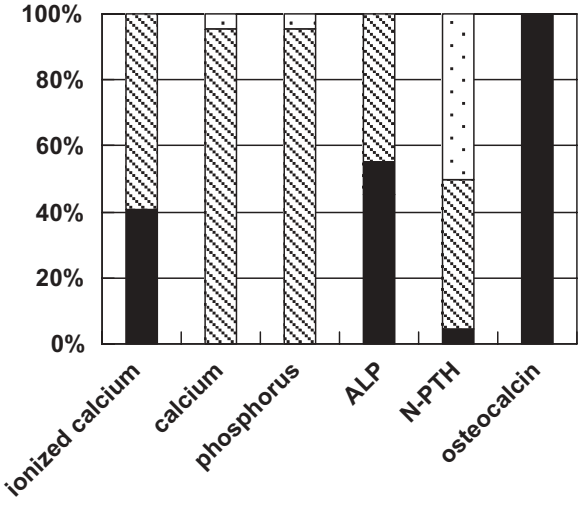

Fig. 2. Serum levels of ionized calcium, calcium, phosphorus, alkaline phosphatase (*ALP*), N-parathyroid hormone (*N-PTH*), and osteocalcin in gastrectomy patients. The serum level of ionized calcium was higher than the normal range in 9/22 patients (41%), and was not lower than the normal range in any of the patients. The serum calcium level was lower than the normal range in 1/22 patients (5%), and the serum phosphorus level was also lower than the normal range in 1/22 patients (5%). The serum ALP level was higher than the normal range in 12/22 patients (55%). The serum N-PTH level was higher than the normal range in 1/22 patients (5%), while it was lower than the normal range in 11/22 patients (50%). The serum osteocalcin level was higher than the normal range in all of the patients. *White dotted bars*, low level; *striped bars*, normal level; *black bars*, high level

On multivariate analyses, factors associated with the change in VD metabolites did not remain (Table 3).

Table 3. Multivariate analysis (logistic regression) of differences in surgical procedures, passage of food through the duodenum, and postoperative period after gastrectomy

Factor	Variable	Significance	Odds ratio
Surgical procedure			
	25(OH)VD (≧13 vs <13 ng/ml)	0.855	9179.8
	$1,25(OH)_2$VD/25(OH)VD (≧3 vs <3 ng/ml)	0.863	0.000
Duodenal passage			
	25(OH)VD/$24,25(OH)_2$VD (≧12 vs <12 ng/ml)	0.167	5.000
	$1,25(OH)_2$VD/25(OH)VD (≧3 vs <3 ng/ml)	0.251	0.278
Postoperative period			
	25(OH)VD (≧13 vs <13 ng/ml)	0.289	0.262
	$1,25(OH)_2$VD/25(OH)VD (≧3 vs <3 ng/ml)	0.647	1.658

