

## Clinical Study

# Prevalence of Anemia and Related Deficiencies in the First Year following Laparoscopic Gastric Bypass for Morbid Obesity

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**Background.** Anemia associated with deficiencies in iron, folic acid, and vitamin B12 are very common after Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) surgery for morbid obesity. This study was conducted to evaluate the prevalence of anemia after LRYGB. **Patients and Methods.** A total of 377 morbid obese patients were included in our study. All patients underwent a LRYGB. Hematologic parameters were obtained prior to and after surgery on standardized time intervals. **Results.** Anemia was present in 21 ( $P = 0.02$ ) patients after surgery. Iron, folic acid, and vitamin B12 deficiencies were diagnosed in 66%, 15%, and 50% of patients, respectively. In 86% of patients, anemia was accompanied by one of these deficiencies. **Conclusion.** These results show that anemia and deficiencies for iron, folic acid deficiency, and vitamin B12 are very common within the first year after LRYGB. We advise a minimal daily intake of 65 mg of iron in male and 100 mg in female patients, 350  $\mu\text{g}$  of vitamin B12, and 400  $\mu\text{g}$  of folic acid. Patients undergoing LRYGB must be closely monitored for deficiencies pre- and postoperative and supplemented when deficiencies occur.

## 1. Introduction

Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) is one of the most commonly performed bariatric procedures to establish weight loss in morbid obese patients. A sustained Excess Weight Loss (EWL) of 50–70% is obtained in at least 50% of the patients by combining restrictive and malabsorption techniques. Sustained weight loss is associated with a decrease in obesity-related morbidity and mortality and an increase in quality of life [1–5].

However, due to malabsorption and insufficient intake, LRYGB patients are prone to develop deficiencies in many macro- and micronutrients. Most common are deficiencies in iron, folate, and vitamin B12, all of which can lead to anemia. Once these deficiencies are present, they can be difficult to treat by oral vitamin and mineral supplements. Therefore, patients who undergo RYGB should be evaluated prior to surgery for deficiencies and treated accordingly. After surgery, supplementation and close monitoring is warranted [1, 2, 6–8].

A number of possible risk factors for developing anemia have been previously researched. Differences in sex as well

as length of Roux-en-Y limb are described as contributing factors for the development of certain deficiencies [3]. Also we researched whether the amount of weight loss or an Adjustable Gastric Band (AGB) prior to the LRYGB influenced the amount of deficiencies.

Although weight loss effects of RYGB are well established, the number of studies addressing nutrient deficiencies and anemia is limited. Furthermore, the studies conducted so far often include only a small number of patients and are incongruent in their findings [1, 7]. For this reason we conducted a prospective study to investigate the prevalence of anemia and deficiencies in iron, folate, and vitamin B12 in the first year after LRYGB in our patients.

## 2. Patients and Methods

Between January 2005 and October 2009 a total of 416 patients underwent an LRYGB in our hospital. All patients were screened by a multidisciplinary team preoperatively and met the criteria stated by the NIH Consensus Development Conference Panel for bariatric surgery [9]. Patients who were unable to attend our standardized follow-up protocol

TABLE 1: Demographics.

Parameter	Values (standard deviation)
Number of patients	377
Male	102 (27.1%)
Female	275 (72.9%)
Age	43.4 (18–63)
Age male	46.0 (20–63)
Age female	42.5 (18–62)
Initial weight in kg	137.5 ( $\pm$ 22.6)
Male	151.4 ( $\pm$ 22.1)
Female	132.4 ( $\pm$ 20.6)
Initial BMI in kg/m <sup>2</sup>	46.8 ( $\pm$ 6.3)
Male	47.0 ( $\pm$ 6.4)
Female	46.7 ( $\pm$ 6.2)

were excluded. Also excluded were patients with laboratory evaluations that surpassed the six- and 12-month evaluation with two and three months respectively. Research nurses assured a minimum of data loss. Hence being part of our standard intake protocol, all patients were informed about this study. A total number of 377 (91%) patients scheduled for LRYGB were included in this study. We included 102 (27%) male patients and 275 (73%) female patients with a mean age of 43 (18–63) years. Medium follow-up time was 13.7 months. Demographics are shown in Table 1.

