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Nutritional Demand after Gastric Surgery

*Abdulaziz Al-Nasser[1], Nasser Alzerwi[2], Marwah Sami M Hussain[3], Khuloud Omar Bukhari[4], Helayel Almodhaiberi[3] and Bandar Idrees Ali[3,4]**

[1]Department of Biological & Medical Research, King Saud University, Saudi Arabia

[2]Department of Surgery, Al-Majmah University, Saudi Arabia

[3]Department of Surgery, Prince Sultan Military Medical City, Saudi Arabia

[4]Ministry of Health, Saudi Arabia

Abstract

Incidence of gastrectomies has been increased rapidly worldwide in the last four decades. There is a wide variety of gastric benign or malignant pathology which necessitate a partial or complete removal of the stomach. This includes peptic ulcer diseases, gastric submucosal tumors, obesity and its related diseases and gastric malignancy. Therefore, the importance of stomach surgery from a nutritional point of view should be reviewed. It is not uncommonly neglected by clinicians despite being important and frequent long-term metabolic complications. The incidence and timing of the occurrence of malnutrition following gastrectomy are closely associated with the extent of gastrectomy and the reconstruction method used patient's general initial condition and the underlying pathology.

Keywords: Gastrectomy; Gastric disease; Cancer; Malnutrition vitamin B12; Intrinsic factor

Introduction

Nowadays, gastric surgery has mainly two paradigms: Gastric cancer and bariatric surgery. Gastric cancer remains one of a major health-related concern and one of the leading causes of cancer death worldwide. It is the second most common cause of cancer-related death worldwide [1,2]. Over 10 years, from 2003 to 2013, the number of bariatric surgeries increased from 150,000 to almost 470,000 annually [3]. The total number of bariatric procedures worldwide was estimated at 340,768 in 2011 [4]. This is not the only reasons for gastrectomy, patients with a diagnosis of gastric trauma or complicated peptic ulcer disease may also require gastrectomy.

The primary function of the stomach is to act as a reservoir, initiate the digestive process, and release its contents gradually into the duodenum (first part of small bowel), so that digestion in the small bowel is optimally performed. However, the nutritional role of the stomach is not always well understood.

The anatomical changes that may result after gastrectomy surgery affect the emptying time of the stomach. If the pyloric (anatomical valve) located between the stomach and first part of the small intestine (duodenum) is removed, the stomach will not be able to retain food long enough for partial digestion to occur by gastric juices. Abnormal vitamin metabolism after gastric surgery for gastric cancer has been reported over the past 20 years and food then travels too rapidly into the small intestine producing a condition known as post-gastrectomy syndrome.

As a sequence, malnutrition occurs in short or long term. It is one of the main complications following gastric surgery and more in gastric cancer patients. Total Gastrectomy (TG), by altering the physiology of digestion and damaging the delicate mechanisms at the gastro-esophageal junction, will inevitably lead to malnutrition.

Dietary life after gastric surgery in patients with gastric cancer may differ from that in patients with morbid obesity: in contrast to patients with obesity, patients having gastrectomy for gastric cancer do not restrict their dietary intake for weight reduction followed up in the long term. Although weight loss is not uncommon among cancer patients and can be due to many causes, including depression, vomiting, inability to ingest or absorb adequate calories because of a mechanical problem with the alimentary tract, loss of appetite, and metabolic aberrations. Unintentional weight loss may be associated with decreased Quality of Life (QOL) and a poorer prognosis.

Generally speaking, significant weight loss defined as at least a 10% loss of body weight in 6

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Correspondence:
Bandar Idrees Ali, Department of Surgery, Prince Sultan Military Medical City, Riyadh, Saudi Arabia, E-mail: biaa1003@yahoo.com

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months' time [5]. It has been shown that at the time of diagnosis, 80% of patients with upper gastrointestinal cancer and 60% of patients with lung cancer have already experienced a significant weight loss, Good nutrition practices can help cancer patients maintain weight and the body's nutrition stores, offering relief from nutrition impact symptoms and improving quality of life [3,5]. Nutrition impact symptoms are those symptoms that impede oral intake. They include but are not limited to, anorexia, nausea, vomiting, diarrhea, constipation, stomatitis, mucositis, dysphagia, alterations in taste and smell, pain, depression, and anxiety [6]. Early recognition and detection of risk for malnutrition through nutrition screening followed by comprehensive assessments are increasingly recognized as imperative in the development of standards of quality of care in oncology practices [2]. Nutritional status is often jeopardized by the natural progression of neoplastic disease. Anorexia, the loss of appetite or desire to eat, is typically present in 15% to 25% of all cancer patients at diagnosis and may also occur as a side effect of treatments.

