Risks and limits of bariatric surgery: old solutions and a new potential option

R. GAMBIOLI[1], E. LEPORE[1], F.G. BIONDO[2], L. BERTOLANI[3], V. UNFER[4,5]

[1]R&D Department, LoLi Pharma, Rome, Italy
[2]Department of Surgery, Sacred Heart of Jesus Hospital, Benevento, Italy
[3]Department of Bariatric Surgery, Clinical Institute "Beato Matteo", Vigevano, Italy
[4]UniCamillus-Saint Camillus International University of Health Sciences, Rome, Italy
[5]The Expert Group on Inositol in Basic and Clinical Research (EGOI) Rome, Italy

Abstract. – The present review focuses on the side effects that ex-obese patients face following bariatric surgery.
We searched through the principal medical indexes (SCOPUS, Web of Science, PubMed, MEDLINE) using the following words, both alone and in combinations: bariatrics; bariatric surgery; anemia; vitamin B12; cobalamin; folate; folic acid; iron; iron supplements; gut microbiota; lactalbumin; α-lactalbumin. To perform exhaustive research, we considered articles published since 1985.
Bariatric surgery induces states of nutritional deficiencies. In particular, the surgery results in a drastic fall in the levels of iron, cobalamin, and folate. Despite the dietary supplements which can counteract such decrease, some limitations exist in the nutraceutical approach. Indeed, the gastrointestinal side effects of supplements, the alterations in the microbiota, and the reduced absorption induced by the surgery may impair the effect of dietary supplements, exposing the patients to the risk of developing nutritional deficiencies. Recent literature reports the effect of promising molecules to counteract such limitations, which include α-lactalbumin, a whey protein with prebiotic activities, and new pharmaceutical forms of iron supplements, namely micronized ferric pyrophosphate. If on the one hand, α-lactalbumin enhances intestinal absorption and helps in restoring a physiological microbiota, micronized ferric pyrophosphate has a high tolerability and low or null risk of gastrointestinal side effects.
Bariatric surgery represents a valid solution to obesity and obesity-related disease. However, the procedure may induce deficiencies in micronutrients. Data exists on the promising activities of α-lactalbumin and micronized ferric pyrophosphate, which may help in preventing bariatric-induced anemia.

Key Words:
Bariatrics, Anemia, Iron, Folate, Cobalamin, α-lactalbumin.

Introduction

The World Health Organization (WHO)[1] defines obesity as a body-mass index (BMI) higher than 30 kg/m^2 and reports that such pathology is a growing threat to global health, affecting around 13% of adults worldwide. The worldwide prevalence of obesity has increased more than three-fold since the 1970s, and today it constitutes a relevant issue even among children and adolescents, to the extent that the WHO identifies obesity as an epidemy. Obesity increases the risk of developing cardiovascular diseases, diabetes, musculoskeletal disorders, and several cancer types[1]. Therefore, physicians generally recommend that obese people undergo lifestyle and diet changes to avoid further complications. Nonetheless, patients might fail to modify their lifestyle and habits or such modifications could not be sufficient to gain health benefits, thus requiring second-line options such as bariatric surgery[2]. Bariatric surgery is a second-line approach that may help in recovering from severe obesity. Bariatric surgeries exert their weight-loss effects by rearranging the digestive system. Indeed, bariatric surgeries reduce the absorption of macronutrients, allowing fast weight loss. Despite the positive effects, bariatric surgeries also reduce the quantities of micronutrients absorbed, thus requiring bariatric patients to take food supplements. The National Institute of Health (NIH) recommends such a surgical approach in those patients with a BMI higher than 40, or 35 with severe obesity-related comorbidities. Growing evidence also spreads its potential application to diabetic patients with a BMI higher than 30[2]. This review aims to summarize the utility and the effects of bariatric surgery, also considering the side effects of the procedures and proposing valid alternatives to the classical supplementation regimen.

Corresponding Author: Vittorio Unfer, MD; e-mail: vunfer@gmail.com

Bariatric Surgery: to Each Type its Utility

Bariatric surgery encompasses all the procedures designed to counteract severe obesity by interfering with the physiological processes of eating, digesting, and absorbing. Depending on the type of surgery, this interference can act at three levels: (i) by blocking the absorption of food, (ii) by restricting the stomach *via* obstruction or resection, or (iii) by a hybrid procedure. Nowadays the blocking procedures are less and less performed, as literature evidence highlights a major efficiency of restrictive and hybrid procedures. Among those, sleeve gastrectomy, adjustable gastric band, and gastric bypass are the most performing – and thus the most performed – surgical interventions[3].

Sleeve gastrectomy, also known as gastric sleeve surgery, is the most-performed type of bariatric surgery worldwide. It consists of the resection of about 75% of the greater curvature of the stomach, including the fundus, body, and proximal antrum. The resulting stomach has a tubular shape and a reduced volume, accounting for early satiety that leads to extensive weight loss. Moreover, after sleeve gastrectomy patients experience weight-loss-independent benefits: for instance, in the case of diabetes mellitus, the surgical procedure induces the reduced expression of digestive enzymes and genes involved in glucose absorption[3,4]. Thanks to the observed effects on gene expression, sleeve gastrectomy is considered part of metabolic surgery. Indeed, metabolic surgery is a sub-field of bariatric surgery, including all the intervention that modifies genic expression.

