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Clinical Course of Vitamin B12 Deficiency and Associated Risk Factors in Patients After Total Gastrectomy for Gastric Cancer

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Abstract. *Background/Aim: Patients are at-risk for vitamin B12 deficiency after total gastrectomy due to a lack of intrinsic factors. The aim of the study was to clarify the clinical course and risk factors for vitamin B12 deficiency after total gastrectomy for gastric cancer patients. Patients and Methods: Patients who underwent curative resection for gastric cancer were selected from the medical records of the Yokohama City University from 2000 to 2020. A logistic regression analysis was performed to identify risk factors for vitamin B12 deficiency. Results: We evaluated 47 patients. The median serum vitamin B12 levels before surgery were 359 pg/ml, while those at 3, 6, 9, and 12 months after surgery these were 255 pg/ml, 197.5 pg/ml, 195 pg/ml, and 206 pg/ml, respectively. Univariate analyses to identify factors associated with vitamin B12 deficiency at 6 months after surgery showed that the occurrence of postoperative complications was a significant risk factor (OR=6.347, 95%CI=1.607-25.774, p=0.009), while adjuvant chemotherapy was a marginally significantly risk factor (OR=3.562, 95%CI=0.877-14.477, p=0.076). Conclusion: Almost half of the patients were diagnosed with vitamin B12 deficiency at 6 months after total gastrectomy for gastric cancer. In addition, the occurrence of postoperative complications and adjuvant chemotherapy were risk factors for vitamin B12 deficiency at 6 months after surgery.*

Gastric cancer is the fifth-most common cancer and the second leading cause of cancer-related mortality (1, 2). Gastrectomy with lymphadenectomy is the standard curative treatment for locally advanced gastric cancer (3, 4). When a tumor is located at a proximal site, total gastrectomy is the standard treatment option. On the other hand, after total gastrectomy, patients have an increased risk of developing vitamin B12 deficiency (5, 6). Normally, vitamin B12 is absorbed with intrinsic factors that are released from gastric parietal cells (7). Intrinsic factors bind to vitamin B12 then these complexes are absorbed in the distal ileum. However, patients who receive total gastrectomy cannot release intrinsic factors; thus, they easily become vitamin B12 deficient. Vitamin B12 deficiency causes neurological symptoms and megaloblastic anemia. Vitamin B12 deficiency syndromes affect the patient's quality life after total gastrectomy.

Although there have been significant improvements in survival of gastric cancer patients due to improvements in perioperative adjuvant treatment, the treatment of vitamin B12 deficiency after total gastrectomy has not improved (8, 9). In addition, the clinical course and risk factors for vitamin B12 deficiency are not well studied. If physicians were able to detect the clinical course and risk factors for vitamin B12 deficiency after total gastrectomy for gastric cancer, they can optimize the treatment of vitamin B12 deficiency. Moreover, the vitamin B12 deficiency syndrome may be prevented in patients who receive total gastrectomy. The present study aimed to clarify the clinical course and risk factors for vitamin B12 deficiency after total gastrectomy for gastric cancer patients.

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Key Words: Vitamin B12 deficiency, gastric cancer, vitamin B12 treatment.

Patients and Methods

Patients. Patients who underwent curative resection for gastric cancer at the Yokohama City University from 2000 to 2020 were selected for study inclusion. The inclusion criteria were as follows: 1) histologically proven adenocarcinoma, 2) curative total gastrectomy for gastric cancer as a primary treatment, and 3) serum vitamin B12 level >200 pg/ml before surgery. Patients who received vitamin B12 medication before surgery were excluded.

Follow-up, definition of vitamin B12 deficiency, and treatment of vitamin B12 deficiency. Hematological tests and physical examinations were performed at least every three months. Vitamin B12 deficiency was defined as serum vitamin B12 levels <200 pg/ml, irrespective of symptoms and follow-up period. Patients who were diagnosed with vitamin B12 deficiency received intramuscular vitamin B12 injection treatment (500 to 1,000 μg every 1 to 3 months) or oral vitamin B12 tablets (500 to 1,500 μg daily).

