Original Article

# High prevalence of vitamin B-12 deficiency before and early after gastrectomy in patients with gastric cancer

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**Background and Objectives:** Gastrectomy causes vitamin B-12 deficiency since vitamin B-12 requires gastric acid and intrinsic factor for its absorption. Vitamin B-12 deficiency is considered to develop years after gastrectomy because of large hepatic storage. However, most gastric cancer develops after long-standing atrophic gastritis with vitamin B-12 malabsorption. **Methods and Study Design:** We have investigated vitamin B-12 status in 22 patients before gastrectomy and 53 patients after gastrectomy due to gastric cancer, also with consideration on post-gastrectomy anemia. **Results:** Blood vitamin B-12, folic acid, homocysteine concentrations, parameters of anemia, and dietary intake were evaluated. Percentage of patients with severe vitamin B-12 deficiency (serum vitamin B-12 < 150 pmol/L), vitamin B-12 deficiency (150 pmol/L to < 258 pmol/L) was 19.0 %, and 52.4 % respectively in patients gastrectomized within three years. Before gastrectomy, three and seven patients exhibited severe deficiency and deficiency, respectively. In gastrectomized patients, plasma homocysteine concentration was inversely associated with serum vitamin B-12 concentration, and vitamin B-12 deficiency- and iron deficiency- anemia coexisted with their mean corpuscular volume within the reference range. **Conclusions:** Vitamin B-12 deficiency is prevalent in patients early after and before gastrectomy. Coexistence of vitamin B-12 and iron deficiency obscures the diagnosis of post-gastrectomy anemia, and necessitates the blood vitamin B-12 measurement.

**Key Words: vitamin B-12, homocysteine, gastric cancer, gastrectomy, anemia**

## INTRODUCTION

Vitamin B-12 is one of the water-soluble vitamins, but it differs from other water-soluble vitamins in several ways. First, it is absorbed from the gastrointestinal tract by a unique system. After its release from foods by the action of gastric acid, vitamin B-12 binds to intrinsic factor (IF) secreted from the gastric parietal cells, then vitamin B-12-IF complex is specifically absorbed from the distal ileum.[1] Second, there is a large amount of vitamin B-12 storage in the liver, which is in sharp contrast to other water-soluble vitamins.[2] For example, vitamin B-1 has little bodily storage since it is easily excreted in the urine on their excess.[3]

Since stomach has crucial roles in the absorption of vitamin B-12, its malabsorption inevitably occurs after gastrectomy, causing serious health problems such as macrocytic anemia, neurological dysfunction, and various diseases through hyperhomocysteinemia.[1, 4-6] Gastric cancer is mainly treated by gastrectomy. In Japan, common description in the guidelines, papers or textbooks has been and even now is that vitamin B-12 deficiency and consequently occurring anemia do not develop immediately after gastrectomy because of the large amount of storage in the liver, and it becomes manifest four or five years after gastrectomy when hepatic storage is depleted.[7] However, recent papers from abroad have shown that vitamin B-12 deficiency develops immediately after gastrectomy.[8,9] Also, most cases of gastric cancer are considered to be secondary to atrophic gastritis.[10] Then, it is likely that impaired vitamin B-12 absorption had occurred years before developing gastric cancer and receiving gastrectomy. Based on these considerations, we have made a hypothesis that hepatic storage of vitamin B-12 is already decreased at surgery in patients with gastric cancer because of malabsorption which has lasted for years, and vitamin B-12 deficiency occurs much earlier than previously believed.

In patients after gastrectomy, malabsorption of many nutrients occurs including vitamin B-12 and iron, causing

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vitamin B-12-deficiency and iron-deficiency anemia, respectively.[11] Then, substantial percentage of patients are quite likely to be deficient in both nutrients. Nevertheless, little attention has been paid on the coexistence of these nutritional anemias in patients after gastrectomy.

In the present study, we have investigated the vitamin B-12 status before and early after gastrectomy in patients with gastric cancer, and studied the post-gastrectomy anemia taking the above-mentioned co-existence into account.