Roux-en-Y gastric bypass surgery (RYGB) consists of a rearrangement of the stomach and the upper small intestine to create a structure resembling a “Y” shape. The surgery divides the stomach into two parts: (i) a small upper stomach, which is still connected to the esophagus and surgically linked to the jejunum, and (ii) a lower greater stomach, which is instead still connected to the duodenum, rejoining the jejunum downward. This shape with a lower stomach laterally joining the jejunum resembles the shape of a “Y”, giving its name to the procedure. As in sleeve gastrectomy, the stomach is also resected, but in the case of gastric bypass, the integrity of the stomach is conserved, even though the part of the proximal digestive system is never again intended to digest food[3].

The laparoscopic adjustable gastric band, also known as lap-band, is a less invasive type of bariatric surgery, developed to avoid interrupting the continuity and integrity of the digestive system. Moreover, different from both sleeve gastrectomy and gastric bypass, lap-banding is an always-reversible procedure. The procedure consists of the application of a silicone band around the upper stomach, which creates an upper pouch that fills up with less food, anticipating satiety and reducing the amount of the ingested food. Thanks to the subdermal access port, physicians can fill the pouch with saline solution, so adjusting its volume. Such infusion determines a higher pressure that stiffens the band, thus anticipating the satiety and reducing the amount of the ingested food[3].

Among these three techniques, only lap-banding prevents the need for supplements in patients. Both gastric bypass and gastrectomy strongly reduce the absorption of macronutrients as part of their mechanism of action, besides preventing the adsorption of some pivotal micronutrients[5]. In fact, despite the positive effects of bariatric surgery, patients must periodically check blood levels of vitamins and minerals and eventually take dietary supplements to overcome surgery-induced deficiencies. The importance of micronutrients in physiology is well-known, as the human body strictly requires minerals and vitamins to perform most reactions. However, although the high efficiency of dietary supplementations, some patients may still present pathological signs of a lack of micronutrients.

Side Effects of Bariatrics: Anemia

Anemia is one of the most burdensome issues that may arise from a surgery-induced lack of micronutrients. It is a non-negligible condition, as it consists of a lack of erythrocytes that can lead to major threats to patients’ health. It can derive from three different causes: (i) lack of iron; (ii) scarce production of red blood cells; (iii) and/or excessive disruption of these cells. The malabsorption after bariatric surgery can lead to both the lack of iron and the scarce production of erythrocytes, due to the deficit of different micronutrients[6-11]. Iron, folate, and cobalamin play a central role in erythrocyte production. The involvement of iron in the onset of anemia is well known. Low levels of iron affect the levels of heme, which is the iron-containing co-factor of hemoglobin that binds oxygen. On the contrary, folate and cobalamin intervene in the cellular process of mitosis, so their deficiency represents a risk factor for the reduced production of erythrocytes, which is the second cause of anemia. Indeed, folate represents a family of water-soluble molecules that, once converted to tetrahydrofolate, intervene in the one-carbon metabolism. Specifically, such processes include the synthesis of nucleobases, thus participating in pivotal processes for cellular survival and mitosis[12]. Cobalamin, instead, is a molecule based on a corrinoid ring that binds a cobalt atom. The metabolism of fatty acids that influences membrane composition, and the conversion of folate to tetrahydrofolate, are the two most important processes in which cobalamin intervenes as a cofactor. The digestion of cobalamin starts in the acid environment of the stomach and proceeds with the binding to a protein called intrinsic factor, which is produced by the fundus of the stomach and is pivotal for its absorption[13].

Sleeve gastrectomy and gastric bypass reduce the absorption of cobalamin, thus bariatric patients are strongly recommended to take food supplements containing this micronutrient. Regarding iron and folate, patients should supplement their levels only when needed, as in the case of anemia[14,15]. In fact, iron-deficient patients take iron supplementation as the first line – and usually resolutive – treatment. Conversely, in the case of iron-independent anemia supplementing levels of folate is recommended. Nonetheless, bariatric patients may still display anemia also under iron, cobalamin, and folate supplementation. Conflicting evidence exists on this topic, as some papers[15,16] report an increase in the rate of iron-deficiency anemia following bariatric surgery, while others[14,17] fail to find similar evidence. A recent work by Shipton et al[16] followed bariatric patients until 48 months after the surgery, monitoring anemia-related parameters. They examined the levels of cobalamin, folate, iron, ferritin, and hemoglobin under a strict supplementation regimen, finding contrasting results. On the one hand, they pointed out an improvement in levels of ferritin, cobalamin, and folate with respect to the preoperative levels, but on the other hand levels of iron and hemoglobin exhibited a peculiar pattern. In fact, blood levels of iron rose until the first 12 months following the surgery, thereafter they started decreasing. Similarly, levels of hemoglobin increased until the first 4 months following the surgery, but thereafter they started decreasing, even dropping below pre-surgery levels at the end of the study, thus reshaping a condition of long-term anemia. The authors[16] tried to correlate such long-term worsening of anemia with a heightening of the inflammatory state. Indeed, the inflammatory state and the levels of pro-inflammatory cytokines represent risk factors for a particular type of anemia called chronic disease anemia, which is unrelated to iron levels. In this scenario, obese people are more likely to develop anemia, as obesity determines a constant low-grade inflammation. However, the strong inflammatory response following the severe weight loss due to the surgery, lasts only for the period of fast weight loss, generally about a year after the procedure. After that period the weight loss stops, and the body weight tends to stabilize[17,18]. Therefore, the worsening of anemia-related parameters observed even 12 months after the surgery, is probably related to other factors rather than the inflammatory state. Only about 14% of the total cases of anemia occurring within the first year after the gastric bypass are related to chronic inflammation. On the contrary, the prevalence of iron deficiency anemia among gastric bypass patients who achieved stable body weight rises to 75% of the total anemic patients. These data clearly confirm the higher prevalence of iron deficiency anemia rather than chronic disease anemia in gastric bypass patients, thus delinking the worsening of anemia with the inflammatory response[17]. Notably, studies[9,17] on sleeve gastrectomy report conflicting results on iron deficiency and chronic disease anemia. Indeed, a meta-analysis reports a double frequency following gastric bypass than sleeve gastrectomy, even though another meta-analysis failed to find significant differences in the prevalence of anemia among patients after gastric bypass or sleeve gastrectomy.