Adjuvant chemotherapy. Patients diagnosed with pathological stage II and III disease received S-1-based adjuvant chemotherapy for 6 weeks after surgery (10, 11).

Definition of postoperative surgical complications. Grade 2-5 postoperative complications (according to the Clavien-Dindo classification) that occurred during hospitalization or within 30 days after surgery were retrospectively determined from the patient records (12).

Evaluation and statistical analysis. A logistic regression analysis was performed to identify risk factors. An unpaired χ^2 test or Student's *t*-test was used to compare each group. *p*-Values <0.05 were considered to indicate statistical significance. The SPSS software program (v27.0 Win; SPSS, Chicago, IL, USA) was used to perform statistical analyses.

Table I. *Baseline characteristics of included patients*.

Characteristics	Patient numbers (%)
Age (years), median (range)	70 (46-87)
Sex	
Male	37 (78.7%)
Female	10 (21.3%)
BMI, Median (range)	22.1 (15.6-29.8)
ASA-PS	
0-1	10 (21.3%)
2-	37 (78.7%)
Comorbidities	
Hypertension	25 (53.2%)
COPD	14 (29.8%)
Diabetes mellitus	11 (23.4%)
Lymph node dissection	
D1+ dissection	19 (40.2%)
D2 dissection	28 (59.8%)
Intra operative transfusion	
Yes	9 (19.1%)
No	38 (80.9%)
Surgical complications	
Yes	27 (57.4%)
No	20 (42.6%)
Pathological T factor	
Pathological T1-T2	23 (48.9%)
Pathological T3-T4	24 (51.1%)
Pathological N factor	
Negative	24 (51.1%)
Positive	23 (48.9%)
Postoperative adjuvant chemotherapy	
Yes	29 (61.7%)
No	18 (38.3%)

BMI: Body mass index; ASA-PS: American Society of Anesthesiology physical status; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein.

Results

Patient background factors and the clinical course of the serum vitamin B12 levels. We evaluated 47 patients (Table I). The median patient age was 70 years (range=46-87 years). Thirty-seven patients were males and 10 were females. The preoperative median body mass index was 22.0 (range=15.6-29.8). Figure 1 shows the clinical course of median serum vitamin B 12 levels. Median serum vitamin B12 levels before surgery were 359 pg/ml, while those at 3, 6, 9, and 12 months after surgery were 255 pg/ml, 197.5 pg/ml, 195 pg/ml, and 206 pg/ml, respectively. Among 47 patients, 7 patients were diagnosed with vitamin B12 deficiency at 3 months after surgery, 24 patients were diagnosed with vitamin B12 deficiency at 6 months after surgery, 30 patients were diagnosed with vitamin B12 deficiency at 9 months after surgery, and 33 patients were diagnosed with vitamin B12 deficiency at 12 months after surgery. All patients who were diagnosed with vitamin B12 deficiency received vitamin B12 treatment.

Risk factor analysis. The median serum vitamin B12 levels were <200 pg/ml at 6 months after surgery; thus, we evaluated the risk factors for serum vitamin B12 levels of <200 pg/ml at 6 months after surgery. At 6 months after surgery, 24 patients showed vitamin B12 deficiency, while 23 patients did not. The comparison of patients with and without vitamin B12 deficiency revealed no differences in their background factors (Table II). On the other hand, it was found that the incidence of postoperative complications in patients with vitamin B12 deficiency was significantly higher than in those without vitamin B12 deficiency (75.0% *vs*. 39.1%, *p*=0.0013) (Table III). Univariate analyses to identify factors associated with vitamin B12 deficiency at 6 months after surgery revealed that the occurrence of postoperative complication was a significant risk factor. The occurrence of postoperative complications was, therefore, selected for the final multivariate analysis model (OR=6.347, 95%CI=1.607-25.774, *p*=0.009). The incidence of vitamin B12 deficiency at 6 months was 75.0% in patients who had postoperative complications, and 39.1%