In our clinic, the proximal gastric volume is reduced by stapling of a 30 cc proximal gastric pouch and connecting a 100 or 150 cm roux-en-y limb as an enteroenterostomy to the jejunum 40 cm from the ligament of Treitz. Limb length was based on the patients BMI between 2005 and 2007. Patients with a BMI > 40 kg/m<sup>2</sup> received a 100 cm limb. Patients with a BMI > 50 kg/m<sup>2</sup> or a failing gastric band were treated with a 150 cm limb. Since 2007, all patients received a 150 cm limb. After surgery, patients were followed up at 1, 3, 6, and 12 months. Standard laboratory evaluation was performed preoperatively consisting of a complete blood count, a mean cell volume (MCV), and kidney function. After six and twelve months, laboratory evaluation was repeated along with plasma levels for iron, total iron binding capacity (TIBC), serum folate levels, and serum vitamin B12 levels.

Patients were instructed to take a standard multivitamin tablet three times daily. These tablets contained at least 7 mg of iron, 100  $\mu$ g of folic acid, and 0.5  $\mu$ g of vitamin B12 per tablet. Our standard postoperative medication consisted of a CaD 1000/880 sachet to prevent bone loss, Omeprazol 40 mg once daily to prevent ulceration of the staple line and the remaining stomach, and 5700 U of Fraxiparine once daily for six weeks postoperative for preventing thrombosis. During each visit patients were asked about their medication use so as to estimate their compliance to our described medication.

Anemia was defined as a hemoglobin (Hb) level <8.4 mmol/L in men and <7.4 mmol/L in women. MCV was defined normal between 80 and 100 fL. Iron deficiency was defined by serum levels <9.0  $\mu$ mol/L. Total iron binding capacity was defined as high when >80%. Folate deficiency

TABLE 2: Laboratory outcomes before RYGB.

	Level	Number of patients (%)
Hb	Low	27 (7,9%) of which 9 microcytic
	Normal	350 (92,9%) of which 13 microcytic and 5 macrocytic
	Microcytic	22 (5,8%)
MCV	Normocytic	350 (92,9%)
	Macrocytic	5 (1,3%)

was defined by serum levels <9.0 nmol/L. Cobalamin deficiency was defined by serum levels <150 pmol/L. Once a deficiency was identified treatment was started accordingly.

### 3. Statistics

Data were prospectively collected and evaluated using SPSS16 for Windows. All data are reported as mean  $\pm$  standard error of the mean. To evaluate the results between groups, logistic regression was used. Evaluation of laboratory results was performed using a paired *T*-tests.  $P < 0.05$  was considered significant.

Patients who were anemic preoperative were excluded for the 12 months evaluation (Table 3  $N = 350$ ) and were evaluated separately (Table 4  $N = 27$ ).

### 4. Results

Before surgery, anemia was present in 27 (7%) patients. After twelve months, 66 (19%) patients had developed anemia de novo, of which 19 (29%) were microcytic. In these patients mean Hb levels dropped from 8.2 mmol/L to 7.1 mmol/L ( $P < 0.001$ ). Total prevalence of anemia diagnosed in the first year, including preoperative anemic patients, was 25%. Preoperative laboratory results are shown in Table 2. A total of 93 patients were diagnosed with or developed anemia during the first postoperative year. The percentage of deficiencies in patients with anemia are separately shown in Table 3. The percentage of patients with iron, folic acid, and vitamin B12 deficiencies were 66%, 15%, and 50%, respectively. In 86% of patients, anemia was accompanied by one of these deficiencies.