Taken together, all these findings[14-18] suggest that post-surgery anemia strongly depends on the malabsorption of micronutrients. Indeed, patients' low compliance to a strict supplementation regimen may represent a relevant factor for anemia insurgence. Indeed, patients usually fail to follow an iron supplementation regimen due to the high rate of gastrointestinal side effects of iron-based drugs. Finding the correct pharmaceutical form for each patient should address this factor. Indeed, a study from Ben-Porat et al[19] highlighted that more than 90% of bariatric patients take multivitamin supplements until one year after surgery, however, the percentage drastically drops to less than 40% after four years. This is a critical point, as the four-year timepoint analyses revealed a high rate of nutritional deficiencies. Regarding malabsorption, a recent line of research focused on improving intestinal absorption of drugs and supplements, with a special focus on the role of prebiotics and gut microbiota.

Side Effects of Bariatrics: Alterations in Gut Microbiota

Obesity, as well as bariatric surgery, is related to a high rate of micronutrient deficiency, and it also correlates with reduced gut microbiota diversity. In 2006, a pioneering study[20] highlighted the differences in gut microbiota composition between healthy people and obese patients, revealing an increase in Firmicutes and a concomitant decrease in Bacteroidetes. Moreover, preclinical studies[21] revealed that experimentally induced alterations in gut microbiota may cause weight gain, while microbiota restoration may lead to weight loss. Bariatric surgery as well alters the composition of the gut microbiota as another consequence of this procedure. The exact extent of these changes is still a matter of debate, although the topic is of growing interest. However, the results[22-28] of the analysis of gut microbiota in bariatric patients highlighted wide heterogeneous data. It is worth noting that differences in diet and lifestyle, different clinical backgrounds of patients, different research protocols and time points of the analysis can make the comparison among the studies hard work, often reaching conflicting evidence.

A research work from Murphy et al[24] on diabetic patients highlighted that different types of surgery differently affect the composition of gut microbiota. They first pointed out a different and opposite effect between sleeve gastrectomy and gastric bypass on microbiota composition. Their results indicated that gastric bypass induces an increase in Firmicutes and Actinobacteria, while decreasing Bacteroidetes; on the contrary, sleeve gastrectomy only stimulates an increase of Bacteroidetes. Several years later, Paganelli et al[25] analyzed the composition of the gut microbiota in bariatric patients, either diabetic or non-diabetic, founding different evidence with respect to the ones of Murphy et al's group[24]. Indeed, they characterized 6-month changes in gut microbiota composition of bariatric patients, highlighting an increase in the relative abundance of several bacterial families, including *Streptococcaceae, Enterobacteriaceae, Veillonellaceae, Clostridiales*; meanwhile, the relative abundance of *Bifidobacteriaceae* decreased. Notably, they[25] did not report any differences between sleeve gastrectomy and gastric bypass in gut microbiota composition. However, as previously indicated, the differences between the results by Murphy et al[24] and Paganelli et al[25] may derive from some bias, regarding the selection of diabetic or non-diabetic patients, a specific diet for patients, the software used for the analysis and the level of depth of the analysis (Phyla, Classes, Orders, or Families). A recent review by Ciobârcă et al[22] pointed out that most of the studies agree on the decreased relative amount of *Lactobacillus* and *Bifidobacterium* after bariatric surgery. Indeed, they[22] also pointed out that bacteria belonging to these genera are commonly used as prebiotics in bariatric patients, even though literature still lacks a study on the efficiency of such treatments.

Despite the contrasting evidence on the effects of obesity and bariatric surgery on gut microbiota composition, most of the authors agree on some key findings: (i) obesity is related to altered microbiota; (ii) in some cases, the altered microbiota can hamper weight loss; (iii) bariatric surgery decreases some specifical bacterial genera, including *Lactobacillus* and *Bifidobacterium*[22,23,25,29-32]. These last play a central role in human physiology, as they can produce folate in the intestinal lumen, addressing the need for such molecule[33]. Moreover, *Bifidobacterium* requires iron to grow and proliferate, and some species of *Lactobacillus* may recover gut adsorption of folate[31,34-36]. Moreover, the occurrence of *Lactobacillus* and *Bifidobacterium* in the human gut improves the inflammatory state of patients by promoting the release of anti-inflammatory cytokines[37]. Therefore, the adequate relative amount of *Lactobacillus* and *Bifidobacterium* may strongly promote physiological intestinal absorption and gut homeostasis, contributing to guaranteeing the adequate intake of micronutrients, such as iron and folate, in patients.