## METHODS

### *Study design*

This is a cross-sectional study conducted from February in 2018 to September in 2019. Written consent to participate in this study was obtained from each patient after explanation of the objective and protocol of this study. The study protocol was approved by the Ethical Committee of Rakuwa-kai Otowa Hospital (Ethics Approval number; Rakuon-Rin-17-044) and Hirakata Kosai Hospital (Ethics Approval number; 2017-023), and done complying with the Declaration of Helsinki.

### *Patients before gastrectomy*

The patients were 22 patients with gastric cancer scheduled for gastrectomy in Rakuwa-kai Otowa Hospital. The exclusion criteria were those who were treated with oral vitamin B-12 medicines or supplements, intravenous or intramuscular vitamin B-12 injection or under cancer chemotherapy. After excluding four patients who declared using vitamin B-12 supplement, we have also excluded patients with their serum vitamin B-12 concentration above the third quartile + 1.5 * interquartile range, to rule out the possibility of undeclared use of vitamin B-12 supplementation.[12]

A total of 16 (eight men, eight women) patients were included in this analysis. Also, one patient with their serum folic acid concentration above the third quartile + 1.5 * interquartile range and two patients with their intake of energy above mean +/- 2 SD were excluded from applicable analyses.

### *Patients after gastrectomy*

The patients were 53 patients (16 in Rakuwa-kai Otowa Hospital and 37 in Hirakata Kosai Hospital) who had undergone gastrectomy within seven years due to gastric cancer. The exclusion criteria were those who were under treatment with oral vitamin B-12, either as a therapeutic drug or as a supplementation, intravenous or intramuscular vitamin B-12 injection, or chemotherapy within three months. After excluding one patient who declared using vitamin B-12 supplement, we have also excluded patients with their serum vitamin B-12 concentration above the third quartile + 1.5 * interquartile range to exclude patients with undeclared use of vitamin B-12 supplementation.[12] A total of 49 (32 men, 17 women) patients were included in this analysis. Also, one patient with their serum folic acid concentration above the third quartile + 1.5 * interquartile range and four patients with their intake of energy above mean +/- 2 SD were excluded from applicable analyses. In addition, three patients devoid of data on blood hemoglobin concentration were excluded from analyses regarding anemia.

### *Laboratory data*

Non-fasting or fasting blood was obtained. Serum or plasma blood was stored at -30˚C until measurement. Serum vitamin B-12 and folic acid concentrations were measured by chemiluminescent enzyme immunoassay (CLEIA). Plasma homocysteine concentration was measured by HPLC. The cut-off value of serum vitamin B-12 concentration was decided as below; severe deficiency: < 150 pmol/L, deficiency: 150 pmol/L to < 258 pmol/L pmol/L, insufficiency or normal: ≥ 258 pmol/L.[13] The more detailed consideration on the cut-off value of serum vitamin B-12 concentration will be made in the "Discussion". The cut-off value of plasma homocysteine was decided 15 μmol/L.[13] Anemia was defined according to World Health Organization criteria; Hb < 13 g/dL in men, Hb < 12 g/dL in women.[14,15] Iron deficiency was defined as blood ferritin concentration less than 12 ng/mL.[16] Also, mean corpuscular volume (MCV) ≤ 80 fL and MCV ≥ 99 fL were defined as microcytic and macrocytic, respectively.[17]

### *Dietary intake data*

Dietary intake data were obtained by dietary history method using a brief-type self-administered diet history questionnaire (BDHQ).[18] Data were adjusted by energy density model.

### *Bodyweight and height data*

Patients' body weight and height were recorded by interviewing them. In case of its unavailability, the latest data on body weight and height were obtained from the medical record.

### *Data regarding gastric cancer*

In patients after gastrectomy, the stage of gastric cancer was confirmed by histopathological examination after surgery according to Japanese Classification of Gastric Carcinoma which is based on TNM classification.[19,20] Data on the stage of gastric cancer were obtained from all patients and 39 out of 49 patients in patients before and after gastrectomy, respectively. In patients before and after gastrectomy, the number of patients in IA, IB, IIA, IIB, IIIA, IIIB, and IIIC was 11, one, two, one, one, zero, zero, and 23, three, four, five, one, two, one, respectively. These data, kinds of medicines, extent of resection, and reconstruction method were obtained from the medical record.