Analysis of deficiencies in all patients is shown in Table 4. Iron deficiency after one year was identified in 33% of patients and in 61% of our patients with anemia de novo ( $P < 0.001$ ). The percentage of patients with folic acid and vitamin B12 deficiency were 14% and 40%, respectively. Three patients developed macrocytic red blood cells, and in two cases a vitamin B12 deficiency was found. Of all patients, 239 (63%) were diagnosed with at least one of the deficiencies mentioned above.

Risk factor analysis is presented in Table 5. Many differences between male and female patients were found in the prevalence of iron (38% versus 17%,  $P = 0.02$ ), and vitamin B12 (42% versus 21%  $P = 0.03$ ) deficiencies. However, the percentage for developing anemia in these groups was similar, 20%. Male patients had a 45% risk of being diagnosed with an iron, folic acid, or vitamin B12 deficiency, whereas female patients had a 68% risk ( $P = 0.004$ ).

TABLE 3: 12 Month evaluation of anemic patients.

		Anemia preoperative (%)	Anemia de novo (%)	Anemia total (%)
N patients		27 (7.1%)	66 (18.8%)	93 (24.7%)
MCV	Micro	10 (37.0%)	19 (18.8%)	29 (31.2%)
	Macro	0 (0%)	1 (1.5%)	1 (1.0%)
High TIBC		4 (14.8%)	10 (15.2%)	14 (15.1%)
Iron deficiency		21 (77.8%)	40 (60.6%)	61 (65.6%)
Folic acid deficiency		4 (14.8%)	11 (16.7%)	15 (16.1%)
Vitamin B12 deficiency		14 (52%)	33 (50.0%)	47 (50.4%)
Total deficiency		23 (85.2%)	57 (86.4%)	80 (86.0%)

In the anemia preoperative column, laboratory results are shown of patients with anemia preoperative. In the anemia de novo column, patients with anemia preoperative were excluded. In the anemia total column, all patients are evaluated.

TABLE 4: 12 Month evaluation of all RYGB patients.

		Month 6 (%)	Month 12 (%)	Total (%)
Anemia		50 (13.3%)	71 (18.8%)	93 (24.7%)
MCV	Micro	24 (6.4%)	20 (5.3%)	34 (9.0%)
	Macro	4 (1.1%)	6 (1.6%)	8 (2.1%)
Elevated TYBC		17 (4.5%)	26 (6.9%)	32 (8.5%)
Iron deficiency		79 (21%)	78 (20.7%)	124 (32.9%)
Folic acid deficiency		34 (9.0%)	25 (6.6%)	51 (13.6%)
Vitamin B12 deficiency		89 (23.6%)	71 (18.8%)	152 (40.2%)
Total deficiency		175 (46.4%)	150 (39.8%)	239 (63.4%)

T6 = laboratory findings (%) at 6 months, T12 = laboratory findings (%) at 12 months.  $N = 377$ .

Further analysis was done to investigate the role of Roux-en-Y limb length in the onset of deficiencies. No significant differences were found. A number of patients were treated with a AGB prior to RYGB surgery. A significant difference (24% versus 39%  $P = 0.03$ ) in vitamin B12 deficiencies between these groups was found. Surprisingly the percentages for anemia, folic acid, and vitamin B12 deficiencies were lower in the group who had a previous AGB placement.

Patients who lost over 70% of their excess weight in one year were less likely to develop anemia and deficiencies for folic acid and vitamin B12 compared to patients below 70% EWL.

## 5. Discussion

Bypassing the duodenum and proximal jejunum leads to a decrease in absorption surface for specific nutrients and causes a reduction in the absorptive capacity. After an LRYGB the most common reported are iron and vitamin B12 deficiencies. Deficiencies in these micronutrients are well known

causes for anemia [1, 7, 10]. Published reports on metabolic deficiencies after RYGB with different follow-up periods found anemia varying from 18 to 35%. Iron deficiency was reported in 20–49% in these studies. Folate deficiency was found in 0–18% of the cases. Vitamin B12 deficiency varied from 26 to 70% [11–16]. Although a relative short followup of only one year, we found high percentages in folic acid and vitamin B12 deficiencies, of 19 and 36%, respectively.