Anorexia can be exacerbated by chemotherapy and radiation therapy side effects such as taste and smell changes, nausea, and vomiting. Surgical procedures, including esophagectomy and gastrectomy, may produce early satiety, a premature feeling of fullness [4]. Depression, loss of personal interests or hope, and anxious thoughts may be enough to bring about anorexia and result in PCM [3].

Anorexia can hasten the course of cachexia, a progressive wasting syndrome evidenced by weakness and a marked and progressive loss of body weight, fat, and muscle [3]. Cachexia is estimated to be the immediate cause of death in 20% to 40% of cancer patients; it can develop in individuals who appear to be eating adequate calories and protein but have primary cachexia whereby tumor-related factors prevent maintenance of fat and muscle. Particularly at risk are patients with diseases of the gastrointestinal tract. The etiology of cancer cachexia is not entirely understood. Cachexia can manifest in individuals with metastatic cancer as well as in individuals with localized disease. Several theories suggest that cachexia is caused by a complex mix of variables, including tumor-produced factors and metabolic abnormalities [7]. The basal metabolic rate in cachectic individuals is not adaptive, that is, it may be increased, decreased, or normal [8]. Some individuals respond to nutrition therapy, but most will not see a complete reversal of the syndrome, even with aggressive therapy [6]. Thus, the most prudent and advantageous approach to cachexia is the prevention of its initiation through nutrition monitoring and nutrition intervention [8].

Anemia

Two types have been identified: One is related to a deficiency in iron and the other is related to impairment in vitamin B12 metabolism. Iron-deficiency anemia is more common than vitamin B12 deficiency anemia in patients after gastrectomy. Iron deficiency after gastrectomy is primarily caused by decreased iron absorption due to reduced food intake and bypass of the duodenum in some methods of reconstruction [9,10]. The incidence of iron deficiency, based on physiological changes after gastrectomy, is closely associated with the extent of gastrectomy and method of reconstruction. Folate, either alone or in combination, have been reported after gastric surgery [4-6]. Also, malabsorption of fat after gastrectomy has been reported [2], suggesting potential malabsorption of fat-soluble vitamins such as vitamin D (VD), vitamin A (VA), and vitamin E (VE) after the operation. However, most surgeons are unaware of changes in VD, VA, and VE after gastrectomy for gastric cancer.

Anemia is one of the most common nutritional problems post TG and occurs in over three-quarters of patients. Iron deficiency anemia is usually caused by a reduction in intake. Also, other factors include: the failure to reduce the ferric to the ferrous form of iron due to lack of acid, the bypass of the major resorptive site (the duodenum), decreased liberation of food-bound iron due to lack of proteolysis, rapid GI transit, and increased losses due to occult bleeding.

Iron deficiency

Iron deficiency anemia is a common effect of partial or total gastrectomy. Most iron absorption occurs in the duodenum or upper part of the small intestine. Most partial and total gastrectomy procedures will bypass the duodenum, making iron absorption more difficult. In addition, rapid transit of food through the intestine allows for decreased time for absorption of iron. Finally, after partial or total gastrectomy, less acid is available in the small intestine. Gastric acid converts iron to a form more readily absorbed by the body. These factors along with a decreased intake of foods that are good sources of iron contribute to post-gastrectomy iron deficiency.

Your health care provider will test your serum ferritin level to determine iron deficiency. If you are deficient, you may need oral iron supplementation. Adults are usually requiring a supplementation of 60 mg to 200 mg elemental iron daily. Oral iron is available as ferrous sulfate (65 mg elemental iron), ferrous gluconate (26 mg elemental iron), or ferrous fumarate (106 mg elemental iron). Iron supplements are usually given three times per day to maximize absorption. Taking iron supplements with foods rich in Vitamin C will also enhance absorption. Sustained release tablets may result in decreased absorption for patients who have had a total gastrectomy.

Some people have difficulty taking iron supplements due to side effects such as nausea and constipation. If this is the case, it may help to start slowly at a reduced dose and work up to the recommended amount. Some supplementation is usually better than no supplementation. It may also help to include iron-rich foods in your diet. Meat, fish, and poultry contain heme iron which more available to your body than non-heme iron.

Good dietary sources of iron include beef, veal, clams, oysters, shrimp, sardines, bran flakes and other fortified cereals, cream of wheat, oatmeal (fortified), baked potato with skin, dry beans (navy, lima, lentils, kidney), soybeans, tofu, spinach and dried prunes and dried apricots.

