

# IRON DEFICIENCY ANAEMIA AND ANAEMIA OF INFLAMMATION IN ENTEROPATHIES CAUSED BY COMMONEST SMALL INTESTINE DISORDERS: CURRENT EVIDENCE

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*It is no mystery that iron deficiency is the most common anaemia and multiple studies have shown that anaemia is a main factor for decreased quality of life. The focus of our article is an up-to-date review of different enteropathies caused by specific disorders and the prevalence of iron deficiency anaemia (IDA), starting with the understanding of physiology of iron absorption and regulation in the intestine. The pathologies that we tried to cover were celiac disease, Crohn's disease, nonsteroidal anti-inflammatory drugs (NSAID)-induced enteropathy and protein losing enteropathy. Unfortunately, not everything still understood and questions still remain. The main questions are associated with our understanding of iron regulation beyond the ferroportin-hepcidin axis and what mechanism is behind changes of epithelium in different conditions. Depending on the study and pathology of enteropathy, almost half of the studied patients had iron deficiency anaemia. However, in all enteropathies, IDA is more an additional finding or an additional symptom that needs further investigations. That is why many authors consider that IDA is caused by secondary mechanisms and not enteropathy per se and should be correlating with undernourishment, severe mucosal atrophy, malabsorption, and bleeding.*

**Keywords:** iron deficiency, small intestine disorders, celiac disease, Crohn's disease, NSAID-induced enteropathy and protein losing enteropathy.

## INTRODUCTION

Iron deficiency (ID) is the most common anaemia and multiple studies have shown that anaemia is a main factor for decreased quality of life (QoL). Also, it is well known that correction of anaemia can significantly improve the QoL of patients. It is therefore recommended that all patients, who may have increased risk, are regularly screened for iron deficiency and anaemia. If detected, appropriate workup and treatment should be initiated (Niepel *et al.*, 2018).

The mechanism of iron absorption and how body controls iron levels is also known, but this mechanism might be altered in different diseases. Thus, many authors specifically imply that correction of anaemia in patients with enteropathy is equally important as the treatment of their intestinal disease and greatly improves QoL for these patients (Gascher *et al.*, 2004). In addition, this leads to increased iron loss and progressing iron deficiency in patients with small intestine mucosal defects — enteropathies due to ongoing gastrointestinal (GI) blood loss through the inflammatory process in mucosa (Cronin *et al.*, 2001).

The focus of our article is a review of different enteropathies caused by specific disorders and the prevalence of iron deficiency anaemia, although the pathophysiological aspect of anaemia can be rather similar among different enteropathies. The international guidelines were limited to those with a peer-review process and published in a journal present in a citation index database.

## PHYSIOLOGY OF IRON ABSORPTION

Normal iron homeostasis is sustained by two mechanisms: absorption of nutritional iron by enterocytes in the duodenum and upper jejunum (1–2 mg/d), and recycling of iron via phagocytosis of senescent red blood cells (20–25 mg/d) (Evstatiev *et al.*, 2012).

Nutritional iron in foods exists in two forms — as haem and non-haem or inorganic iron. The source of haem iron is predominantly haemoglobin and myoglobin in meat. Non-haem iron exists predominantly in the oxidised or ferric ( $\text{Fe}^{3+}$ ) form.

**Haem iron absorption.** It is well known that haem is the most efficient way to absorb iron (Shayeghi *et al.*, 2005; Gulec *et al.*, 2014; Le Blanc *et al.*, 2012). The absorption into enterocytes is supported by the vesicular transport system — there haem binds to a haem transporter or haem receptor. Haem can be transferred directly by haem carrier protein 1 (HCP1) into enterocytes. Haem can be transferred by Haem-responsive gene 1 protein (HRG-1) into the cytoplasm, and then metabolised by haem oxygenase-1 (HO-1) from endoplasmic reticulum. Another option is when haem gets metabolised by haem oxygenase-2 (HO-2) which is present on the vesicle membrane and transferred into cytoplasm by divalent metal-ion transporter 1 (DMT1). Cytoplasm iron ( $\text{Fe}^{2+}$ ) forms a common stock that can be released into the blood stream by ferroportin (FPN) on the basolateral membrane (BLM) (West *et al.*, 2008; Hooda *et al.*, 2014).

In cases when haem quantity is high in the enterocyte, to protect the cell, haem can be excreted into the either the lumen of the intestine or directly in the blood stream by haem exporter FLVCR1 (Hooda *et al.*, 2014).