Counteract Side Effects Through Dietary Supplementations

Folate

Negative effects of bariatric surgery on the folate status of patients are clear, however, the exact magnitude of the different types of surgeries is still debated. Gehrer et al[38] highlighted that the prevalence of folate deficiency is slightly higher following sleeve gastrectomy rather than gastric bypass. This is due to the mechanisms of digestion and absorption of folate. In fact, tetrahydrofolate is synthesized in acid environments, and the sleeve gastrectomy hampers the proper acidification of the stomach. Conversely, gastric bypass partially bypasses the jejunum, where folate is primarily absorbed, thus folate adsorption is reduced as well as in the case of sleeve gastrectomy, even though through different mechanisms. One year before, Hakeam et al[39] described that sleeve gastrectomy impacts folate concentration in red blood cells. In their study[39], sleeve gastrectomy had no effects on anemia and iron-related parameters such as ferritin and transferrin, nonetheless, intracellular levels of folate fell regardless of the supplementation regimen. Differently from previous studies[38,39], the group of Capoccia et al[40] reported that folate deficiency is less common in bariatric patients after sleeve gastrectomy, precisely because after gastric bypass patients lose part of the absorption of folate in the jejunum. In accordance with these results, Toh et al[41] revealed no evidence of reduced red blood cell folate following sleeve gastrectomy, but only following gastric bypass.

Despite bariatric surgery worsens folate status, its supplementation seems to be effective in fulfilling the renewed need in most of the patients. Indeed, bariatric patients under a strict supplementation regimen display improved levels of folate and a reduced prevalence of folate deficiency, as reported in most of the studies[38,39]. Nonetheless, physicians should pay attention to the folate status of patients, since inefficient supplementation regimens or low patients' compliance can lead to downstream burdensome effects, including anemia[42].

Iron

Patients after bariatric surgery present a higher prevalence of iron deficiency compared with the general population, as 15.2% of patients lack iron preoperatively, significantly rising around 16.6% postoperatively[43]. Intriguingly, sleeve gastrectomy and gastric bypass display a diverse trend in the prevalence of postoperative iron deficiency. In fact, sleeve gastrectomy exhibits a postoperative prevalence of iron deficiency of 12.4%, while gastric bypass of 24.5%[43]. In 2016, the American Society of Metabolic and Bariatric Surgery (ASMBS) published guidelines[44] for the supplementation of different micronutrients, including iron. They pointed out that physicians should prescribe routine screening before and after bariatric surgery, including both the blood analyses of iron and ferritin and the assessment of clinical signs and symptoms common to anemia, such as fatigue, weakness, and cold extremities. In 2019, an update of such guidelines[45,46] strongly recommended the initiation of daily oral supplementation of iron following bariatric surgery, also suggesting the administration of intravenous iron for patients who do not respond to the therapy. Interestingly, the guidelines recommended periodical controls and supplementation regimens regardless of the specific type of surgery, indicating as necessary the supplementation of iron.

Postoperative oral assumption of iron is the most used route of administration, despite a non-optimal efficiency and low compliance due to the reduced tolerability. In fact, most iron supplements may cause relevant side effects, especially gastrointestinal disturbs[47,48]. Nonetheless, oral supplementation of iron as a primary intervention is effective in preventing iron deficiency anemia[6]. Therefore, improving the tolerability of iron supplements has gained a strong interest in pharmaceutical research of the latest years. Among various pharmaceutical forms of iron supplements, micronized ferric pyrophosphate displays a higher efficiency and tolerability profile. Such type of supplement consists of a micro-coated iron, which is a safe intervention with null or very low reported side effects[49]. Indeed, Pappalardo et al[50] conducted a study on cancer patients with iron deficiency, testing the efficiency and safety of such pharmaceutical form. They confirmed the high efficiency of the micronized ferric pyrophosphate, without the occurrence of any adverse events among patients.

Limits of Supplementation in Bariatric Patients

Most of the scientific articles[51-55] about dietary supplementations in bariatric patients highlighted that physicians usually neglect their reduced efficacy in the long run. This may be due to the high incidence of side effects (e.g., in the case of iron supplements), but also to the reduced absorption and altered microbiota. To date, the process of intestinal absorption is a crucial and debated topic for most of the treatments and it is still a growing field. Different drugs have different rates of absorption, and the precise amount of the molecule that is absorbed can vary largely among patients and it depends on several factors. Among the known factors that influence intestinal absorption of nutrients, the most relevant include (i) the permeability of the membranes to the molecules, (ii) the expression of the carriers that internalize the molecules, (iii) the functionality of the digestive tract,

(iv) the intestinal microbiota. A complex network of interactions among these factors may alter the absorption of micronutrients and their effect[5,51-55].

In the case of bariatric patients, the clinical picture is even more complicated, as an external surgical intervention may modify the physiology of the digestive system. Indeed, bariatric surgery is a metabolic procedure that influences the production of proteins in the digestive tract, thus altering the expression of carriers and enzymes involved in micronutrient absorption. Moreover, as previously indicated[51-55], bariatric surgery may induce relevant changes in gut microbiota composition. In this sense, bariatric surgery may modify the processing of micronutrients, their absorption through carriers, and their synthesis and processing by bacteria. Both the metabolic and the microbiota changes that follow bariatric interventions may account for a part of the altered absorption of dietary supplements.