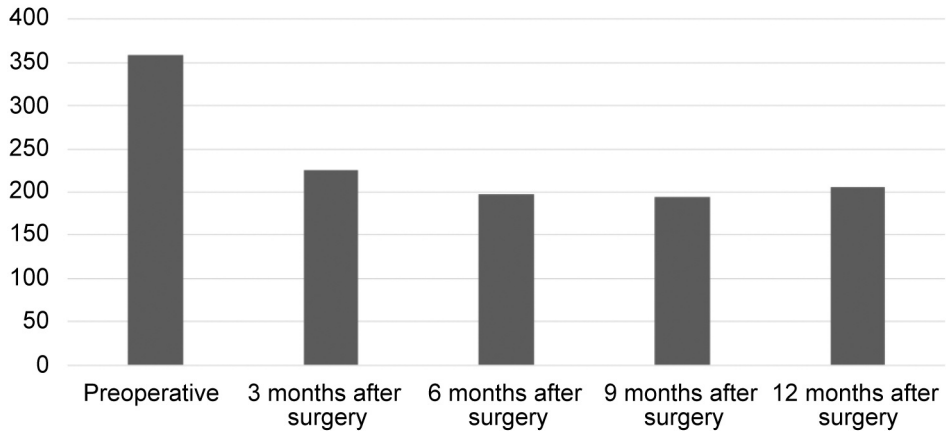

Figure 1. *Clinical course of median serum vitamin B12 levels in patients who underwent total gastrectomy.*

in patients who did not have postoperative complications. In addition, adjuvant chemotherapy was identified as a marginally significant risk factor in multivariate analysis (odds ratio: 3.562, 95%CI=0.877-14.477, p=0.076) (Table IV). The incidence of the vitamin B12 deficiency at 6 months was 70.8% in patients who received adjuvant chemotherapy, and 52.2% in patients who did not receive adjuvant chemotherapy.

Discussion

The aim of the study was to investigate the clinical course of vitamin B12 deficiency and identify associated risk factors in patients who received total gastrectomy for gastric cancer. The major finding was that almost half of the patients were diagnosed with vitamin B12 deficiency at 6 months after surgery. In addition, the occurrence of postoperative complications and adjuvant chemotherapy were risk factors for vitamin B12 deficiency. Our results show that vitamin B12 treatment is required from 6 months postoperatively in patients who have undergone total gastrectomy, especially patients who develop postoperative complications and patients undergoing adjuvant therapy.

The present study showed that half of the patients had vitamin B12 deficiency at 6 months after surgery and 70% of the patients had vitamin B12 deficiency at 12 months after surgery. Limited studies have presented the changes in vitamin B12 levels after total gastrectomy. Namikawa *et al*. investigated the efficacy of enteral supplementation of vitamin B12 for vitamin B12 deficiency in patients who had undergone total gastrectomy for gastric cancer (13). They reported that vitamin B12 deficiency was observed in >70% of patients who underwent total gastrectomy for gastric cancer. In addition, Kim *et al*. evaluated the efficacy and safety of oral vitamin B12 replacement for vitamin B12 deficiency after total gastrectomy in gastric cancer patients in a prospective clinical trial (14). In the trial, they showed that the time interval for the occurrence of vitamin B12 deficiency was 15.2-16.0 months. Thus, our results are in line with previous studies. In the risk factor analysis of the present study, the occurrence of postoperative complications and postoperative adjuvant chemotherapy were found to be risk factors for vitamin B12 deficiency at 6 months after surgery. Why are these factors associated with vitamin B12 deficiency in patients with total gastrectomy? Although vitamin B12 absorption rate of the intrinsic factor-independent pathway is 1% from oral food intake, the passive absorption of vitamin B12 with daily oral intake is the major alternative pathway of vitamin B12 absorption in patients after total gastrectomy (7, 15). Thus, oral intake is the key factor for the supply of vitamin B12. However, both the occurrence of postoperative complications and postoperative adjuvant chemotherapy affect the daily oral intake due to postoperative surgical complications itself and adverse events of chemotherapy. Postoperative surgical complications, such as anastomotic leakage, pancreatic fistula, and abdominal abscess as well as adverse events of adjuvant chemotherapy, such as nausea, vomiting, and diarrhea affect the daily oral intake, resulting in vitamin B12 deficiency (16-18). Therefore, careful attention is needed to detect vitamin B12 deficiency in patients who develop postoperative complications or who receive postoperative adjuvant chemotherapy.