### *Statistical analyses*

The normality of distribution was judged by Shapiro Wilk test. The difference between two groups was analyzed by Student's t test or Mann Whitney's U test. Correlations between two independent variables were analyzed by Spearman's correlation. Jonckheere-Terpstra test was used to assess trends among the groups according to serum vitamin B-12 concentration. Statistical analyses were done using SPSS version 22 (IBM Japan, Tokyo). The significance level of the associations was set at $p < 0.05$.

## RESULTS

The patients' characteristics including data from blood examination and nutrient intakes are shown in Table 1. Compared to patients after gastrectomy, those before gastrectomy had significantly higher BMI and lower serum albumin concentration, suggesting that serum albumin and BMI are negatively influenced by gastric cancer and gastrectomy, respectively. Serum vitamin B-12 concentration was 200 ± 71 pmol/L in patients after gastrectomy. The number of patients with "severe deficiency", "deficiency", and "insufficiency or normal" was 11, 27 and 11, respectively. Among them, 21 out of 49 (42.9 %) were within three years after surgery, of whom the percentage of patients with severe deficiency and deficiency was 19.0 % and 52.4 %, respectively. Also, their serum vitamin B-12 concentration and time after surgery were not significantly correlated (data not shown). Serum vitamin B-12 concentration in patients before gastrectomy was 249 ± 98 pmol/L with the number of patients with severe deficiency, deficiency, and insufficiency or normal being three, seven and six, respectively.

Table 2 shows the comparison of patients' status based on the extent of resection in patients after gastrectomy. Compared to patients with subtotal gastrectomy, those with total gastrectomy had significantly lower BMI, blood concentration of albumin, hemoglobin, and vitamin B-12, and significantly higher plasma homocysteine concentration. Even in patients with subtotal gastrectomy, the number of patients with severe vitamin B-12 deficiency and deficiency was four and 16, respectively.

There was a significant trend toward higher plasma homocysteine concentration with lower serum vitamin B-12 concentration ($p$<0.001) and hyperhomocysteinemia was observed in severe deficiency group (Table 3). Also, plasma homocysteine concentration was significantly correlated with serum vitamin B-12 concentration ($p$<0.001), but not with serum folic acid concentration ($p$=0.204) (Table 4).

In patients with anemia, BMI, red blood cell count, MCV, blood concentrations of albumin, iron, ferritin and vitamin B-12 were significantly lower, and plasma homocysteine was significantly higher than those without anemia (Table 5). In patients with anemia, as for serum vitamin B-12 concentration, ten and eight patients had severe deficiency and deficiency, respectively.

Although the mean serum vitamin B-12 concentration in anemic patients fell in the range of "deficiency", their MCV did not show macrocytic anemia. Also, of the 21

**Table 1.** Characteristics of the patients

| | Before gastrectomy (n=16) | After gastrectomy (n=49) | *p* value |
|---|---|---|---|
| Sex (male / female) | 8 / 8 | 32 / 17 | - |
| Age (years) | 70.5 (57.5, 77.8) | 71.0 (67.5, 77.0) | 0.464 |
| Height (cm) | 159 ± 8 | 162 ± 9 | 0.246 |
| Bodyweight (kg) | 60.8 ± 12.7 | 53.7 ± 9.6 | 0.021 |
| BMI (kg/m$^2$) | 23.8 ± 4.3 | 20.3 ± 2.6 | 0.006 |
| Time after surgery (month) | - | 40.9 ±16.1 | - |
| Albumin (g/dL) | 3.6 (3.4, 3.8) | 4.1 (3.9, 4.4) | <0.001 |
| Total cholesterol (mg/dL) | 161 (150, 194) | 188 (165, 205) | 0.122 |
| Hb (g/dL) | 11.6 ± 1.8 | 12.9 ± 1.9 | 0.017 |
| MCV (fL) | 88.1 ± 9.0 | 91.8 ± 6.3 | 0.079 |
| Iron (μg/dL) | 105 (77, 130) | 89 (61, 123) | 0.218 |
| Ferritin (ng/mL) | 64 (18, 163) | 21 (10, 82) | 0.064 |
| TIBC (μg/dL) | 275 (255, 338) | 344 (309, 423) | 0.001 |
| Vitamin B-12 (pmol/L) | 249 ± 98 | 200 ± 71 | 0.035 |
| Folic acid (nmol/L) | 15.9 (13.4, 19.5) | 22.3 (13.7, 28.6) | 0.056 |
| Homocysteine (μmol/L) | 11.1 (7.0, 13.4) | 12.1 (9.2, 16.9) | 0.132 |
| Energy (kcal/day) | 1810 ± 636 | 1700 ± 436 | 0.460 |
| Intakes of vitamin B-12 (μg/day) | 9.2 (5.2, 12.7) | 7.9 (6.1, 12.7) | 0.664 |
| Intakes of vitamin B-12 (μg/1000 kcal/day) | 4.9 (3.4, 6.5) | 4.8 (3.7, 6.5) | 0.716 |