**Non-haem iron absorption.** Non-haem iron found in both meat and plant foods is highly insoluble and its bioavailability is influenced by many dietary components, for example gastric acid and ascorbic acid, and it promotes absorption of dietary ferric iron. On the other hand, dietary factors commonly found in plants, such as phytate, oxalate, polyphenols, and tannins, decrease the absorption of non-haem iron (Collins *et al.*, 2012).

Also, the ferric iron ( $\text{Fe}^{3+}$ ) form has to be reduced to ferrous iron ( $\text{Fe}^{2+}$ ), as most likely that is the form that can be transported into enterocytes. Several authors propose that this process is mediated by ferrireductase and duodenal cytochrome b (DCYTB) on the brush-border membrane (BBM) (Mc Kie *et al.*, 2001). Since DCYTB facilitates the reduc-

tion of ferric iron via electron transfer from intracellular ascorbate (Vlachodimitropoulou *et al.*, 2010; Luo *et al.*, 2014), this may provide one potential mechanism how vitamin C enhances iron absorption.

However, in the similar way, ferrous iron ( $\text{Fe}^{2+}$ ) is transported across the BBM by the action of DMT1 (Mackenzie *et al.*, 2005). DMT1 is a transmembrane protein that is associated with absorption of proton-mediated elements. Interestingly, DMT1 can transport other divalent cations, including manganese and cobalt. However, protons for ferrous iron, uptake likely occurs via the sodium/hydrogen exchanger (NHE3) on BBM, which acidifies the unstirred water layer (Gunshin *et al.*, 1997; Shawki *et al.*, 2012).

**Iron transmission in the enterocytes.** Unfortunately, not much is understood about which processes exactly are involved in iron transfer inside the cytoplasm of enterocyte. However, but supposedly ferrous iron, after the transport across BBM is likely chelated by small-molecular-weight organic acids, amino acids, or intracellular proteins. The poly-r(C)-binding proteins are iron-trafficking proteins (chaperones) (Shi *et al.*, 2008; Leidgens *et al.*, 2013).

When the body iron demands are high, ferroportin 1 (FPN1) can quickly transfer intracellular iron across the BLM. When the demand is low, iron can be stored as ferritin. In addition, the existence of a heavy chain in ferritin has a protective role in iron overload situations, which helps to regulate intestinal iron absorption (Vanoaica *et al.*, 2010).

In mammals, FPN1 (encoded by the *SLC40A1* gene) is the only ferrous iron export protein (Mc Kie *et al.*, 2000). FPN1 is present in enterocytes, hepatocytes and RE macrophages and also plays a major role in iron absorption and recycling (Donovan *et al.*, 2005).

**Regulation of iron absorption.** The liver-derived peptide hormone hepcidin (HEPC) is the most important regulator of iron homeostasis (Nicolas *et al.*, 2001). HEPC blocks iron release from storage and blocks intestinal absorption of iron molecules, and as a result, decreasing circulating of iron in the blood stream (Nicolas *et al.*, 2002). HEPC expression is induced when body iron reserves are elevated, and during infection and inflammation, with the net result being lower serum iron levels. In addition, HEPC secretion in the liver affects the activity of duodenal iron transporters — DMT1, FPN1 (Frazer *et al.*, 2002). This effect and importance of HEPC for maintaining balance occurs in patients with mutations in the HAMP gene (Roetto *et al.*, 2003), who develop termed juvenile haemochromatosis, a disease that is associated with inappropriately increased intestinal iron absorption.

The interaction of HEPC with FPN1 on the plasma membrane results in internalisation and eventual degradation of FPN1 (De Domenico *et al.*, 2007), thus limiting iron efflux (Nemeth *et al.*, 2004). In the small intestine, HEPC stimulates proteosomal degradation of DMT1, thus modifying intestinal iron flux (Rivera *et al.*, 2005; Brasse-Lagnel *et al.*,

2011). Conceivably, additional aspects of HEPC may be discovered in the future.

Corresponding to the role of iron homeostasis regulator, HEPC expression is altered in part to iron needs, and HEPC production declines during iron deficiency (Nicolas *et al.*, 2002), hypoxia, and pregnancy (Millard *et al.*, 2004), and when erythropoiesis is stimulated, allowing adequate iron absorption and efficient iron release from reserves. When body iron levels are restored or elevated, HEPC expression increases and limits intestinal absorption, also allowing excess iron to be stored in hepatocytes and RE macrophages. Inflammation also induces HEPC expression, which leads to hypoferrremia, which is a regular phenomenon of chronic inflammatory conditions (Nicolas *et al.*, 2002).