Eating food rich in vitamin C with these foods high in iron will enhance iron absorption. Food rich in vitamin C include orange, grapefruit, cantaloupe, pineapple, strawberries, raspberries, tomatoes, broccoli, cauliflower, spinach, kale, asparagus, potatoes and sweet potatoes.

It is caused by various mechanisms and most cases of anemia in gastrectomized patients are due to iron deficiency, abnormal vitamin B12 metabolism, or both [11,12]. It is highly associated with impaired quality of life and performance status in patients with cancer [5,6]. Anemia also has the potential to adversely affect the therapeutic efficacy and survival of patients with cancer because it compromises the efficacy of radiotherapy and the response to chemotherapy. Anemia after gastrectomy is commonly neglected by clinicians despite being an important long-term metabolic sequela with high prevalence [8-12]. However, identifying individuals with iron deficiency or iron-

deficiency anemia after gastrectomy is difficult because the symptoms are general, vague and nonspecific, and physicians focus only on improving the survival of these patients with cancer. Previous studies of iron deficiency after gastrectomy were performed a half-century ago with small study populations. Moreover, most studies did not regularly examine hematologic and nutritional profiles related to iron deficiency. The incidence of iron deficiency, based on physiological changes after gastrectomy, is closely associated with the extent of gastrectomy and method of reconstruction.

Vitamin B12: Vitamin B12 deficiency is usually evoked in presence of compatible hematologic or clinical (usually neurologic) signs. However, many cases of deficiency are little or asymptomatic. Pernicious anemia, caused by a deficiency in intrinsic factor, is a rare cause of vitamin B12 deficiency. The most frequent causes are gastric disorders, pancreatic insufficiency, or chronic drug treatment (proton pump inhibitors or metformin) that interfere with the digestion of vitamin B12 digestion, or disorders of the ileum mucosa reducing the absorption of vitamin B12. Oral treatment of vitamin B12 deficiency is possible whatever the etiology, but it has only been validated in small series. Parenteral treatment remains indicated for severe neurologic deficits or whenever patient adherence with treatment is doubtful.

People who have had a total gastrectomy will need to supplement their diet with regular vitamin B12 injections. Two components necessary for vitamin B12 absorption, gastric acid, and intrinsic factor, are less available or not available at all with the removal or all or part of the stomach. Therefore, people who have had a partial or complete gastrectomy will need to supplement their diet with oral vitamin B12 or intramuscular or subcutaneous injections of vitamin B12. Vitamin B12 levels were in the lower third of the reference range without supplementation. Therefore, it is likely that, without supplementation, vitamin B12 deficiencies can occur, especially more than two years after operation due to the emptying of vitamin B12 storage. Therefore, a general vitamin B12 supplementation is advisable to avoid pernicious anemia and to prevent neuropathic pain. Normal B12 levels vary with the laboratory used but are usually in the range of 200 pg/ml to 900 pg/ml. Levels below 200 pg/mL may indicate a deficiency. Symptoms of Vitamin B12 deficiency may include numbness, weakness, abnormal gait, memory loss, depression, and anemia among others. It is important to have your B12 levels monitored by your healthcare provider at baseline following surgery and then every 3 months until they are normalized. Ongoing monitoring of B12 levels should occur on a yearly basis.

Traditionally B12 has been treated with intramuscular injections. For B12 deficiency states, this supplementation may begin with 1,000 mcg every day for 1 week followed by 1,000 mcg every week for 4 weeks. Or, alternatively, weekly injections of 1000 mcg of vitamin B-12 for 5 to 6 weeks, followed by monthly injections. To maintain normal B12 levels, monthly 1,000 mcg injections are usually required for life. It is important to discuss with your health care provider as there may be individual cases were more or less supplementation is appropriate. There are a variety of ways to administer vitamin B12. The traditional approach is intramuscular injections. More recently subcutaneous injections have been used. Both of these types of administration routes are effective. It is important to discuss with your physician which route would be best for you. In addition to the intramuscular and subcutaneous administration, research has shown that oral B12 supplementation (B12 tablets) with 1,000 to 2,000 mcg per day is as beneficial as intramuscular supplementation (B12 shots) – especially once you are at baseline. There is evidence that your small intestine can start producing some intrinsic factor following a gastrectomy. Sublingual and intranasal are other possible ways to supplement with B12 once B12 levels have stabilized. It is important to discuss alternative methods of administration of B12 with your health care provider to determine which supplementation route works best for you. Depending on your lifestyle you may find it easier to have a monthly injection while others would be more compliant with a daily tablet. If you do change administration route of B12 i.e. from injection to oral, more frequent monitoring may be needed until baseline levels are achieved.