α-Lactalbumin: a Potential Candidate to Improve Intestinal Condition

Among the molecules with positive effects on gut microbiota homeostasis and intestinal adsorption, α-lactalbumin (α-LA) has drawn attention in the latest years in various clinical pictures. α-LA is a whey globular protein commonly detectable in both human and bovine milk. It is the second most abundant protein in whey, and it is an important source of tryptophan, cysteine, and bioactive peptides. α-LA has peculiar characteristics: it undergoes digestion in the duodenum *via* pancreatic enzymes rather than in the stomach, and its derived bioactive peptides promote several pivotal activities in the jejunum. In fact, literature highlights that α-lactalbumin-derived peptides can act at different levels on gut homeostasis. The main reported activities include anti-inflammation, anti-hypertension, and immunomodulation. Moreover, under specific circumstances, as in the presence of a cofactor of human casein, α-LA undergoes structural changes, exhibiting a folding variant that displays pro-apoptotic, antiviral, and bactericidal properties[56-58].

Among other properties, α-LA is a key agent in improving bacterial growth and generally promotes the establishment of healthy gut microbiota. Indeed, α-LA stimulates the growth of bacteria such as *Bifidobacterium* and *Lactobacillus*, while preventing the proliferation of pathogenic bacteria such as *Escherichia coli, Salmonella typhimurium, Staphylococcus aureus* and *Klebsiella pneumonia*[57,59]. Thanks to its positive effects on gut microbiota, α-LA gained a growing interest in improving some chronic pathological conditions.

As previously stated, bariatric surgery may exert negative effects on gut microbiota homeostasis. In particular, such an intervention reduces the relative amount of *Lactobacillus* and *Bifidobacterium*, which are positive symbiotes for human health. In 2019, Boscaini et al[59] carried out a pre-clinical study evaluating the effects of α-LA on gut microbiota, highlighting the genera that are influenced by a diet enriched in α-LA or in casein. Their analyses revealed that α-LA promotes healthy microbiota, increasing the relative amount of *Bifidobacterium* and *Lactobacillus*. Indeed, the increase in the relative abundance of *Lactobacillus* strictly correlates with a decrease in inflammatory cytokines and BMI, thus confirming the positive effects of such bacteria on metabolic aspects. On the other hand, the correct relative amounts of Bifidobacterium are strongly related to a healthy BMI. Conversely, several studies[25,29] highlighted that a low relative amount of *Bifidobacterium* correlates to obesity. Therefore, promoting the growth of beneficial bacteria, the use of α-LA may help to counteract both obesity-induced and bariatrics-induced alterations of gut microbiota. Recovering a physiological intestinal flora may also positively impact micronutrient synthesis thus avoiding the worsening of side conditions, such as anemia.

A recent meta-analysis[60] evaluated the results on metabolic parameters of the supplementation with probiotics, including *Lactobacillus* and *Bifidobacterium*, in diabetic patients. Indeed, the authors pointed out that the use of probiotics induces a significant improvement in the homeostatic model assessment for insulin resistance (HOMA-IR), also reducing plasma glycated hemoglobin. This effect may also derive from the activities of the *Bifidobacterium* induced by α-LA, as the bacteria produce short-chain fatty acids that correlate to an improved glycemic profile. Other reports highlighted the efficiency of *Lactobacillus* and *Bifidobacterium* in reducing weight, triglycerides, glycemia, and insulinemia[61]. Preclinical studies[62,63] reported similar results in mice, also highlighting a reduction in proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6.

Notably, a recent study by Laganà et al[64] highlighted the beneficial effect of α-LA in improving the intestinal absorption of micronutrients.

Indeed, they found out that a combination of α-LA and micronized ferric pyrophosphate is more efficient than ferrous gluconate in restoring iron-related blood parameters. They analyzed hemoglobin, ferritin, serum iron, and hematocrit, finding improved values in the group treated with α-LA and micronized ferric pyrophosphate after a one-month treatment compared to the group treated with ferrous gluconate. Moreover, since they enrolled pregnant women with iron-deficiency anemia in the study, they also investigated the safety of both drugs. Intriguingly, they[64] highlighted a 24% rate of side effects incidence in the ferrous gluconate group, while the group treated with α-LA and micronized ferric pyrophosphate reported no adverse events. Considering the condition of anemia and the altered gut microbiota of bariatric patients, α-LA may represent an excellent candidate for supplementation therapies, matching the needs of such population.

Conclusions

Bariatric surgery encompasses procedures in rapid development, as obesity is a disease that is constantly spreading worldwide. Among the complications occurring in bariatric patients, the need for dietary supplementation, the irreversible alterations of the digestive tract, and the lack of micronutrients play a primary role. Anemia is one of the most burdensome issues that may affect bariatric patients, and it is caused by the inadequate intake of folate, iron, and cobalamin. In addition, gut microbiota changes following bariatric surgery may contribute to exacerbating such conditions of inadequate intake and intestinal malabsorption. Even though food supplements seem to be effective in counteracting these effects, their efficiency may decline in the long run. Several scientifical articles[49,50,64] report that new formulas can overcome these problems. For instance, micronized ferric pyrophosphate seems to be a high-valuable candidate, as such pharmaceutical form avoids the occurrence of gastrointestinal side effects, which are among the primary causes of discontinuation of the treatments. On the other hand, a newly characterized protein occurring in human and bovine milk, the α-LA, could be an optimal candidate for the treatment of bariatric patients, as it plays crucial roles in balancing microbiota, and restoring gut homeostasis. Moreover, when combined with micronized ferric pyrophosphate, its efficacy is higher than ferrous gluconate in iron-deficient anemic patients. On these bases, α-LA, folate, and micronized ferric pyrophosphate may constitute a putative optimal food supplementation approach for bariatric patients to avoid the insurgence of anemia.