In the present study, the measured serum vitamin B12 levels were almost 200 pg/ml at all points after surgery, even in patients who received vitamin B12 treatment. Moreover, serum vitamin B12 levels did not recover to the preoperative vitamin B12 level. Similar results have been reported in previous studies. Namikawa *et al*. reported that the median serum vitamin B12 level was 136 pg/ml at 3 months after parenteral

Table II. *Comparison of patient background between patients with vitamin B12 deficiency at 6 months after surgery and those without vitamin B12 deficiency at 6 months after surgery.*

Characteristics	Patients with vitamin B12 deficiency at 6 months after surgery	Patients without vitamin B12 deficiency at 6 months after surgery	*p*-Value
	No. of patients (%) (n=24)	No. of patients (%) (n=23)	
Age (years),	70	71	0.341
Median (range)	46-87	59-87	
Sex			0.177
Male	17 (70.8)	20 (87.0)	
Female	7 (29.2)	3 (13.0)	
BMI, Median	22.3	21.9	0.950
(range)	15.6-29.8	16.0-28.7	
ASA-PS			0.054
0-1	8 (33.3)	2 (8.7)	
2-	16 (66.7)	21 (91.3)	
Comorbidities			
Hypertension	13 (54.2)	12 (52.2)	0.891
COPD	8 (33.3)	6 (26.1)	0.587
Diabetes mellitus	3 (12.5)	8 (34.8)	0.071
Pre-operative laboratory data			
Albumin (g/dl)	3.9	3.9	0.788
Hemoglobin(g/dl)	12.5	12.3	0.229
White bold cell	6140	6280	0.420
CRP (mg/dl)	0.18	0.84	0.061

BMI: Body mass index; ASA-PS: American Society of Anesthesiology physical status; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein.

Table III. *Comparison of surgical and pathological findings between patients with vitamin B12 deficiency and patients without vitamin B12 deficiency.*

Characteristics	Patients with vitamin B12 deficiency	Patients without vitamin B12 deficiency	*p*-Value
	No. of patients (%) (n=24)	No. of patients (%) (n=23)	
Lymph node dissection			0.440
D1+ dissection	11 (45.8)	8 (34.8)	
D2 dissection	13 (54.2)	15 (65.2)	
Blood loss (ml),	548	862	0.072
Median (range)	18-1,894	30-3,170	
Intraoperative transfusion		0.659	
Yes	4 (16.7)	5 (21.7)	
No	20 (83.3)	18 (78.3)	
Surgical complications			0.013
Yes	18 (75.0)	9 (39.1)	
No	6 (25.0)	14 (60.9)	
Pathological T factor			0.882
Pathological T1-T2	12 (50.0)	11 (47.8)	
Pathological T3-T4	12 (50.0)	12 (52.2)	
Pathological N factor			0.664
Negative	13 (54.2)	11 (47.8)	
Positive	11 (45.8)	12 (52.2)	
Postoperative adjuvant chemotherapy		0.188	
Yes	17 (70.8)	12 (52.2)	
No	7 (29.2)	11 (47.8)	