Iron deficiency after RYGB is due to a combination of factors and is the main cause for developing anemia after an RYGB [17, 18]. Absorption is dependent on the pH of the stomach. Acid reduces iron from a ferric state ( $\text{Fe}^{3+}$ ) to a ferrous state ( $\text{Fe}^{2+}$ ), which is readily absorbed in the duodenum and proximal jejunum. Due to the RYGB configuration, iron passes through the small gastric pouch without being reduced to the ferrous state. This effect is further enhanced by the prescribed protonpump inhibitors and calcium. After ingestion, iron bypasses the absorptive surface of the duodenum and jejunum. Iron intake is further reduced by the frequently found intolerance for red meat [10, 19]. A normal individual requires 1–2 mg of iron daily as a minimum. Especially premenopausal female are prone for developing iron deficiency [3, 11, 12, 17].

Preoperative 8% of our patients were anemic and another 5% had micro- or macrocytic red blood cells. These findings are most likely due to an unvaried intake of macro- and micronutrients by these patient [10, 19]. This shows that testing patients for anemia and deficiencies in iron, folate, and vitamin B12 preoperative is needed to achieve the best medical care for the bariatric patient. Patients should be treated for their deficiencies preoperative to prevent symptomatic anemia, deficiencies, and possible complications during and after surgery. In case of preoperative deficiencies, patients in our clinic are treated with high doses of iron (200 mg a day), vitamin B12 injections (3000  $\mu\text{g}$  every week), and folic acid (2 mg a day). These amounts are used until an adequate serum level is reached.

In our study, 56% of the patients who developed anemia de novo also had an iron deficiency and 42% had microcytic red blood cells. Of the patients who did not develop anemia within the first year, another 32% appeared to be iron deficient and may develop anemia in the near future if not treated. In our study, we prescribed all patients Omeprazol

TABLE 5: Risk factors for anemia and deficiencies.

	Male	Female	P	100 cm	150 cm	P	BMI > 50	BMI ≤ 50	P	EWL > 70%	EWL < 70%	P
N patients	96	254		127	233		105	245		132	218	
Anemia	17 (18%)	49 (19%)	0.74	25 (20%)	41 (18%)	0.77	18 (17%)	48 (20%)	0.59	24 (18%)	42 (19%)	0.80
Micro	2 (2%)	22 (9%)	<b>0.001*</b>	7 (6%)	17 (8%)	0.69*	10 (10%)	14 (6%)	0.35	5 (4%)	19 (9%)	0.11*
Macro	4 (4%)	4 (2%)	0.14*	3 (2%)	5 (2%)	0.89*	3 (3%)	5 (2%)	0.72	4 (3%)	4 (2%)	0.54*
Elevated TIBC	3 (3%)	25 (10%)	<b>0.037*</b>	8 (6%)	20 (9%)	0.38*	5 (5%)	23 (9%)	0.14	7 (5%)	21 (10%)	0.11*
Iron deficiency	16 (17%)	87 (34%)	<b>0.001</b>	68 (31%)	35 (28%)	0.56	40 (38%)	63 (26%)	<b>0.02</b>	40 (30%)	63 (29%)	0.78
Folic acid deficiency	14 (15%)	33 (13%)	0.70	33 (15%)	14 (11%)	0.32	20 (19%)	27 (11%)	<b>0.047</b>	18 (14%)	29 (13%)	0.91
Vitamin B12 deficiency	26 (27%)	112 (44%)	<b>0.004</b>	50 (39%)	88 (40%)	0.99	46 (44%)	92 (38%)	0.27	53 (40%)	85 (39%)	0.82
Total deficiency	46 (48%)	170 (67%)	<b>0.001</b>	137 (61%)	79 (62%)	0.74	74 (71%)	142 (58%)	<b>0.03</b>	82 (62%)	134 (61.5%)	0.90