Folate deficiency: Although not common, folate deficiency may develop after gastrectomy due to malabsorption and impaired digestion. If folate deficiency is suspected, your health care provider should obtain a Red Blood Cell (RBC) folate level (rather than serum folate) to determine if there is an actual folate deficiency. Vitamin B12 is needed to activate folate and supplementing with folate may mask a vitamin B12 deficiency so vitamin B12 levels should be considered before supplementing with folate. For this reason, it is important to discuss any concerns you have about folate deficiency with your health care provider.

Vitamin D

VD is synthesized in the skin in response to ultraviolet radiation and is also absorbed from the diet. It is then transported to the liver, where it undergoes 25-hydroxylation, resulting in the formation of 25-hydroxyvitamin D3. This metabolite is the major circulating form of VD. The final step in hormone activation, 1α-hydroxylation, occurs in the kidney [3]. Changes in serum VD levels after gastrectomy were reported in 2007 [4]. The serum level of 1,25(OH)2VD, the most active metabolite of VD, was found to be normal after gastrectomy in all 22 patients studied. The serum 1,25(OH)2VD level did not decrease with time after gastrectomy and was unaffected by the type of gastrectomy procedure. In contrast, the serum level of 25(OH)VD, which is weakly active, was below the lower limit of normal in 7 (32%) of the 22 patients. One (17%) of the 6 patients tested less than 1 year postoperatively had a serum 25(OH)VD level below the normal range, versus 6 (38%) of the 16 patients tested 1 year or more after surgery, although the difference between the groups was not statistically significant. However, the mean serum level of 25(OH)VD was significantly lower in patients tested 1 year or more postoperatively than in those tested less than 1 year postoperatively ($p=0.041$) and was also significantly lower in patients who had received a total gastrectomy than in those who had received other gastrectomy procedures. The level of 24,25(OH)2VD, a weekly active metabolite of 25(OH)VD, was below the normal range in 19 (86%) of the 22 patients. The level of 24,25(OH)2VD was below the normal range in 5 (83%) of 6 patients tested less than 1 year postoperatively, as compared with 14 (88%) of 16 patients tested 1 year or more postoperatively. Although the difference between the groups was not significant, one of the patients tested 1 year or more postoperatively had a 24,25(OH)2VD level above the normal range. The mean 24,25(OH)2VD level was slightly but not significantly lower in patients tested 1 year or more postoperatively than in those tested less than 1 year postoperatively, as was the case for 25(OH)VD. The mean 24,25(OH)2VD level was slightly but not significantly lower in patients who had received a total gastrectomy. The patients thus showed decreased serum levels of 25(OH)VD3 and 24,25(OH)2VD3, which are weakly active metabolites of VD. This finding suggests that

a homeostatic response maintains a normal level of 1,25(OH)2VD3, which has a pivotal role in the regulation of calcium metabolism. These data were obtained in Japanese patients. Studies in American patients have reported that the serum 25(OH)VD3 level decreased and the serum 1,25(OH)2VD3 level increased after gastrectomy [5]. There may be racial differences in VD metabolism. Vitamin D VD is synthesized in the skin in response to ultraviolet radiation and is also absorbed from the diet. It is then transported to the liver, where it undergoes 25-hydroxylation, resulting in the formation of 25-hydroxyvitamin D3. This metabolite is the major circulating form of VD. The final step in hormone activation, 1α-hydroxylation, occurs in the kidney [3]. Changes in serum VD levels after gastrectomy were reported in 2007 [4]. The serum level of 1,25(OH)2VD, the most active metabolite of VD, was found to be normal after gastrectomy in all 22 patients studied. The serum 1,25(OH)2VD level did not decrease with time after gastrectomy and was unaffected by the type of gastrectomy procedure. In contrast, the serum level of 25(OH)VD, which is weakly active, was below the lower limit of normal in 7 (32%) of the 22 patients.

Bone disease: The bone disease occurs in 15% to 30% of patients after TG. Poor dietary intake, reduced absorption of vitamin D due to fat malabsorption, impaired calcium uptake due to calcium soap formation with steatorrhoea, and bypass of the duodenum have been proposed as causes.