Data are expressed as mean ± SD or median (Q1, Q3), and Student's t test is used for the former, and Mann Whitney's U test for the latter

**Table 2.** Comparison of patients' status based on the extent of resection in patients after gastrectomy

| | Total gastrectomy (n=19) | Subtotal gastrectomy (n=30) | *p* value |
|---|---|---|---|
| Age (years) | 71.0 (66.0, 73.0) | 73.0 (68.0, 79.3) | 0.159 |
| BMI (kg/m$^2$) | 19.1 ±1.8 | 21.1 ± 2.8 | 0.004 |
| Albumin (g/dL) | 4.0 (3.8, 4.3) | 4.1 (4.0, 4.4) | 0.043 |
| Hemoglobin (g/dL) | 12.1 ±1.7 | 13.5 ± 1.9 | 0.016 |
| Iron (μg/dL) | 75 (44, 111) | 90 (62, 127) | 0.267 |
| Vitamin B-12 (pmol/L) | 162 ± 44 | 224 ± 75 | 0.001 |
| Folic acid (nmol/L) | 24.2 ± 11.0 | 21.4 ± 9.6 | 0.345 |
| Homocysteine (μmol/L) | 16.2 (10.8, 19.9) | 11.2 (9.1, 12.9) | 0.009 |
| Intakes of vitamin B-12 (μg/1000kcal/day) | 4.7 (3.9, 5.4) | 5.3 (3.6, 7.2) | 0.980 |

Data are expressed as mean ± SD or median (Q1, Q3), and Student's t test is used for the former, and Mann Whitney's U test for the latter

**Table 3.** Comparison of patients' status based on the vitamin B-12 status in patients after gastrectomy

| | Severe deficiency (n=11) | Deficiency (n=27) | Insufficiency or normal (n=11) | *p* value |
|---|---|---|---|---|
| Age (years) | 71.0 (69.0, 80.0) | 69.0 (66.0, 73.0) | 78.0 (75.0, 80.0) | 0.171 |
| Albumin (g/dL) | 4.1 (3.8, 4.3) | 4.1 (3.9, 4.4) | 4.1 (3.9, 4.4) | 0.495 |
| Vitamin B-12 (pmol/L) | 131 (97, 147) | 193 (162, 216) | 289 (269, 326) | <0.001 |
| Folic acid (nmol/L) | 22.2 (14.7, 25.4) | 19.0 (12.9, 28.6) | 25.4 (17.1, 33.1) | 0.467 |
| Homocysteine (μmol/L) | 17.5 (14.9, 22.8) | 11.5 (9.1, 15.7) | 9.7 (7.8, 11.3) | 0.001 |
| Intakes of vitamin B-12 (μg/1000kcal/day) | 5.1 (4.7, 9.3) | 4.8 (3.7, 7.4) | 4.7 (3.6, 6.3) | 0.190 |

Data are expressed as median (Q1, Q3), and p values represent the results from Jonckheere-Terpatra test

