Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2021; 38(3): 318-321
doi: 10.52142/omujecm.38.3.21

Can histopathology of gastric tissue resected in sleeve gastrectomy be informative about serum iron levels?

Yasemen ADALI[1,*], Özge ERTENER[1], Hatice BEŞEREN[2], Kenan BİNNETOĞLU[3]

[1] Department of Pathology, Faculty of Medicine, Izmir University of Economics, Izmir, Turkey
[2] Department of Pathology, Faculty of Medicine, Kafkas University, Kars, Turkey
[3] Department of General Surgery, Faculty of Medicine, Kafkas University, Kars, Turkey

Received: 19.01.2021 • **Accepted/Published Online:** 02.02.2021 • **Final Version:** 23.04.2021

Abstract

One of the most common post-operative deficiencies after bariatric surgery is iron deficiency and one of the important determinants of post-operative iron deficiency is the preoperative condition. In this study, it was aimed to investigate the relationship between iron levels and histopathological findings observed in gastric tissue resected in sleeve gastrectomy. Preoperative and postoperative iron levels were compared with the presence of inflammation, atrophy, *Helicobacter pylori*, intestinal metaplasia, lymphoid follicles, and lymphoid aggregates observed in patients operated due to morbid obesity. The postoperative serum iron levels and preoperative values were compared and a statistically significant increase was found due to the use of iron-containing preparations after the operation. Among the parameters evaluated, inflammation, atrophy, *Helicobacter pylori*, intestinal metaplasia, and the presence of lymphoid follicles were not found to be associated with iron levels, but it was noted that the presence of lymphoid aggregate in all cases and male cases was correlated with preoperative low iron levels (p values 0.047 and 0.015 respectively). In this study, which investigated the role of histopathological findings in the prediction of iron deficiency in sleeve gastrectomies, the relationship between preoperative iron levels, which was reported to be predictive for post-operative iron deficiency, and the presence of lymphoid aggregates was revealed. It is thought that other histopathological findings such as the presence of lymphoid follicle and *Helicobacter pylori* are also important in terms of iron levels but could not be revealed due to the limitations of the study.

Keywords: iron deficiency, sleeve gastrectomy, histopathology, lymphoid aggregate

1. Introduction

Obesity, one of the most important health problems of present and future time, is defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that poses a risk to the health of the person. (World Health Association, 2020). Obesity, which can be considered pandemic in developed and developing countries; is an important cause of mortality due to increased risk in neoplasms such as breast, endometrium, kidney and colon cancer apart from it's morbidity and accompanying diseases like diabetes mellitus (DM), heart diseases, hypertension, fatty liver disease and sleep apnea syndrome (Sjostrom et al., 2004); Stephenson and Rose, (2003); International Agency for Research on Cancer, 2002). Obesity grading is generally made according to WHO and a body mass index (BMI) above 30 is called obesity. Although there are various treatment options in the treatment of obesity, the method chosen is mostly surgical in patients with BMI above 40, which is called class III obesity. The methods used in obesity surgery are mostly function limiting and are examined under the title of bariatric surgery. Gastric band application, sleeve gastrectomy and gastric bypass are among the methods commonly used today. In sleeve gastrectomy, the stomach is removed along the greater curvature and this resected stomach tissue is sent to the pathology laboratory for histopathological evaluation. Although histopathological evaluation is made according to Sydney classification, additional findings such as the presence of lymphoid follicles and aggregates, and possible benign or malignant neoplasms are also included in the pathology report.

Insufficient intake and malabsorption are two main etiological reasons for nutritional deficiencies. In cases undergoing sleeve gastrectomy or gastric bypass, various vitamin and mineral deficiencies are observed due to absorption defects, as gastric functions decrease or completely disappear (Coupaye et al., 2014; Saif et al., 2012; Al-Mutawa et al., 2018). These deficiencies may be at subclinical levels or, if left untreated, may present with pictures such as anemia or neurological deficits (Al-Mutawa et al., 2018). Vitamin B12 and iron are the most important molecules associated with stomach in terms of absorption. Iron, which is in the structure of hemoglobin and myoglobin, is vitally important. Although

* Correspondence: yasemenadali@hotmail.com

iron absorption is performed primarily in the duodenum and jejunum, iron absorption is negatively affected if gastric acidity is not sufficient. In this study, we aimed to evaluate the relationship between preoperative and postoperative iron levels and histopathological findings in morbid cases by evaluating resection material after sleeve gastrectomy.

2. Materials and methods

Sixty patients who underwent sleeve gastrectomy in a 3-year period due to morbid obesity were evaluated in the study. Cases without pathology archive material were not included in the study. The sections stained with hematoxylin & eosin (H&E), giemsa and alcian blue were obtained from the pathology preparation archive and re-examined. The presence and activity of gastritis, as well as atrophy, lymphoid follicle and lymphoid aggregate were evaluated in H&E sections. *Helicobacter pylori* presence were evaluated in giemsa stained sections, and intestinal metaplasia in alcian blue stained sections. Demographic data and serum iron levels of the cases were obtained from the hospital information management system. Cases with unknown preoperative and/or postoperative iron levels were excluded from the study. For preoperative iron data, the data closest to the operation date in the same week with the operation date and the data measured at the 6th month postoperatively for postoperative evaluation were used. Histopathological findings and iron levels were compared with the t test for independent variables, and preoperative and postoperative iron values were compared with the t test for dependent variables at 95% confidence interval. SPSS 15.0 package program was used for statistical analysis SPSS Inc. (Released 2006. SPSS for Windows, Version 15.0. Chicago, SPSS Inc.).