Informed Consent and Ethics Approval

Not applicable.

Conflict of Interest

RG, EL, and VU are employed at Lo.Li. Pharma. Other authors declare that they have no conflict of interests in this paper.

ORCID ID

R.G.: 0009-0000-2877-1075; V.U.: 0000-0002-1805-3181.

Availability of Data and Materials

Not applicable.

Authors' Contributions

Conceptualization, FGB, LB, and VU.; methodology, RG, EL, and VU; resources, FGB, LB, and VU; writing—original draft preparation, RG and EL; writing—review and editing, FGB, LB, and VU; supervision, VU; project administration, RG and VU. All authors have read and agreed to the published version of the manuscript.

Funding

The present work was not funded.

References

1) Organization WH. Obesity and Overweight 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2) Health NIo. Weight-loss (Bariatric) Surgery 2020. Available at: https://www.niddk.nih.gov/health-information/weight-management/bariatric-surgery.
3) Gandhi D, Boregowda U, Sharma P, Ahuja K, Jain N, Khanna K, Gupta N. A review of commonly performed bariatric surgeries: Imaging features and its complications. Clin Imaging 2021; 72: 122-135.
4) Mancini MC. Bariatric surgery--an update for the endocrinologist. Arq Bras Endocrinol Metabol 2014; 58: 875-888.
5) Billeter AT, Fischer L, Wekerle AL, Senft J, Müller-Stich B. Malabsorption as a Therapeutic Approach in Bariatric Surgery. Viszeralmedizin 2014; 30: 198-204.
6) Anvari S, Samarasinghe Y, Alotaiby N, Tiboni M, Crowther M, Doumouras AG. Iron supplementation

following bariatric surgery: A systematic review of current strategies. Obes Rev 2021; 22: e13268.

7) Bjørklund G, Peana M, Pivina L, Dosa A, Aaseth J, Semenova Y, Chirumbolo S, Medici S, Dadar M, Costea DO. Iron Deficiency in Obesity and after Bariatric Surgery. Biomolecules 2021; 11: 613.
8) Lewis CA, de Jersey S, Seymour M, Hopkins G, Hickman I, Osland E. Iron, Vitamin B(12), Folate and Copper Deficiency After Bariatric Surgery and the Impact on Anaemia: a Systematic Review. Obes Surg 2020; 30: 4542-4591.
9) Lowry B, Hardy K, Vergis A. Iron deficiency in bariatric surgery patients: a single-centre experience over 5 years. Can J Surg 2020; 63: E365-e9.
10) Muñoz M, Botella-Romero F, Gómez-Ramírez S, Campos A, García-Erce JA. Iron deficiency and anaemia in bariatric surgical patients: causes, diagnosis and proper management. Nutr Hosp 2009; 24: 640-654.
11) Steenackers N, Van der Schueren B, Mertens A, Lannoo M, Grauwet T, Augustijns P, Matthys C. Iron deficiency after bariatric surgery: what is the real problem? Proc Nutr Soc 2018; 77: 445-455.
12) Visentin M, Diop-Bove N, Zhao R, Goldman ID. The intestinal absorption of folates. Annu Rev Physiol 2014; 76: 251-274.
13) Vargas-Ruiz AG, Hernández-Rivera G, Herrera MF. Prevalence of iron, folate, and vitamin B12 deficiency anemia after laparoscopic Roux-en-Y gastric bypass. Obes Surg 2008; 18: 288-293.
14) Gudzune KA, Huizinga MM, Chang HY, Asamoah V, Gadgil M, Clark JM. Screening and diagnosis of micronutrient deficiencies before and after bariatric surgery. Obes Surg 2013; 23: 1581-1589.
15) Arias PM, Domeniconi EA, García M, Esquivel CM, Martínez Lascano F, Foscarini JM. Micronutrient Deficiencies After Roux-en-Y Gastric Bypass: Long-Term Results. Obes Surg 2020; 30: 169-173.
16) Shipton MJ, Johal NJ, Dutta N, Slater C, Iqbal Z, Ahmed B, Ammori BJ, Senapati S, Akhtar K, Summers LKM, New JP, Soran H, Adam S, Syed AA. Haemoglobin and Hematinic Status Before and After Bariatric Surgery over 4 years of Follow-Up. Obes Surg 2021; 31: 682-693.
17) de Cleva R, Cardia L, Riccioppo D, Kawamoto M, Kanashiro N, Santo MA. Anemia Before and After Roux-en-Y Gastric Bypass: Prevalence and Evolution on Long-Term Follow-up. Obes Surg 2019; 29: 2790-2794.
18) Cepeda-Lopez AC, Allende-Labastida J, Melse-Boonstra A, Osendarp SJ, Herter-Aeberli I, Moretti D, Rodriguez-Lastra R, Gonzalez-Salazar F, Villalpando S, Zimmermann MB. The effects of fat loss after bariatric surgery on inflammation, serum hepcidin, and iron absorption: a prospective 6-mo iron stable isotope study. Am J Clin Nutr 2016; 104: 1030-1038.
19) Ben-Porat T, Elazary R, Goldenshluger A, Sherf Dagan S, Mintz Y, Weiss R. Nutritional deficiencies four years after laparoscopic sleeve gastrectomy-are supplements required for a lifetime? Surg Obes Relat Dis 2017; 13: 1138-1144.
20) Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature 2006; 444: 1022-1023.
21) Aoun A, Darwish F, Hamod N. The Influence of the Gut Microbiome on Obesity in Adults and the Role of Probiotics, Prebiotics, and Synbiotics for Weight Loss. Prev Nutr Food Sci 2020; 25: 113-123.
22) Ciobârcă D, Cătoi AF, Copăescu C, Miere D, Crișan G. Bariatric Surgery in Obesity: Effects on Gut Microbiota and Micronutrient Status. Nutrients 2020; 12: 235.
23) Farin W, Oñate FP, Plassais J, Bonny C, Beglinger C, Woelnerhanssen B, Nocca D, Magoules F, Le Chatelier E, Pons N, Cervino ACL, Ehrlich SD. Impact of laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy on gut microbiota: a metagenomic comparative analysis. Surg Obes Relat Dis 2020; 16: 852-862.
24) Murphy R, Tsai P, Jüllig M, Liu A, Plank L, Booth M. Differential Changes in Gut Microbiota After Gastric Bypass and Sleeve Gastrectomy Bariatric Surgery Vary According to Diabetes Remission. Obes Surg 2017; 27: 917-925.
25) Paganelli FL, Luyer M, Hazelbag CM, Uh HW, Rogers MRC, Adriaans D, Berbers RM, Hendrickx APA, Viveen MC, Groot JA, Bonten MJM, Fluit AC, Willems RJL, Leavis HL. Roux-Y Gastric Bypass and Sleeve Gastrectomy directly change gut microbiota composition independent of surgery type. Sci Rep 2019; 9: 10979.
26) Crommen S, Mattes A, Simon MC. Microbial Adaptation Due to Gastric Bypass Surgery: The Nutritional Impact. Nutrients 2020; 12: 1199.
27) Damms-Machado A, Mitra S, Schollenberger AE, Kramer KM, Meile T, Königsrainer A, Huson DH, Bischoff SC. Effects of surgical and dietary weight loss therapy for obesity on gut microbiota composition and nutrient absorption. Biomed Res Int 2015; 2015: 806248.
28) Dhir A, Huang D. Gut Microbiome and Bariatric Surgery. Indian J Surg 2021; 83: 395-397.
29) Seganfredo FB, Blume CA, Moehlecke M, Giongo A, Casagrande DS, Spolidoro JVN, Padoin AV, Schaan BD, Mottin CC. Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. Obes Rev 2017; 18: 832-851.
30) Ulker İ, Yildiran H. The effects of bariatric surgery on gut microbiota in patients with obesity: a review of the literature. Biosci Microbiota Food Health 2019; 38: 3-9.
31) Kumar HP, Tsuji JM, Henderson GB. Folate transport in Lactobacillus salivarius. Characterization of the transport mechanism and purification and properties of the binding component. J Biol Chem 1987; 262: 7171-7179.
32) Kong LC, Tap J, Aron-Wisnewsky J, Pelloux V, Basdevant A, Bouillot JL, Zucker JD, Doré J, Clément

K. Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. Am J Clin Nutr 2013; 98: 16-24.
33) Rossi M, Amaretti A, Raimondi S. Folate production by probiotic bacteria. Nutrients 2011; 3: 118-134.
34) Tamene A, Baye K, Kariluoto S, Edelmann M, Bationo F, Leconte N, Humblot C. Lactobacillus plantarum P2R3FA Isolated from Traditional Cereal-Based Fermented Food Increase Folate Status in Deficient Rats. Nutrients 2019; 11: 2819.
35) Vazquez-Gutierrez P, Lacroix C, Jaeggi T, Zeder C, Zimmerman MB, Chassard C. Bifidobacteria strains isolated from stools of iron deficient infants can efficiently sequester iron. BMC Microbiology 2015; 15: 3.
36) Sugahara H, Odamaki T, Hashikura N, Abe F, Xiao JZ. Differences in folate production by bifidobacteria of different origins. Biosci Microbiota Food Health 2015; 34: 87-93.
37) Gomes AC, Hoffmann C, Mota JF. The human gut microbiota: Metabolism and perspective in obesity. Gut Microbes 2018; 9: 308-325.
38) Gehrer S, Kern B, Peters T, Christoffel-Courtin C, Peterli R. Fewer nutrient deficiencies after laparoscopic sleeve gastrectomy (LSG) than after laparoscopic Roux-Y-gastric bypass (LRYGB)-a prospective study. Obes Surg 2010; 20: 447-453.
39) Hakeam HA, O'Regan PJ, Salem AM, Bamehriz FY, Eldali AM. Impact of laparoscopic sleeve gastrectomy on iron indices: 1 year follow-up. Obes Surg 2009; 19: 1491-1496.
40) Capoccia D, Coccia F, Paradiso F, Abbatini F, Casella G, Basso N, Leonetti F. Laparoscopic gastric sleeve and micronutrients supplementation: our experience. J Obes 2012; 2012: 672162.
41) Toh SY, Zarshenas N, Jorgensen J. Prevalence of nutrient deficiencies in bariatric patients. Nutrition 2009; 25: 1150-1156.
42) Gasteyger C, Suter M, Gaillard RC, Giusti V. Nutritional deficiencies after Roux-en-Y gastric bypass for morbid obesity often cannot be prevented by standard multivitamin supplementation. Am J Clin Nutr 2008; 87: 1128-1133.
43) Enani G, Bilgic E, Lebedeva E, Delisle M, Vergis A, Hardy K. The incidence of iron deficiency anemia post-Roux-en-Y gastric bypass and sleeve gastrectomy: a systematic review. Surg Endosc 2020; 34: 3002-3010.
44) Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L. American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. Surg Obes Relat Dis 2017; 13: 727-41.
45) Mechanick JI, Apovian C, Brethauer S, Garvey WT, Joffe AM, Kim J, Kushner RF, Lindquist R, Pessah-Pollack R, Seger J, Urman RD, Adams S, Cleek JB, Correa R, Figaro MK, Flanders K, Grams J, Hurley DL, Kothari S, Seger MV, Still CD. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by american association of clinical endocrinologists/american college of endocrinology, the obesity society, american society for metabolic & bariatric surgery, obesity medicine association, and american society of anesthesiologists - executive summary. Endocr Pract 2019; 25: 1346-59.
46) Mechanick JI, Apovian C, Brethauer S, Garvey WT, Joffe AM, Kim J, Kushner RF, Lindquist R, Pessah-Pollack R, Seger J, Urman RD, Adams S, Cleek JB, Correa R, Figaro MK, Flanders K, Grams J, Hurley DL, Kothari S, Seger MV, Still CD. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. Surg Obes Relat Dis 2020; 16: 175-247.
47) Kim HJ, Bae SH, Kim HJ, Kim KM, Song JH, Go MR, Yu J, Oh JM, Choi SJ. Cytotoxicity, Intestinal Transport, and Bioavailability of Dispersible Iron and Zinc Supplements. Front Microbiol 2017; 8: 749.
48) Lönnerdal B. Calcium and iron absorption--mechanisms and public health relevance. Int J Vitam Nutr Res 2010; 80: 293-9.
49) Blanco-Rojo R, Pérez-Granados AM, Toxqui L, González-Vizcayno C, Delgado MA, Vaquero MP. Efficacy of a microencapsulated iron pyrophosphate-fortified fruit juice: a randomised, double-blind, placebo-controlled study in Spanish iron-deficient women. Br J Nutr 2011; 105: 1652-1659.
50) Pappalardo A, Currenti W, Ponzio R, Mellini G, Nicolosi D, Longhitano L, Tibullo D, Castorina S, Palumbo G. Effects of micronised microencapsulated ferric pyrophosphate supplementation in patients with advanced cancer and iron deficiency: a single-centre cohort pilot study. Blood Transfus 2019; 17: 196-199.
51) Coupaye M, Rivière P, Breuil MC, Castel B, Bogard C, Dupré T, Flamant M, Msika S, Ledoux S. Comparison of nutritional status during the first year after sleeve gastrectomy and Roux-en-Y gastric bypass. Obes Surg 2014; 24: 276-283.
52) Gletsu-Miller N, Wright BN. Mineral malnutrition following bariatric surgery. Adv Nutr 2013; 4: 506-517.
53) Parkes E. Nutritional management of patients after bariatric surgery. Am J Med Sci 2006; 331: 207-213.
54) Saltzman E, Karl JP. Nutrient deficiencies after gastric bypass surgery. Annu Rev Nutr 2013; 33: 183-203.
55) Shankar P, Boylan M, Sriram K. Micronutrient deficiencies after bariatric surgery. Nutrition 2010; 26: 1031-1037.
56) Pellegrini A. Antimicrobial peptides from food proteins. Curr Pharm Des 2003; 9: 1225-1238.