**Table 4.** Correlation analyses for blood concentrations of vitamins and homocysteine in patients after gastrectomy

| | r | *p* value |
|---|---|---|
| Vitamin B-12, folic acid (n=48) | 0.083 | 0.574 |
| Vitamin B-12, homocysteine (n=49) | -0.511 | <0.001 |
| Folic acid, homocysteine (n=48) | -0.187 | 0.204 |

r is Spearman's correlation coefficient

**Table 5.** Comparison of patients' status according to anemia in patients after gastrectomy

| | Without anemia (n=25) | With anemia (n=21) | *p* value |
|---|---|---|---|
| Age (years) | 71.0 (67.0, 77.5) | 73.0 (69.0, 77.5) | 0.514 |
| BMI (kg/m$^2$) | 21.0±2.8 | 19.4±1.8 | 0.025 |
| Albumin (g/dL) | 4.2 (4.0, 4.4) | 4.0 (3.8, 4.3) | 0.010 |
| eGFR (mL/min/1.73m$^2$) | 70.4±14.4 | 76.1±15.5 | 0.200 |
| Red blood cell (10$^6$/μL) | 4.6±0.4 | 4.0±0.4 | <0.001 |
| Hemoglobin (g/dL) | 14.4±1.0 | 11.2±1.2 | <0.001 |
| MCV (fL) | 94.1±4.8 | 89.0±6.8 | 0.007 |
| Iron (μg/dL) | 100 (76, 133) | 63 (34, 98) | 0.007 |
| Ferritin (ng/mL) | 30.9 (17.0, 91.8) | 10.4 (7.0, 23.0) | 0.004 |
| TIBC (μg/dL) | 336 (303, 391) | 375 (319, 498) | 0.100 |
| Vitamin B-12 (pmol/L) | 222±63 | 179±78 | 0.045 |
| Folic acid (nmol/L) | 17.0 (12.3, 28.4) | 24.5 (17.7, 34.2) | 0.065 |
| Homocysteine (μmol/L) | 11.6±3.5 | 15.8±6.6 | 0.014 |
| Intakes of vitamin B-12 (μg/1000kcal/day) | 4.8 (3.7, 6.3) | 4.7 (3.7, 8.4) | 0.592 |
| Intakes of iron (μg/1000kcal/day) | 3.6 (3.2, 4.4) | 4.4 (3.6, 5.1) | 0.069 |

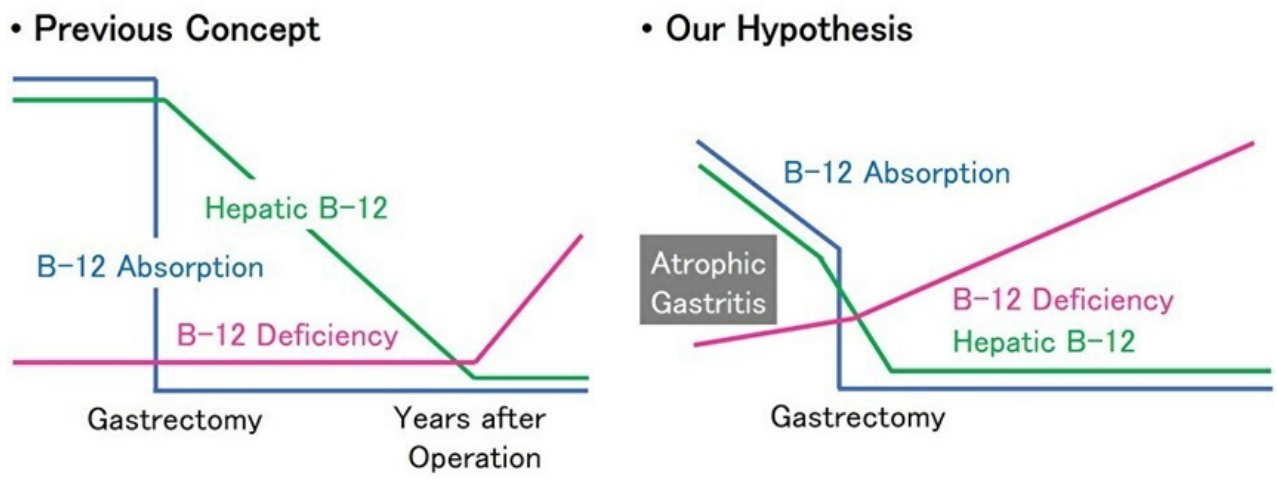
Data are expressed as mean ± SD or median (Q1, Q3), and Student's t test is used for the former, and Mann Whitney's U test for the latter