**Iron absorption and hypoxia.** Intestinal iron absorption is stimulated when iron reserves are starting to decrease (Finch *et al.*, 1994). Iron absorption is also enhanced when erythropoiesis is stimulated (e.g., by blood loss or acute haemolysis), since haemoglobin production in developing erythrocytes requires large amounts of iron (Erlanson *et al.*, 1962; Finch *et al.*, 1994). Iron absorption also increases in response to tissue hypoxia. While in part this may relate to changes in the erythropoietic rate, a component of the response relates specifically to oxygen levels (Raja *et al.*, 1988). For example, iron absorption increases during hypoxia before an increase in erythrocyte production (Hathorn *et al.*, 1971), demonstrating that hypoxia exerts a direct effect on the gut. This implies that iron regulatory molecules and iron transporters should react directly to hypoxia (Peyssonaux *et al.*, 2007).

Iron absorption can increase during pregnancy (Batey *et al.*, 1977). During gestation, iron requirements are high due to expansion of the maternal erythroid mass and the iron needed by the developing foetus. The supposed trigger should be related to both a reduction in maternal iron reserves and tissue hypoxia. Moreover, during the perinatal and neonatal periods, iron requirements of humans are high, and iron absorption from breast milk is very efficient. High neonate iron absorption might be similar to adults and is likely due to active transport mechanisms, but the relative “transparency” of the epithelium, which allows passive absorption of solutes, might make some difference. Another study, which comparing adult and neonatal rats, suggested supposed anatomic adaptation at early developmental stage, and showed more iron absorption in the distal portions of the gastrointestinal tract in neonatal rats (Frazer *et al.*, 2007). Even more, this was demonstrated in neonates even in case of intact and active HEPC (Darshan *et al.*, 2011). Although the mechanisms are not fully understood, this leads to a high capacity to absorb iron from an iron-poor diet at a time of great physiological need.

Additionally, the regulation and control of iron absorption should be much more complex and involves not only the FPN1-HEPC axis. There is a remodeling of epithelium to maximise iron extraction when the demand for iron arises,

probably as iron levels of the same enterocyte change (Gulec *et al.* 2014).

**Anaemia of chronic disease.** Anaemia of chronic disease (ACD) occurs as a result of an abnormal activation of the immune system following the release of inflammatory cytokines — in particular, interferon-gamma (IFN- $\gamma$ ), interleukin-6 (IL-6) and tumour necrosis factor (TNF), which modulate the synthesis of HEPC in the liver. The latter determines the degradation of FPN1 and inhibits the release of iron by macrophages and enterocytes, thus modifying the reallocation outside the serum (Lerner *et al.*, 2016; De Franceschi *et al.*, 2017; Camaschella *et al.*, 2019).

#### PATHOLOGIES WHICH MAY IMPACT DUODENOJUNAL ABSORPTION

**Celiac disease and IDA.** Celiac disease (CD) is one of the most common autoimmune disorders, with approximate prevalence of 0.5–1% (Corazza *et al.*, 1997). However, the respective diagnostics rely on finding of specific antibodies, none of which currently provide sensitivity and specificity of 100%. Mucosal changes are assessed by duodenal biopsies, with consequent histopathologic evaluation using the Marsh classification (Volta *et al.*, 2001).

Mostly commonly, suspicion for CD arises in children younger than three years with diarrhea (Vivas *et al.*, 2008). Older children and adults may complain of diarrhea, bloating, constipation, abdominal pain, or weight loss (Rielly *et al.*, loss of appetite, abdominal distention, and failure to thrive 2011). In adults, however, malabsorption syndrome with chronic diarrhea and weight loss is rather a rare finding. One of the significant findings, which in many cases is only one symptom, is iron deficiency anaemia.

There is no clear understanding of the pathogenesis of iron deficiency in CD. A study on iron transporter protein expression in children with CD (Repo *et al.*, 2021) found increased expression of FPN and a decreased expression of hephestin (HEPH), compared with the non-celiac controls, and no other significant differences between the study groups in the expression of iron transporter proteins. Also, no differences in any of these proteins were found between anaemic and non-anaemic children.

Several studies have investigated whether it is possible to identify potential genetic predisposition. Increased expression of DMT1, DCYTB, FPN 1, efestin and transferrin receptor was observed in CD patients compared to controls (Barisani *et al.*, 2004).