Vitamins A and E: Malabsorption of various nutrients is attributable to environmental changes affecting digestion and absorption after gastric surgery for gastric cancer. Fat malabsorption after gastrectomy for gastric cancer has been reported [2]. Serum VA and VE levels decrease after gastrectomy for gastric cancer. Changes in serum VE and VA levels in patients who had previously undergone gastrectomy for gastric cancer were reported in 2007 [13-15]. In 12 (21.8%) of the 55 patients, serum VE levels decreased. In contrast, serum VA levels decreased in only 1 (1.8%) of 55 patients. The incidence of low VE levels in the total gastrectomy group (34.6%, 9/26) was significantly higher than that in the subtotal gastrectomy group (10.3%, 3/29; p=0.048). When serum VE levels were compared according to the reconstruction procedure, the proportion of patients with low VE levels was significantly higher in the group without food passage through the duodenum (34.4%, 11/32) than in the group with food passage through the duodenum (4.3%, 1/23; p=0.009). When serum VE levels were compared according to the time after gastrectomy, the interval after surgery in the low VE group (7.3 years) was significantly longer than that in the normal VE group (5.1 years; p=0.024). Serum levels of VA and total cholesterol in the low VE group were significantly lower than those in the normal or high VE group. In addition, the white cell count was significantly higher in the low VE group than in the normal or high VE group. The serum total cholesterol level significantly correlated with the serum VE level (r=0.697, p<0.001). Gender, age, body weight, body mass index, total protein, albumin, red cell count, hemoglobin, hematocrit, platelet, vitamin B12, and triglyceride levels were unrelated to low VE levels. Among the 55 patients, 7 (12.7%) had peripheral neuropathy. Sensory polyneuropathy developed in 7 (58.3%) of the 12 patients in the low VE group and was characterized by the glove-and-stocking type of superficial sensory loss and decreased deep tendon reflexes. All patients with sensory polyneuropathy responded to treatment with oral VE. On multivariate analyses, the white cell count and total cholesterol level were associated with low VE levels. The total cholesterol level was the most salient contributing factor. Decreased VE levels ascribed to VE malabsorption after gastrectomy for gastric cancer were observed in approximately 15% of patients, some of whom also had sensory polyneuropathy. Patients with a low serum level of VE, a fat-soluble vitamin, tended to have significantly decreased levels of total cholesterol, which may be attributed to vitamin E malabsorption as well as fat malabsorption. In patients with neurologic symptoms and low serum total cholesterol levels that do not respond to treatment with vitamin B12, hypovitaminosis E should be suspected. Malabsorption of various nutrients is attributable to environmental changes affecting digestion and absorption after gastric surgery for gastric cancer. Fat malabsorption after gastrectomy for gastric cancer has been reported [2]. Serum VA and VE levels decrease after gastrectomy for gastric cancer. Changes in serum VE and VA levels in patients who had previously undergone gastrectomy for gastric cancer were reported in 2007 [14,15]. In 12 (21.8%) of the 55 patients, serum VE levels decreased. In contrast, serum VA levels decreased in only 1 (1.8%) of 55 patients. The incidence of low VE levels in the total gastrectomy group (34.6%, 9/26) was significantly higher than that in the subtotal gastrectomy group (10.3%, 3/29; p=0.048). When serum VE levels were compared according to the reconstruction procedure, the proportion of patients with low VE levels was significantly higher in the group without food passage through the duodenum (34.4%, 11/32) than in the group with food passage through the duodenum (4.3%, 1/23; p=0.009). When serum VE levels were compared according to the time after gastrectomy, the interval after surgery in the low VE group (7.3 years) was significantly longer than that in the normal VE group (5.1 years; p=0.024). Serum levels of VA and total cholesterol in the low VE group were significantly lower than those in the normal or high VE group. In addition, the white cell count was significantly higher in the low VE group than in the normal or high VE group.

Discussion

Nutritional deficits preoperatively existing deficits should be supplemented. Laboratory parameters should be monitored regularly to detect early nutritional deficiencies and to initiate appropriate therapies. Moreover, supplementation of zinc should be based on symptoms (hair loss, immune deficiency, dry skin). High zinc intake reduces absorption of copper and iron and vice versa. Medication of zinc and calcium should be suggested to intake at different times because zinc reduces calcium absorption. Supplementation of selenium is not generally necessary because postoperative deficiencies normalize on their own without supplementation, and an adequate, varied food intake seems to be sufficient. Regular determination of laboratory parameters should be performed 3 and 6 months after the operation and semiannually thereafter; if the patient's weight stabilizes, laboratory parameters should be determined once a year. Iron deficiency in the main nutritional deficit of patients after gastrectomy, and its incidence was different according to the extent of gastrectomy and method of reconstruction. The number of patients who developed iron deficiency gradually increased with time from their gastrectomy due to poor nutritional intake by the patients, which lead to depletion of body store or malabsorption effect of surgery. Moreover, the necessity for iron replacement and repeated iron supplementation vary according to the underlying patient's overall condition, underlying disease, duration post-surgery, and the extent of resection and reconstruction methods. Although the mechanisms of negative iron balance after gastrectomy are not fully established, there are several hypotheses to explain body iron depletion in patients after gastric resection. Body iron deficiency is aggravated by