3. Results

The mean age of the cases was 35.5 ± 9.3, 45 (75%) cases were female and 15 (25%) cases were male. The mean age of female cases included in the study was 35.4 ± 9.2, and the mean age of male cases was calculated as 35.3 ± 10.3. The frequency of the histopathological findings observed separately in all cases, female and male cases are given in Table 1. A statistically significant increase was found when postoperative iron levels were compared with preoperative values (p = 0.000), since all patients were using a multivitamin tablet containing 14 mg iron once a day after the operation. The same significance was noticed in female and male cases (p values 0.011, 0.000, respectively). Preoperative and postoperative iron values of all cases, male and female cases are given in Table 2.

In the evaluation of all cases, chronic gastritis was observed in 48 cases (80%) and active chronic gastritis in 12 cases (20%). There was no statistical significance between the activity of gastritis and pre and postoperative serum iron values (p values 0.544, 0.617, respectively). When the female and male cases were evaluated separately, the rate of active chronic gastritis was calculated as 22.2% in female cases, while this rate was determined as 13.3% in men. Similar to all cases, there was no statistically significant difference between the activity of gastritis and pre and post-operative serum iron levels in male and female patients (p values 0.200, 0.751, 0.401, 0.291, respectively).

Table 1. The frequency of the histopathological findings observed separately in all cases, male and female cases (columns were evaluated within themselves)

Histopathological findings	All cases (N/%)	Female (N/%)	Male (N/%)
Gastritis	60 (%100)	45 (%100)	15 (%100)
Atrophy	37 (%61.7)	26 (%57.8)	11 (%73.3)
Helicobacter pylori	52 (%86.7)	39 (%86.7)	13 (%86.7)
Intestinal metaplasia	9 (%15)	6 (%13.3)	3 (%20.0)
Lymphoid follicle	31 (%51.7)	24 (%53.3)	7 (%46.7)
Lymphoid agregate	50 (%83.3)	38 (%84.4)	12 (%80.0)

No statistically significant relationship is revealed with preoperative and postoperative serum iron values and histopathologically evaluated parameters as atrophy (p values 0.202 and 0.186, respectively), intestinal metaplasia (p values 0.391 and 0.719, respectively), *Helicobacter pylori* (p values 0.612 and 0.630 respectively) and lymphoid follicle (p values 0.519 and 0.426 respectively). In cases with lymphoid aggregate, preoperative iron values were found to be statistically significantly lower than those without (p = 0.047). The same significance was not observed in the mean postoperative iron values (p = 0.321).

In the analysis of female and male cases in terms of histopathological parameters: the presence of atrophy (p values 0.612 and 0.355, respectively), *Helicobacter pylori* (p values 0.940 and 0.958, respectively), intestinal metaplasia (p values 0.200 and 0.377, respectively), lymphoid follicle (p values 0.791 and 0.318 respectively), lymphoid aggregates (p values 0.179 and 0.412, respectively) and pre-postoperative iron values did not show any statistically difference in female cases. In male cases, the presence of lymphoid aggregate was found to be associated with the mean preoperative low iron values (p = 0.015), similar to that observed in all cases, while the same correlation could not be shown with postoperative iron levels (p = 0.750). Likewise statistically significance was not observed with atrophy (p values 0.430 and 0.293, respectively), intestinal metaplasia (p values 0.566 and 0.389 respectively), *Helicobacter pylori* (p values 0.401 and 0.062 respectively) and lymphoid follicle (p values 0.170 and 0.982 respectively) in male cases.

Table 2. Preoperative and postoperative serum iron values of all cases, female and male cases

	All cases- Means (mcg/dL) /SD	Female- Means (mcg/dL) /SD	Male- Means (mcg/dL) /SD
Preoperative serum iron levels	56.3±27.8	48.7± 24.3	79.1± 25.7
Postoperative serum iron levels	151.2±79.3	146.6± 78.0	165.1± 84.0