57) Permyakov EA. α-Lactalbumin, Amazing Calcium-Binding Protein. Biomolecules 2020; 10: 1210.

58) Cardinale V, Lepore E, Basciani S, Artale S, Nordio M, Bizzarri M, Unfer V. Positive Effects of α-Lactalbumin in the Management of Symptoms of Polycystic Ovary Syndrome. Nutrients 2022; 14: 3220.

59) Boscaini S, Cabrera-Rubio R, Speakman JR, Cotter PD, Cryan JF, Nilaweera KN. Dietary α-lactalbumin alters energy balance, gut microbiota composition and intestinal nutrient transporter expression in high-fat diet-fed mice. Br J Nutr 2019; 121: 1097-1107.

60) Tao YW, Gu YL, Mao XQ, Zhang L, Pei YF. Effects of probiotics on type II diabetes mellitus: a meta-analysis. J Transl Med 2020; 18: 30.

61) Kocsis T, Molnár B, Németh D, Hegyi P, Szakács Z, Bálint A, Garami A, Soós A, Márta K, Solymár M. Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: a meta-analysis of randomized clinical trials. Sci Rep 2020; 10: 11787.

62) Taverniti V, Cesari V, Gargari G, Rossi U, Biddau C, Lecchi C, Fiore W, Arioli S, Toschi I, Guglielmetti S. Probiotics Modulate Mouse Gut Microbiota and Influence Intestinal Immune and Serotonergic Gene Expression in a Site-Specific Fashion. Front Microbiol 2021; 12: 706135.

63) Li T, Gao J, Du M, Mao X. Bovine α-lactalbumin hydrolysates ameliorate obesity-associated endotoxemia and inflammation in high-fat diet-fed mice through modulation of gut microbiota. Food Funct 2019; 10: 3368-3378.

64) Laganà AS, Costabile L, Filati P, Noventa M, Vitagliano A, D'Anna R. Effects of micronised dispersible ferric pyrophosphate combined with alpha-lactalbumin in pregnant women affected by iron deficiency anemia: results from a prospective, double-blind, randomized controlled trial. Eur Rev Med Pharmacol Sci 2018; 22: 3602-3608.