poor nutritional status and decreased dietary iron intake [12,16,17]. Increased iron depletion can also result from gastrointestinal blood loss, usually at the anastomotic site [9,18]. Bacterial overgrowth in the blind loops can result in iron-losing enteropathy [19]. However, alterations in digestion and impaired iron absorption are considered the leading factors contributing to an iron deficiency after gastrectomy [8]. Malabsorption of dietary iron possibly results from the reduction of gastric acid secretion and bypassing of the duodenum [12,13]. Reduced gastric acidity, a common consequence of gastrectomy, impairs the conversion of non-heme iron (Fe3+) to the ferrous form (Fe2+), which is more absorbable [18]. Moreover, some methods of reconstruction after gastrectomy may lead to decreased iron absorption due to bypass of the major sites of iron absorption: the duodenum and the proximal jejunum. It has been shown that primary absorption of dietary iron occurs in the duodenal mucosa in mammals. Through the entire small intestine, iron absorption is mediated by proteins on biological membranes; however, the majority of the absorption of molecular iron and heme iron occurs across the apical and basolateral membranes of duodenal enterocytes [9]. A transport protein named "heme carrier protein 1" was recently identified in the duodenum [18]. Moreover, patients who underwent total gastrectomy with preservation of the duodenal passage by a type of jejunal pouch interposition had significantly higher concentrations of iron and hemoglobin than those patients with a Roux-en-Y reconstruction [13]. Thus, the duodenal passage is necessary for the absorption of dietary iron. With these mechanisms of negative iron balance after gastrectomy, the incidence of iron deficiency will be different according to the extent of gastrectomy and reconstruction method. Considering the long-term sequela of iron metabolism, the surgeons' first choice of reconstruction after distal gastrectomy would be gastroduodenostomy rather than gastrojejunostomy, provided it is surgically and oncologically safe. In this context, pylorus-preserving gastrectomy would be an effective alternative to gastroduodenostomy, although its indication is a bit limited. Because pylorus-preserving gastrectomy conserves the pyloric ring and duodenal passage, it may prevent the sequelae of gastroduodenostomy such as reflux gastritis or dumping syndrome associated with rapid gastric emptying and may have better nutritional status and hemoglobin levels than gastroduodenostomy [12]. Thus far, total gastrectomy has been regarded as the standard treatment of gastric cancer located in the upper body. Other types of surgery such as total gastrectomy with jejunal interposition and proximal gastrectomy with preservation of the duodenal passage using various methods of reconstruction may have a theoretical benefit for iron metabolism [17,18]. Thus, a comparative study regarding different degrees of resection and reconstruction methods is needed to clarify iron metabolism after total gastrectomy. The prophylactic iron supplementation can be considered to prevent the occurrence of iron deficiency after gastrectomy. Although little has been studied about this idea in patients with gastric cancer, it has been shown in a randomized study that prophylactic supplementation of oral iron successfully prevented iron deficiency after Roux-en-Y gastric bypass for morbid obesity [16]. Even with iron supplementation in patients with anemia, serum ferritin levels decreased continuously in all groups according to the method of reconstruction, and these levels were slightly higher in the gastroduodenostomy group than in the gastrojejunostomy group. Ferritin is the cellular storage protein for iron, and serum ferritin is an important parameter for assessing total body iron stores [10]. The measurement of ferritin provides the most useful laboratory marker for body iron stores [17]. Thus, repeated measurement of serum ferritin is a suitable method for estimating changes in iron balance. In addition, transferrin levels continuously increased among our patients. These changes in serum ferritin and transferrin levels were different from those of BMI, which was stabilized 3 months after gastrectomy regardless of the method of reconstruction. Therefore, weight loss and decreased dietary iron absorption may be caused by different mechanisms. Interestingly, TIBC levels reached a plateau 3 months after surgery in the gastroduodenostomy group, whereas these levels increased continuously in the gastrojejunostomy and total gastrectomy groups. These differences in TIBC levels are correlated with the incidence of iron deficiency according to the method of reconstruction; however, further investigation is needed.