\* Fishers Exact test. Rest was tested using Chi-square.

tablets and CaD 1000/880 sachets. This may increase the percentage of iron deficiencies because Omeprazol reduces acid secretion and subsequent iron absorption. Calcium can, when taken around the same time as iron, decrease the uptake of iron up to 60% [20]. The amount of iron (21 mg daily) supplemented did not prevent iron deficiency in a large number of patients. Most recent recommendations in the literature advise a daily intake of 40 to 65 mg of elemental iron per day for male and 100 mg per day for female patients. Vitamin C added to this regimen may also improve absorption [15, 18, 19].

Folic acid is present in food as polyglutamates and must be hydrolyzed to monoglutamates by the intestinal brush border. Folic acid absorption predominantly takes place in the upper third of the small intestine but can be absorbed throughout the small intestine [18]. Absorption is pH dependent and therefore partially facilitated by hydrochloric acid. Additionally, vitamin B12 acts as a coenzyme in converting folic acid to an absorbable form thus a vitamin B12 deficiency may result in a folate deficiency [20, 21]. Due to the low acid production of the proximal pouch and the bypassing of the upper third of the small intestine, RYGB patients are at risk for developing folic acid deficiency [21, 22]. Enterohepatic recirculation is an important factor in preserving the body pool of folate [19]. Another contributing factor for developing a folic acid deficiency may be due to the malabsorption and the short bowel in RYGB patients. Despite these apparent mechanisms for folate deficiency, decreased dietary intake of folic acid seems the dominant cause. Since folic acid reserves are low with an average of 10 mg, a daily requirement of 50  $\mu$ g, and a deficit absorption, deficiency can occur rapidly [20, 23].

In this study, 19% of the patients were diagnosed with folic acid deficiency. A number of studies found a substantial decrease in folic acid deficiencies over the years. An explanation for this decrease may be that folic acid absorption in the distal small intestine compensates for the reduced absorption capacity. Another mechanism might be based on bacteria in the upper small bowel who produce more folic acid over time [24, 25].

The 300  $\mu$ g of folic acid prescribed per day appears insufficient to avoid a deficiency in the first year. A sufficient quantity of folic acid should be at least 400  $\mu$ g per day, while most authors prescribe 1 mg of folic acid a day [12, 20]. Folic acid deficiency may be of great concern in female patients who want to become pregnant in the near future after RYGB. Although uncommon, reports of neural tube defects have been reported in infants after RYGB surgery [12, 26]. Woman of reproductive age should be monitored closely, bearing in mind that one of the reasons for undergoing an RYGB is decreased fertility due to morbid obesity.

Vitamin B12 in food is bound to proteins and first needs to be released by pepsin and hydrochloric acid before it can be bound by intrinsic factor (IF). When the released vitamin B12 in a normal individual enters the duodenum, it is bound to IF released from the parietal cells of the stomach facilitated by pepsin and pancreatic enzymes. In this state, the bound vitamin B12 is eventually absorbed in the terminal ileum. After RYGB, vitamin B12 cannot be released from

the food and is hardly bound to IF due to the bypassing of the stomach and duodenum and the reduced amount of IF released [27, 28]. The frequently found intolerance for red meat and milk might also play a role, as these products are rich in vitamin B12. In healthy subjects, a daily minimal dose of 2  $\mu$ g vitamin B12 per day is needed. A normal individual has a vitamin B12 reserve of 2000  $\mu$ g, which should last for a minimum of two years [19, 24, 29, 30].