4. Discussion

Obesity, which is a global health problem with its rapidly increasing prevalence, brings along an increasing frequency of comorbid diseases with increasing BMI (Guh et al., 2009). Apart from the morbid and mortal situations caused by the disease itself the disease has a serious cost to the society therefore treatment and if possible prevention of obesity has a significant importance. Although non-surgical options such as nutritional change and getting away from sedentary life help to reduce body weight in the short term; surgical approaches provide more benefits in terms of efficient long-term weight loss, maintenance of reduced body weight and reduction of comorbid disease frequency. (Mitka, 2003; Chang et al., 2014). Unfortunately, the methods that are among the surgical approaches also comes out with various problems. Since the stomach and small intestine have an important role in the absorption of nutrients, the loss of tissue in these regions as a result of resections is one of these problems (Mechanick et al., 2013). The main clinical reflection of nutritional deficiencies frequently observed after bariatric surgery is anemia. It is noteworthy that the frequency of anemia is observed at different rates in various bariatric surgery methods. In a study published in 2015, the frequency of anemia after Roux-en-Ygastric bypass method was reported as 4% (Del Villar Madrigal et al., 2015), while in a study conducted on 306298 bariatric surgery cases in France, anemia was reported to be 5.6% in 143733 sleeve gastrectomy cases (Bailly et al., 2008). Theoretically, sleeve gastrectomy causes nutritional deficiencies with a reduction in intake, while gastric bypass has both food intake restriction and malabsorption (Ponsky et al., 2005). In addition, one of the reasons in the pathophysiology of nutritional insufficiency in sleeve gastrectomy is accelerated gastric emptying (Melissas et al., 2008; Braghetto et al., 2009). Moreover, decreased intrinsic factor and hypochloric acid production also negatively affect vitamin B12 and iron absorption, and the use of proton pump inhibitors (PPI) observed in cases worsens this situation (Coupaye et al., 2014).

Most of the studies on hemogram, serum iron and ferritin levels, B12 levels, folate levels, vitamin D and parathyroid hormone levels to assess nutritional deficiencies are aimed at determining the deficiency and its frequency, the breakdown of the time of occurrence, and the times of recovery in levels (Saif et al., 2012; Moizé et al., 2011; Hakeam et al., 2009). Iron is one of the important factors in the etiology of anemia, and studies have shown that serum iron has a wide distribution (Al-Mutawa et al., 2018, Hakeam et al., 2009; Alvarez et al., 2014); therefore, it has been suggested that ferritin may be a more appropriate marker (Al-Mutawa et al., 2018). However, despite all these studies and the theoretical knowledge of the pathopysiology of nutritional deficiencies, the factors to predict the possible deficiency and / or the depth of the deficiency are not clearly known. In one of the few studies conducted for predictive evaluation, Guan et al. (2018) reported that the hemoglobin value, an indicator of nutritional deficiencies, was associated with the post-operative hemoglobin value after adjustment for dependent covariates. In another study, Eroğlu et al. (2019) suggested that the presence of *Helicobacter pylori* in the resected gastric tissue was associated with preoperative red blood cell (RBC), hematocrit (HCT) and hemoglobin (HGB) values, so preoperative evaluation of *Helicobacter pylori* may be predictive in terms of postoperative.

In the present study, postoperative serum iron levels were found to be higher than before the operation, since all patients were using a multivitamin tablet containing iron. Among the histopathological parameters evaluated, there was no statistical relationship between the presence of gastritis and activation status, presence of atrophy and / or intestinal metaplasia, *Helicobacter pylori* status and the presence of lymphoid follicles; and pre- and postoperative iron values. However, it was noted that preoperative iron values were statistically significantly lower in patients with lymphoid aggregate in resected gastric tissue compared to patients without ($p= 0.047$). When the male and female cases were examined separately, it was observed that the mean preoperative iron value decreased in male cases with lymphoid aggregate ($p = 0.015$), while the same difference was not found in female cases. Considering that preoperative iron status is an important indicator of postoperative iron status, it is suggested that the presence of lymphoid aggregates is important histopathologically. Among the main causes of iron deficiency and anemia that develop after sleeve gastrectomies, decreased hydrochloric acid production caused by parietal cell scarcity due to fundus removal plays a role, but this is not the only factor (van Rutte et al., 2014; Snyder-Marlow et al., 2010). There are not many studies evaluating the role of histopathological findings in iron deficiency developing after sleeve gastrectomy, in which preoperative iron deficiency, decreased intake of iron-containing foods, and inefficient use of nutritional supplements for various reasons can be counted as the etiological factors. The fact that the presence of lymphoid aggregate detected in all cases and in male cases is associated with low preoperative iron levels in the present study indicates that the role of *Helicobacter pylori* in this process should be questioned in detail. It is known that lymphoid follicles and / or aggregates are often associated with *Helicobacter pylori*, but may

occasionally be associated with other inflammatory and neoplastic processes (Chakhachiro et al., 2020). Although it is thought that obesity being a low-grade chronic inflammatory condition (Esposito et al., 2003) which may be effective in the formation of lymphoid aggregates, there are also reports that lymphoid clusters that do not contain a germinal center are a normal component of the gastric mucosa without being associated with *Helicobacter pylori* (Carpentieri et al., 2000).

In conclusion, in this study, in which the role of histopathological findings observed in the stomach tissue removed in sleeve gastrectomies in predicting iron deficiency; Preoperative iron levels, which are reported to be predictive for post-operative iron deficiency, have been shown to be associated with the presence of lymphoid aggregates. Our study had limitations such as the small number of cases and the use of iron-containing preparations. It is thought that other histopathological findings such as the presence of lymphoid follicle and *Helicobacter pylori* are also important in terms of iron levels but could not be determined due to the limitations of the study.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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