The retrospective nature of our study limited our ability to evaluate the relationship between the timing of the occurrence of iron deficiency and patients' dietary iron intake. It is crucial to evaluate the development of iron deficiency in patients with gastric cancer and in healthy persons. Limited information regarding iron supplementation after gastrectomy may have influenced the incidence and occurrence of iron deficiency among the patients included in the analyses. In addition, the incidence of iron deficiency may have been underestimated because some patients may have received iron supplementation outside of our hospital. However, it was impossible to obtain the entire medication histories of the patients retrospectively. Moreover, we did not use the ferritin criteria for iron replacement. The lack of evaluation of the quality of life of patients, including the presence of symptoms related to iron deficiency, is another limitation of our study. These limitations primarily arose from the retrospective nature of this study, and thus, well-designed prospective studies would supplement our findings and overcome these limitations.

Although the study was performed in a retrospective manner, the hematologic profiles of all of the patients included in the study were evaluated prospectively. These detailed hematologic profiles were serially examined in a large cohort of patients. Moreover, the patients analyzed had early gastric cancer without any evidence of recurrence during the follow-up period, and these patients had no other history of cancer. Therefore, the influence of the myelosuppressive effects of chemotherapy and anemia caused by the chronic disease process associated with malignancy was completely eliminated. Thus, the obtained results regarding the incidence of iron deficiency and iron-deficiency anemia were relatively objective.

In conclusion, the results of this study revealed that the incidence of iron deficiency is remarkably high in patients who underwent gastrectomy in a relatively early period after surgery. Therefore, frequent routine examination of serum ferritin levels is recommended during the follow-up for gastrectomized patients.

Moreover, the incidence of iron deficiency was different according to the extent of gastrectomy and method of reconstruction. To preserve iron metabolism, gastroduodenostomy would be considered the optimal method of reconstruction after distal gastrectomy when it is possible to perform the surgery in an oncologically safe manner.

Complications of the post-gastrectomy syndrome include anemia as a result of vitamin B12 or iron malabsorption and osteoporosis. These problems generally occur months or even years after gastric surgery. Vitamin B12 malabsorption occurs when a protein known as an intrinsic factor is either not produced by the stomach (this is a condition called pernicious anemia) or when the proximal stomach is resected (the portion of the stomach that produces intrinsic factor). In either case, that absence of intrinsic factor leads to the poor

absorption of vitamin B12. Under normal circumstances, intrinsic factor binds to vitamin B12 and assists with the absorption of this vitamin in the lower portion of the small bowel. When vitamin B12 is poorly absorbed, anemia and, in some cases, poor nerve function can occur. This generally does not happen for several years because vitamin B12 is stored in large amounts in the liver.

Iron deficiency anemia develops because removal of the stomach often leads to a marked decrease in the production of gastric acid. This acid is necessary to convert dietary iron to a form that is more readily absorbed in the duodenum. Anemia usually does not occur for a few years after gastric surgery because iron is stored in moderately large amounts in the bone marrow, where red blood cells are produced.

Osteoporosis develops as a result of poor calcium absorption, another problem that occurs after gastric surgery. Under normal circumstances, calcium absorption, which occurs in the duodenum and proximal small bowel, is modest at best, with large amounts being lost in the bowel movement. Following gastric surgery, calcium absorption is even less efficient as a result of rapid emptying of the stomach. Calcium also binds tightly to unabsorbed dietary fat which further interferes with its absorption. Symptoms of osteoporosis may develop ten or more years after gastric surgery because of a large amount of calcium that is normally stored in bone.

Treatment of post-gastrectomy syndrome includes initiation of a post-gastrectomy diet, which is high in protein, low in carbohydrates, and low in concentrated sweets. This diet should be consumed as five or six small meals, with limited fluid intake during meals. On occasion, medications may be required to help control these symptoms. Vitamin B12 deficiency can be prevented by providing vitamin B12 shots once each month indefinitely. Oral iron and calcium supplements are often needed to prevent the development of deficiencies in these minerals.

Postoperative artificial feeding

Traditionally, TG patients were kept fasting or given TPN (Total Parenteral Nutrition) because of fear of oesophagojejunal anastomosis, oral intake being forbidden until all risk of anastomotic leakage had passed (8-12 days). Since food intake will not be normal for some time after this, even most well-nourished patients will suffer postoperative malnutrition unless some form of alternative feeding is instituted.

The use of nutritional support for malnourished patients in the post-operative period has been shown to decrease weight loss and to improve recovery. Enteral feeding via a percutaneous catheter jejunostomy, placed at the conclusion of laparotomy, is a safe and effective means of administering enteral nutrition. This procedure rules out the risks of aspiration or anastomotic leakage which are possible with nasojejunal tubes.