patients with anemia, ten patients had iron deficiency (ferritin < 12 ng/mL), 16 patients had vitamin B-12 deficiency (vitamin B-12 < 258 pmol/mL) and nine had both iron deficiency and vitamin B-12 deficiency.

## DISCUSSION

In the current study, the percentage of patients with "severe vitamin B-12 deficiency" and "vitamin B-12 deficiency" was 19.0 % and 52.4 %, respectively in patients who had received gastrectomy within three years. In patients before gastrectomy, their serum vitamin B-12 concentration was 249 ± 98 pmol/L, and ten out of 16 patients (62.5%) had severe vitamin B-12 deficiency or deficiency. Also, although serum vitamin B-12 concentration was significantly lower in patients with total gastrectomy than that in patients with subtotal gastrectomy, even subtotal gastrectomy was responsible for vitamin B-12 deficiency.

As described in "Materials and Methods", we have defined the vitamin B-12 status as follows with the corresponding serum vitamin B-12 concentration in the parentheses; severe deficiency (< 150 pmol/L), deficiency (150 pmol/L to < 258 pmol/L pmol/L), and insufficiency or normal (≥ 258 pmol/L) based on the following consideration. At present, there exists no widely acknowledged cut-off value for blood vitamin B-12 concentration. In a recently published review citing 69 articles, diverse cut-off values for blood vitamin B-12 concentration are described ranging from < 100 pmol/L to < 350 pmol/L.[13] It was 150 pmol/L, 148 pmol/L, and 258 pmol/L in 13, 13, and six papers, respectively. Vitamin insufficiency, milder than deficiency, does not cause any phenotypic abnormalities, but is associated with increased risk for diseases, the most well-known example of which would be the increased fracture risk in vitamin D insufficiency.[21] In the case of vitamin B-12, pernicious anemia and subacute combined degeneration of the spinal cord are its deficiency diseases.[2] Its insufficiency causes hyperhomocysteinemia, which is a risk for various diseases such as atherosclerosis, fracture, and dementia.[4,6,22] Based on these considerations, we have defined the cut-off value of serum vitamin B-12 concentration as described above. In the current




**Graphical abstract**

study, hyperhomocysteinemia was observed in only severe deficiency group, which may be attributed to the fact that patients' folic acid status was high.[23,24] In Japan, general belief holds that vitamin B-12 deficiency occurs four or five years after gastrectomy because of large hepatic storage. However, we have shown that vitamin B-12 deficiency can exist even before gastrectomy. Gastrectomy is indicated for gastric cancer, and most cases with gastric cancer is secondary to long-lasting atrophic gastritis.[10] For its absorption, vitamin B-12 must be liberated from food by gastric acid. Then, impaired secretion of gastric acid in atrophic gastritis leads to vitamin B-12 malabsorption, and it is quite possible that patients with gastric cancer scheduled for operation is already vitamin B-12 deficient. In the current study, severe vitamin B-12 deficiency or deficiency was observed in 62.5 % of patients before gastrectomy. In contrast, some gastrectomized patients did not experience vitamin B-12 deficiency after gastrectomy for more than three years, which could be due to the difference in the duration of atrophic gastritis and preoperative vitamin B-12 status.

