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Editorial

Anemia Following Roux-En-Y Gastric Bypass (RYGB) Surgery

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Editorial

Obesity is a global pandemic and bariatric surgery is currently the most effective anti-obesity intervention method [1]. Although the preference rate over other bariatric surgeries has been decreased in the last five years, Roux-en-Y Gastric Bypass (RYGB) is still the most commonly performed bariatric surgery worldwide [2]. The effective weight loss achieved by RYGB is thought to be caused by the reorganization of the gastrointestinal (GI) tract leading to the restriction and malabsorption of the nutrients and altering the gut-brain communication on energy balance. During RYGB, a small proximal pouch (typically < 30 ml) is created from the stomach, which is attached to a segment of the jejunum that has been brought rostrally after being transected. The large gastric remnant is joined to the mid- to distal jejunum, creating the Roux-en-Y limb. RYGB causes restriction by reducing stomach capacity by ~95%, and malabsorption by re-directing the flow of nutrients, which results in ingested foods bypassing the 95% of the stomach, entire duodenum, and a small portion (15-20 cm) of the proximal jejunum, and directly being shunted into the mid- to distal jejunum [3]. This re-arrangement of the GI tract has been associated with clinically significant weight loss. However, despite its proven benefits, RYGB is not devoid of complications [4]. Anemia, along with other forms of cytopenias (i.e. leukopenia and thrombocytopenia) [5], that is diagnosed immediately after RYGB [6] which may persist long-term [7,8] is one such complication with multiple mechanisms contributing to its development. It is defined as low hemoglobin levels, and a widespread public health concern with possible serious comorbidities [9].

Due to the reduced food intake and reduced nutrient absorption in the GI tract, as well as other postoperative complications such as early dumping syndrome symptoms; vomiting and diarrhea [10], multiple deficiencies [4] such as iron, vitamins (B1, B12, folic acid, A, K, D, E) [11,12], and trace elements [13] are common following RYGB. Iron deficiency is the most common nutritional deficiency in RYGB and the top cause of RYGB-related anemia [8,14-17]. Iron homeostasis is largely dependent on iron absorption [18] which mostly takes place at in the duodenum and proximal part of the jejunum [19]. Thus, iron absorption capacity may decrease following any surgical procedure involving the bypassing of the duodenum [11] and the resection of the stomach –the site for gastric acid secretion, [20] which may lead to the occurrence of Iron Deficiency Anemia (IDA) following RYGB. IDA has also been shown in RYGB patients who had pre-existing hemochromatosis –iron overload [21], and RYGB has been suggested as a therapeutic procedure for this condition [22]. In addition to iron deficiency, copper [7], folic acid (vitamin B9) and vitamin B12 [8] deficiencies contribute to the development of anemia following RYGB, although to a lower extent. Hypocupremia -copper deficiency, can cause hematologic (cytopenias and myelodysplasia) and rare but serious neurological disorders (i.e. myeloneuropathy) [23]. The hematologic complications are thought to be caused by the impairing effects of hypocupremia on iron metabolism [24]. Gastric acidity facilitates copper dissociation and dietary copper absorption has been proposed to take place in the proximal duodenum as well as stomach and ileum [24]. In RYGB, the resection of stomach results in a decreased ability to metabolize molecular copper and the duodenum bypass induces copper malabsorption [25,26] all of which leading to hypocupremia. Thus, IDA caused by copper deficiency interfering with iron transport and utilization is a potential complication following RYGB [7], which has been shown to be responsive to supplementation therapies [27]. However, despite the prescribed oral supplementations and intravenous iron therapies, many patients continue to display anemia after RYGB [16,17]. Other origins of anemia must be considered in such cases since the overload of iron may cause secondary hemosiderosis leading hemochromatosis and liver injury [28].

Inflammation induced by various causes (e.g. infection, autoimmune disorders, aging etc.) is known to promote anemia [29]. A chronic subacute state of systemic inflammation in adipose tissue and liver has been associated with obesity which may be exacerbated by fat oxidation and lipolysis immediately after RYGB [30]. Elevation of a variety of proinflammatory cytokines increases the likelihood of anemia by a mechanism of decreasing iron absorption and reducing the release of the stored iron. Elevation in cytokines upregulates hepcidin [31,32] -a key peptide synthesized in liver and adipocytes regulating iron trafficking and secreted in proportion to the body iron storage. It plays a crucial role in iron absorption by regulating the iron efflux transporter; ferroportin as excessive hepcidin downregulates ferroportin reducing iron absorption [19] and also associated with diminished response to oral iron therapy in patients with pre-existing IDA [33]. Elevation in the inflammatory cytokines also may lead dyshematopoiesis which may reduce the release of storage iron [34]. Anemia associated with the inflammatory state may be further complicated by other micronutrient deficiencies [32], thus anti-inflammatory therapeutic interventions should be considered where necessary.

Helicobacter pylori (H. pylori) are common bacteria colonized in the human gastric mucosa and cause various conditions such as chronic inflammation, ulcers, diabetes mellitus as well as gastric cancer. Studies show a correlation between *H. pylori* infection and IDA [35,36] possibly by a decremented effect on iron absorption. *H. pylori* decrease iron absorption by competing for free iron and

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utilize several iron-binding molecules as iron sources in the host, reducing vitamin B12 and causing microbleeding [37]. Moreover it has been suggested that patients undergoing RYGB may have higher *H. pylori* infection prevalence [38], however several groups reported no difference in prevalence of *H. pylori* infection between RYGB patients and general population [39]. Regardless of the inconsistency in literature about the prevalence of *H. Pylori* in RYGB patients, this infection is prevalent enough in general population that it should be taken into account as a pre-existing condition in patients before the RYGB surgery. Moreover, it should be noted that after the procedure, the detection of the bacteria is difficult in the excluded portion of the stomach, therefore prescreening would be crucial before the patients undergo RYGB. Overall, *H. pylori* infection should be considered among the possible causes of anemia following RYGB as it makes the human host unresponsive to supplementary iron and eradication of *H. pylori* infection has been shown to increase responsivity to iron supplementation [40].

Although IDA is not uncommon in patients who underwent RYGB, it clearly does not account for all cases. Several considerations should be taken into account regarding the evaluation of anemia and other cytopenias following any type of bariatric procedure; the nutritional baseline levels at the pre-surgery especially pre-existing deficiencies, the elapsed time till the post-surgery check-up, and the percentage of weight loss, as well as the type and the dose of vitamin–mineral supplements taken before and after surgery [7]. Attention to the time of onset of the cytopenia is particularly important, because inflammation and infections are more likely to occur shortly after surgery [41]. Moreover, it has been shown that the segments of the cecum and proximal colon are also able to absorb iron to a certain extent [42] and thus it is possible that patients may have some degree of adaptation to the exclusion of the duodenum and partial jejunum after RYGB surgery. Finally, anemia seems to occur less commonly in patients with regular medical follow-ups [43,44] and therefore, bariatric surgery patients require appropriate postsurgical management which may include lifelong checkups for hematological and metabolic parameters.

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