LRYGB patients appear to have much lower vitamin B12 reserves than healthy individuals, probably due to inadequate dietary intake preoperatively. The multivitamins prescribed contains 1,5  $\mu$ g of vitamin B12 per day. Several studies have shown that a 300–500  $\mu$ g dose of vitamin B12 is sufficient. Others recommend sublingual administration or intramuscular injections of 1000–3000  $\mu$ g every month to every six months and report similar outcomes for resulting vitamin B12 levels [12, 15, 28, 31–33]. In the case of vitamin B12, the prescribed Omeprazol may also decrease absorption [20]. Although none of our patients became symptomatic for B12 deficiency, there have been reports of patients developing Wernicke's encephalopathy and megaloblastic anemia years after RYGB [34–39].

The risk factors studied for developing metabolic deficiencies showed a number of interesting results. A number of studies reported a difference for developing anemia and iron deficiency between male and female patients who had underwent RYGB [11, 12, 17]. Anemia and iron deficiency are thought to be higher among woman, because premenopausal women lose iron during menstruation every month and often have no iron reserves [11, 12, 17, 40]. This study did not find a significant difference in the prevalence for anemia between the sexes. In fact, the prevalence was identical at 20%. This shows that the first year after LRYGB the risk for developing anemia is equal between male and female patients after RYGB surgery for morbid obesity. We did, however, find significant higher percentages for iron and vitamin B12 deficiencies in female patients. From these data one could conclude that on the long run female patients may have a higher risk for developing anemia. The difference in iron deficiencies between males and females can be explained by the average lower iron reserves of females, combined with the loss of iron during menstruation. The difference in vitamin B12 might be explained by the average lower daily intake of vitamin B12 by female patients compared to male patients (4  $\mu$ g versus 7  $\mu$ g). Of all the patients who developed anemia, 71% were female. This greater number is due to the fact that a greater number of patients undergoing RYGB were female.

The different lengths of the Roux-en-Y limb did not show any significant outcomes. Although the 150 cm limb group showed a 6% higher prevalence for anemia and lower values for folic acid and vitamin B12 deficiencies, these values were not significant. Brodin et al. also found lower deficiency rates for vitamin B12 with an increase of the Roux-en-Y limb length.

Patients with an AGB prior to an RYGB had a lower prevalence's for anemia, folic acid deficiency, and even a significant lower risk of vitamin B12 deficiency ( $P = 0.03$ ). These patients were already used to taking multivitamin tablets during the period they had an AGB. Thus resulting

in higher baseline values and a better compliance (92 versus 76%). These differences may explain the unexpected differences in deficiencies found.

We expected the group who lost >70% of their EWL to have higher prevalence's of deficiencies due to a decreased intake of macro- and micronutrients. The prevalence of iron deficiency was as expected higher in the >70% group, but all the other prevalence's were lower in this group. The difference in vitamin B12 deficiency was almost significant ( $P = 0.07$ ) and might be explained by the release of vitamin B12 from the shrinking liver and fatty tissue. This mechanism will only protect these patients during the rapid weight loss. After this period, the micronutrient stores will be depleted.

## 6. Conclusion

Our results show that anemia and deficiencies for iron, folic acid, and vitamin B12 are very common the first year after LRYGB. Women are at risk for developing iron deficiency and vitamin B12 deficiency and have a greater overall risk for developing one of the deficiencies researched. Our standard policy for supplementation of multivitamin tablets after LRYGB failed to prevent deficiencies. We advise a minimal daily intake of 65 mg of iron in male and 100 mg in female patients, 350  $\mu\text{g}$  of Vitamin B12 and 400  $\mu\text{g}$  of folic acid. With this paper we want to create awareness for screening RYGB patients for deficiencies and correcting these within the first year. Furthermore, supplementing these patients with multivitamins should only be regarded as a base upon which a patient-specific regimen for micronutrients should be built.

## Conflict of Interests

E. O. Aarts, B. van Wageningen, I. M. C. Janssen, and F. J. Berends have no conflict of interests or financial ties to disclose.

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