Some reports have been available from foreign countries showing comparable results to ours. Lim et al., in a Korean study including 161 patients after total or subtotal gastrectomy due to gastric cancer, reported that the percentage of patients with vitamin B-12 deficiency (< 200 pg/mL (148 pmol/L)) was 16.1 % and 50.0 % at two and three years after total gastrectomy, respectively.[25] In a Turkish study, Bilici et al. reported that 40 out of 72 (55.6 %) patients with gastric cancer developed vitamin B-12 deficiency (< 200 pg/mL) during the mean follow up of 29 months after subtotal or total gastrectomy.[26] We could find few related papers from Japan. Adachi et al. investigated the vitamin B-12 status and the influence of vitamin B-12 treatment in patients after gastrectomy.[27] All gastrectomized patients had vitamin B-12 deficiency (< 200 pg/mL) within 5 years. Also, of the ten patients who were measured for blood vitamin B-12 concentration every six months after gastrectomy, two, four, and three patients developed vitamin B-12 deficiency within one, two, and three years, respectively. In their results, oral vitamin B-12 supplementation significantly increased blood vitamin B-12 concentration, although intravenous or intramuscular vitamin B-12 injection is most popularly used for post-gastrectomy vitamin B-12 deficiency.[27] Other reports from abroad also reported the similar results on oral vitamin B-12 replacement.[28] Considering the high prevalence of vitamin B-12 deficiency early after gastrectomy and noninvasiveness of oral vitamin B-12 treatment, its employment might be considered.

Our results have another implication regarding the diagnosis of anemia. In the current study, patients with anemia had significantly lower serum ferritin and vitamin B-12 concentrations than those without anemia, indicating the coexistence of iron deficiency and vitamin B-12 deficiency. Nutritional anemia is associated with altered MCV; increase in vitamin B-12 deficiency and decrease in iron deficiency.[2,29] However, MCV was within the reference range in both groups; with and without anemia. Since vitamin B-12 deficiency and iron deficiency oppositely affect MCV, their coexistence would cancel out the effects on MCV.[17] Usually, vitamin B-12 deficiency is suspected by increased MCV, since blood vitamin B-12 concentration is not measured routinely. However, our current results that MCV does not necessarily increase even in vitamin B-12 deficiency when coexisted with iron deficiency strongly argue for the measurement of the blood vitamin B-12 concentration in patients with gastric cancer scheduled for gastrectomy. Since neurological impairment due to vitamin B-12 deficiency can be irreversible, overlooking vitamin B-12 deficiency is a serious problem.[1] Sakuta et al. studied blood vitamin B-12 and homocysteine concentrations in 31 gastrectomized men because of peptic ulcer or gastric cancer, and control subjects.[30] Gastrectomized patients had significantly lower blood vitamin B-12 concentration and higher homocysteine concentration than those in controls. In addition, they measured red bold cell distribution width (RDW)-SD, and suggested the coexistence of subclinical vitamin B-12 deficiency and iron deficiency though blood ferritin concentration or TIBC was not measured.

Our study has some limitations. First, this is a cross sectional study, and patients with gastrectomy do not represent the patients who were followed up from before the surgery. Second, we could not measure methylmalonic acid (MMA) concentration as a marker for vitamin B-12

deficiency. MMA has the advantage that it is influenced by vitamin B-12 status alone over homocysteine which is influenced by vitamin B-12, folic acid, and vitamin B-6 status.[1] Third, we could not measure RDW-SD and examine the possibility of chronic inflammation in the analysis in respect of anemia.[17] Finally, regarding the atrophic gastritis, detailed endoscopic findings could not be examined in the current study, and we are planning additional studies targeting the relationship between atrophic gastritis and vitamin B-12 status. Despite these limitations, however, this study is of possible clinical implication in that studies have been scarce studying the vitamin B-12 status in patients before and early after gastrectomy, also taking the diagnostic challenge in post-gastrectomy anemia into consideration.

In conclusion, vitamin B-12 deficiency is present before gastrectomy and after gastrectomy within three years in patients with gastric cancer. In gastrectomized patients, deficiencies of iron and vitamin B-12 often coexist, posing a diagnostic problem on the use of MCV in the evaluation of post-gastrectomy anemia. In an era of long-lasting atrophic gastritis as the leading cause of gastric cancer, much more attention should be paid on vitamin B-12 status in patients with gastric cancer.

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**AUTHOR DISCLOSURES**

The authors declare no conflicts of interest associated with this manuscript.

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