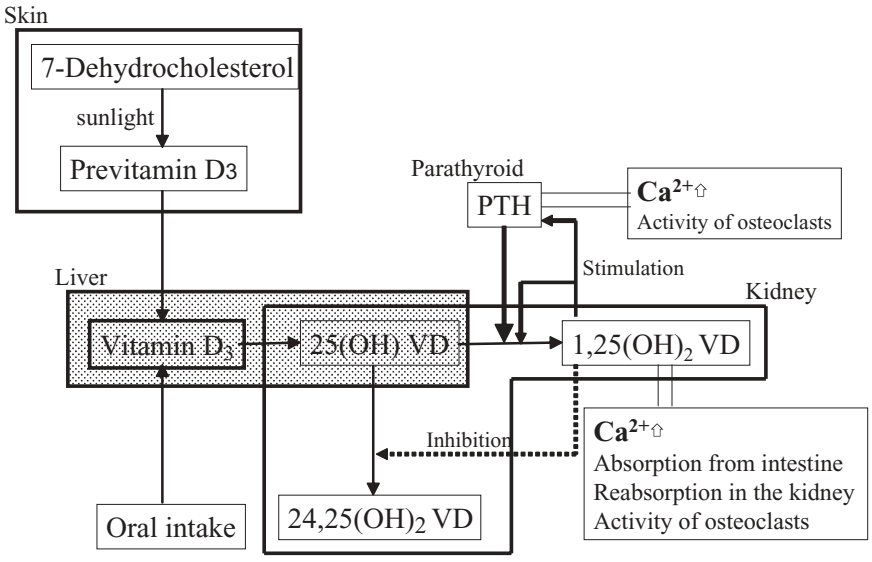

Fig. 3. Formation and hydroxylation of vitamin D3 and feedback control of $1,25(OH)_2$VD. The formation of 25(OH)VD takes place in the liver, and the formation of $1,25(OH)_2$VD and $24,25(OH)_2$VD occurs in the kidneys. Feedback control participates in the formation of $1,25(OH)_2$VD and $24,25(OH)_2$VD from 25(OH)VD in the kidneys. *Dashed arrow* indicates inhibition, and *thick solid arrows* indicate stimulation

Discussion

An extensive number of reports have been published regarding the postoperative complications of gastrectomy for gastric cancer, including the dumping syndrome. Vitamin B12 malabsorption and bone disorders are also widely known post-gastrectomy complications [9], but intensive studies have not been performed and there are few reports with respect to changes in serum VD levels after gastrectomy. A number of investigators have reported that gastrectomy for gastric cancer leads to changes in bone metabolism and an increased risk of fracture [10–14].

We studied changes in circulating VD metabolites in patients who had undergone a gastrectomy for gastric cancer. Although a change in VD metabolism was observed, the increase in PTH that has been reported by other authors was not seen [6]. This suggests that post-gastrectomy bone disorders may progress slowly without an increase in PTH, unlike the findings in hyperparathyroidism.

Figure 3 shows the formation and hydroxylation of VD [15]. The formation of 25(OH)VD takes place in the liver, and the formation of $1,25(OH)_2$VD occurs in the kidneys. In gastrectomized patients, food intake is reduced and malabsorption of fat occurs, and the formation of 25(OH)VD is reduced in the liver. However, the formation of $1,25(OH)_2$ VD in the kidneys does not decrease to maintain the serum Ca level. In the present study, many patients showed a decrease in 25(OH)VD and $24,25(OH)_2$VD, which are metabolites that show weak activity. This suggests that a homeostatic response maintains the normal level of $1,25(OH)_2$VD, which is important in the regulation of Ca.

Figure 4 shows the current understanding of Ca and bone metabolism after gastrectomy, according to the literature and our data. We guess that, because of the normal $1,25(OH)_2$D level in our patients, the pathway of 25(OH)D to $24,25(OH)_2$D was not stimulated and therefore PTH did not increase. However, in spite of the normal levels of $1,25(OH)_2$D, the formation of $1,25(OH)_2$D was stimulated. Because of the gastrec-

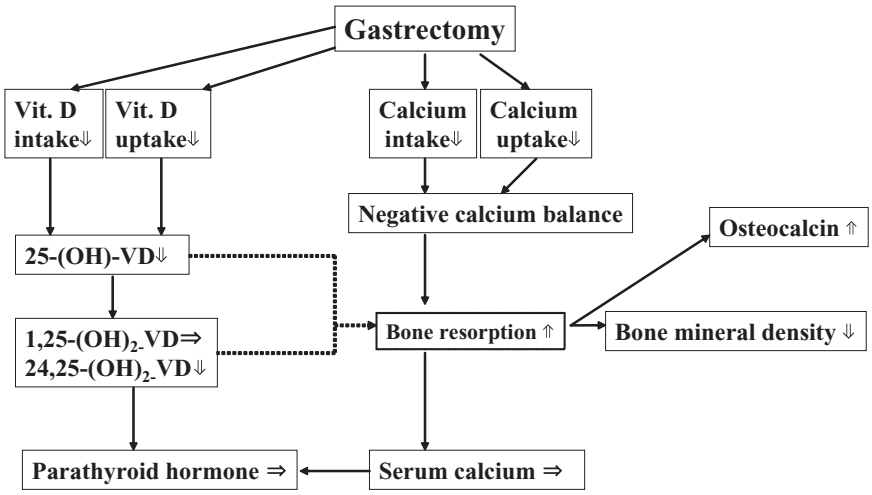

Fig. 4. Current understanding of calcium and bone metabolism after gastrectomy, according to the literature and our data. *Dashed arrow* shows that we have no idea how bone turnover is accelerated by the change in VD metabolites, but the accelerated formation of $1,25(OH)_2D$ would probably stimulate bone turnover