Furthermore, administration of immune enhancing formulas (arginine and omega three fatty acids) can ameliorate host defenses and control the inflammatory response.

The presence of a jejunostomy tube can also mean that for patients with inadequate intakes on discharge, overnight supplemental feeding at home is possible. Night jejunostomy feeding can help reverse malnutrition and allows for continuous entry of liquid nutrition into the upper gut, which to some extent mimics pyloric function and can improve maldigestion. As it is supplied in a continuous manner to pancreatic enzymes and jejunal mucosa, it avoids the periodical 'flooding' typical of a normally ingested meal in the TG patient.

Reduced intake and weight loss

Voluntary reduction in calorie intake due to anorexia, the absence of hunger sensations and post-prandial abdominal discomfort occurs in many patients. The reduction in calorie intake may be drastic and is considered the main factor responsible for weight loss. Several studies have reported on severe weight loss which can be from 18 kg to 29 kg post operatively and can continue for up to four years.

Bozetti, 1 reporting on 44 disease-free patients after a mean of three years after the operation, found that weight loss reaches its nadir by the 15th post-operative month. This study showed that cancer-free patients lose weight after gastrectomy. After 24 months these patients still had intakes far less than the recommended 35 kcals/kg/day.

Eating-related symptoms

Gastrectomy patients have been shown to have an average of three eating-related symptoms. Amongst the most frequently cited symptoms are:

- 48% reporting early satiety
- 26% epigastric fullness
- 26% epigastric pain
- 43% reflux
- 22% diarrhea
- 17% nausea.

Total gastrectomy can dramatically reduce the reservoir into which patients can eat (Figure 1). 'Small stomach syndrome' can mean that patients become very selective in their choice of foods avoiding hyperosmolar, starchy and high-volume foods.

Maldigestion and malabsorption

Maldigestion after TG has been described as pancreaticocibal asynchronism. Factors increasing malabsorption after TG include:

- defective stimulation of biliary and pancreatic secretions by ingested food bypassing the duodenum
- inadequate mixing of biliary and pancreatic secretions with food meaning that biliary and pancreatic secretions reach the gastrojejunostomy only after the food has already emptied from the stomach and bypassed distally into the jejunum
- loss of duodenal absorptive surface which is the principal site for absorption of iron, calcium, fat, and carotene
- stasis in the afferent loop can lead to bacterial overgrowth and abnormalities in bile salt metabolism.

After TG, bypass of the duodenum results in the decreased release of secretin and CCK and a decreased output of pancreatic enzymes leads to impairment of pancreatic function. The exocrine pancreatic function can be assessed by the pancreolauryl test and has been shown to worsen in the second-year post-surgery.

Diarrhea

Diarrhea has been reported in patients within an hour or two of eating and arises from an increased intestinal transit. Bragelman 2 reported on a 22% incidence of shortened intestinal transit in TG patients. Other factors implicated in its etiology include a pre-existing disease such as coeliac disease, bacterial overgrowth and inadequate

digestion and absorption of nutrients because of inadequate time for absorption. Patients with severe steatorrhea can excrete fat in up to four times normal amounts.

Dumping syndrome

Dumping syndrome is extremely rare after TG. Early symptoms (30 min to 60 min post meal) include hypotension and tachycardia and are due to the rapid emptying of the gastric remnant into the jejunum.

Late symptoms (90 min to 180 min post meal) are attributed to reactive hypoglycemia following overproduction of insulin in response to rapid absorption of glucose. It is treated by limiting the amounts of refined sugars and avoiding liquids with meals to slow down gastric emptying.

Several reports note that TG patients become progressively malnourished if they are not controlled by a nutritional follow-up. Unpublished data from our unit showed that 60% of patients seen in OPD experience significant to severe weight loss.

Dietary advice centers on small frequent energy dense meals and snacks, supplementary nutritional drinks and good sources of iron, calcium, and vitamin D. Foods high in fiber should only be taken in small amounts to minimize satiety, fluids should be taken separately from meals to reduce satiety and patients should avoid filling up on nutritionally dilute food and fluids.

Intramuscular vitamin B12 is required and possibly a multivitamin and mineral supplement. Form many patients' proprietary products such as tasteless powered supplements of carbohydrate and protein can be prescribed and are very useful for increasing intake without affecting volume or taste. To obtain an adequate calorie intake strict nutritional follow up should be started as soon as possible to avoid a sharp weight loss in the early postoperative course when the main dietary problems occur.

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