supplementation, 149 pg/ml at 6 months after parenteral supplementation, and 172 pg/ml at 12 months after parenteral supplementation (13). In addition, in the study by Kim *et al*., which compared the efficacy between oral and intramuscular vitamin B12 replacement, the mean serum vitamin B12 levels of the intramuscular administration group peaked after the weekly booster injection period but decreased at 2 months (14). Taken together, intramuscular vitamin B12 may be insufficient for the treatment of vitamin B12 deficiency in patients who have received total gastrectomy for gastric cancer. Recently, oral vitamin B12 treatment was reported to be effective for treating vitamin B12 deficiency after total gastrectomy for gastric cancer (19-20). We conducted a phase II study to evaluate the efficacy and safety of oral vitamin B12 replacement for vitamin B12 deficiency after total gastrectomy for gastric cancer (19). We demonstrated that oral vitamin B12 replacement is safe and effective for vitamin B12 deficiency. In this trial, we also showed that the serum vitamin B12 level was continuously increasing from 3 months after treatment, irrespective of the vitamin B12 dose. Similar results were observed in previous studies. In the study of Namikawa *et al*., vitamin B12 levels before supplementation and at 3, 6, and 12 months after supplementation were significantly higher in patients who received supplementation *via* the enteral route than *via* the parenteral route (13). Moreover, the study of Kim *et al*. showed that oral vitamin B12 replacement increased serum vitamin B12 levels over time (14). Taken together, oral vitamin B12 treatment may have clinical potential for treating vitamin B12 deficiency in patients who receive total gastrectomy for gastric cancer. Based on our findings, we are going to conduct a phase III trial to evaluate preventative effect of oral vitamin B12 therapy against vitamin B12 deficiency in patients who have undergone total gastrectomy. This trial will show the optimal dose and optimal timing for the prevention of vitamin B12 deficiency after total gastrectomy.

The present study was associated with certain limitations. First, the present study was retrospective in nature, and analyzed a relatively small population of patients who were treated at a single Institution from 2000 to 2020. Therefore, there may be a selection bias and time bias. Second, the

Table IV. *Results of univariate and multivariate analyses of risk factors for vitamin B12 deficiency at 6 months after total gastrectomy.*

Characteristics	Number	Univariate analysis			Multivariate analysis		
		OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age				0.871			
<70 years	21	1.000					
≥70 years	26	1.100	0.348-3.477				
Sex				0.187			
Male	37	1.000					
Female	10	2.745	0.613-12.292				
Preoperative BMI				0.882			
<22	24	1.000					
≥22	23	1.091	0.347-3.426				
Preoperative Hb				0.871			
≥13.0	21	1.000					
<13.0	26	1.100	0.348-3.477				
Preoperative Alb				0.475			
≥4.0	27	1.000					
<4.0	20	1.528	0.478-4.888				
Pathological T factor				0.882			
Pathological T1-T2	20	1.000					
Pathological T3-T4	27	1.091	0.347-3.426				
Pathological N factor				0.664			
Negative	24	1.000					
Positive	23	1.289	0.410-4.057				
Adjuvant chemotherapy				0.192			0.076
No	29	1.000			1.000		
Yes	18	2.226	0.669-7.404		3.562	0.877-14.477	
Postoperative surgical complications				0.015			0.009
No	27	1.000			1.000		
Yes	20	4.667	1.341-16.239		6.347	1.607-25.774	

OR: Odds ratio; CI: confidence interval; BMI: body mass index; Hb: Hemoglobin; Alb: Albumin.

optimal timing for evaluation of vitamin B12 was unclear. In the present study, the patient vitamin B12 levels were measured every 3 months in an outpatient clinic. However, vitamin B12 deficiency was variable, and the timing of follow-up needs to be optimized.

In conclusion, 50% of patients were diagnosed with vitamin B12 deficiency at 6 months after surgery. The occurrence of postoperative complications and adjuvant chemotherapy were found to be significant risk factors for vitamin B12 deficiency. In addition, the vitamin B12 levels did not recover to their preoperative levels, even after vitamin B12 replacement. Therefore, our results suggest that optimal vitamin B12 treatment is needed to prevent vitamin B12 deficiency in patients who have undergone total gastrectomy for gastric cancer, especially in patients who developed postoperative complications and patients undergoing adjuvant therapy.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

TA, KH and KK1 (Keisuke Kazama) made substantial contributions to the concept and design. TA, YM, KK2 (Keisuke Komori), HT, AT, KK3 (Kazuki Kano), IH, YM, HC, KS, TI, MI, NY, TO and YR made substantial contributions to the acquisition of data and the analysis and interpretation of the data. TA, JM, HT, TO, NY and YR were involved in drafting the article or revising it critically for important intellectual content. TA, JM, KK and TO gave their final approval of the version to be published.

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