tomy, the decreased intake and absorption of Ca led to Ca insufficiency; bone turnover was accelerated and the osteocalcin level was elevated. The high level of osteocalcin, without high $1,25(OH)_2D$ or PTH levels, showed acceleration of bone turnover induced by the change in VD metabolites. However, we have no idea how the bone turnover was accelerated by the change in VD metabolites; possibly, the accelerated formation of $1,25(OH)_2D$ could have stimulated the bone turnover.

Thus, our findings suggested that gastrectomy had a moderate influence on the metabolism of VD. It was previously reported that no therapeutic response was obtained with Ca or VD supplements in postgastrectomy osteoporosis. [8] Nevertheless, it is reasonable to expect that bone metabolism could be improved by rectifying the changes in VD metabolism. Zittel et al. [6] reported that the serum Ca level was decreased, while the serum levels of Ca-regulating PTH and $1,25(OH)_2VD$ were increased, in patients who had had a total gastrectomy compared with control subjects, and these changes were more prominent after a total gastrectomy than after subtotal gastrectomy. This is a different outcome to the result of our study, and may indicate the necessity for taking ethnic differences into consideration. However, our results showing a high $1,25(OH)_2VD$/25(OH)VD ratio after a total gastrectomy, after gastrectomy procedures avoiding duodenal passage of food, and at 1 year or more postoperatively may indicate a high risk of bone fracture, as noted in the report of Zittel et al. [6].

There have been various reports regarding post-gastrectomy changes in Ca regulation. It was reported that the decrease in the serum Ca level was similar in patients with subtotal gastrectomy and those with total gastrectomy [13, 14]. However, our patients showed virtually no decrease in serum Ca and maintained a serum ionized Ca level that was above the normal range. Free ionized Ca has an important role as a messenger in the blood coagulation response, muscle contraction, and nerve function [15], so our findings suggest that the amount of ionized Ca in gastrectomy patients is adequate to maintain normal biological functions.

In regard to the proportions of the three VD metabolites, a marked decrease in 25(OH)VD was found after a total gastrectomy and after procedures that allowed food to bypass the duodenum. This suggests that VD absorption may be severely disturbed in patients who undergo total gastrectomy or the Roux-en-Y reconstruction to treat gastric cancer.

Few reports are available regarding changes in the levels of other vitamins, such as lipid-soluble vitamin A, vitamin E, and vitamin K after gastrectomy. However, it has been reported that the serum levels of vitamins A and E are decreased by a total gastrectomy [16, 17], and there is a report suggesting that vitamin K may also be decreased in patients who have had a total gastrectomy [16].

The administration of 1α results in activation of the metabolic pathway from 25(OH)VD to $24,25(OH)_2VD$ and obviates the need for compensatory changes in VD metabolism that are needed to maintain a normal $1,25(OH)_2VD$ level, such as the enhancement of the metabolic pathway from 25(OH)VD to $1,25(OH)_2VD$ or the suppression of the pathway from 25(OH)VD to $24,25(OH)_2VD$. Thus, normal VD metabolism can be restored by the use of 1α.

Conclusion

Bone disorders following gastrectomy may occur because Ca and VD absorption are decreased due to a decrease in food intake, rather than because of a loss of hormone balance (including PTH) after gastric resection. Our results suggest that, after gastric resection, some VD metabolites decrease and bone disease devel-

ops gradually, unlike the rapid bone changes caused by hyperparathyroidism. The administration of 1α seems to be effective for the treatment and prevention of bone disorders after gastrectomy for gastric cancer because it improves the balance of VD metabolites. To reach a definitive conclusion on this treatment, it will be necessary to examine a greater number of patients receiving 1α and to conduct additional assessments in the future.

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