Patients with IDA have increased levels of DMT1 and ferroportin, thus this did not correlate with the presence of CD (Sharma *et al.*, 2013). Other studies showed an increase of ferritin in CD patients with IDA compared to non-CD patients.

It was estimated (Tolone *et al.*, 2017) that CD children (387) have a roughly four times higher risk of anaemia compared

to healthy controls (164) in the case of DMT1-IVS4 + 44-AA polymorphism. Thus, it seems that an A allele mutation will result in reduction of DMT1 and lead to IDA.

Other studies investigated if mutations of haemochromatosis genes (HFE) could be the reason for IDA in CD, or if HFE be a protective factor that increases intestinal iron absorption. De Falco *et al.*, (2018) demonstrated HFE variants C282Y, H63D, and TMPRSS6 in 505 patients with CD at diagnosis and a year after gluten-free diet versus 539 subjects in control group, that HFE mutations have protective effect in celiac patients in the development of IDA.

However, controversies still remain since other studies comparing CD patients with healthy controls showed an increased prevalence of TMPRSS6 mutations in CD patients, but no significant difference between IDA and non-IDA CD patients (Martin-Masot *et al.*, 2019).

Interestingly, systemic increase in the levels of inflammatory proteins in patients with CD is a rare event, but local production of IFN- $\gamma$  and IL-6 is quite common and can lead to ACD (Sharma *et al.*, 2013).

The prevalence of ACD in CD is about 17% (Harper *et al.*, 2007; Bergamaschi *et al.*, 2008). However, patients with both CD and ACD did not have systemic inflammatory signs (Harper *et al.*, 2007).

Therefore, the mechanism for developing anaemia should be twofold: increased iron absorption and reduced effects of various inflammatory mediators on iron homeostasis and erythropoiesis. Thus, the reason for anaemia in CD most likely has a multifactorial pathogenesis and secondary to iron deficiency, and should correlate between extensive, severe mucosal atrophy, malabsorption, folate and B12 vitamin deficiencies, blood loss and ACD (Sharma *et al.*, 2013).

IDA was shown to be the most common cause for anaemia in CD patients (81.5%). Other causes were folate deficiency (10.7%), vitamin B12 deficiency (13.6%), mixed nutritional deficiency (16.5%), and ACD (3.9%) (Berry *et al.*, 2018; Mahadev *et al.*, 2018).

**Enteropathy and anaemia in Crohn's disease.** Crohn's disease (CrD) is a chronic relapsing inflammatory disorder affecting the large and small intestine, eventually leading to mucosal ulceration and bleeding (Jimenez and Gasche, 2019). The incidence of anaemia and the associated fatigue in CrD varies widely depending on the study (Stein *et al.*, 2010), with 32% and 85% being specifically IDA (Akhue-monkhan *et al.*, 2017).

A systematic review (Filmann *et al.*, 2014) showed an overall prevalence of about 24% IDA in inflammatory bowel disease (IBD). There is a higher prevalence in CrD (27%) as compared to ulcerative colitis (UC) (21%), and over half of all anaemia cases in IBD are due to iron deficiency. Results differ between study populations, and inpatients vs. outpatients, where IDA is noted in approximately 20% of all out-

patients (Bager *et al.*, 2013) and 68% among inpatients (Gisbert and Gomollon, 2008; Nielsen *et al.*, 2018).

Another study (Miller *et al.*, 2019) on anaemia prevalence in paediatric IBD included a cohort of 2446 patients and 1560 with CrD. Approximately, 85% of CrD cases were screened for anaemia. Anaemia occurred in 51% patients with CrD.

A newer study (Bengi *et al.*, 2018) that included 465 adults (257 with CrD) reported IDA in 57.6% CrD patients. CrD involvement was as follows: 48.2% small intestine involvement, 19% — colonic disease, and in 32.8% ileocolonic disease.

The prevalence of anaemia in IBD was observed to remain high even during a five-year follow-up — 50.1%, (CrD: 53.3% vs. UC: 44.7%), but anaemia was more associated with surgery for IBD (Koutroubakis *et al.*, 2016).

In a study on IDA in IBD (Madanchi *et al.*, 2018) that included 1558 patients with CrD and 1108 with UC, IDA was detected in 19.6% of CrD patients. Further, in CrD patients, low body mass index and non-smoker status were positively associated with anaemia. CrD and UC with the presence of malabsorption syndrome was significantly associated with anaemia (6.2% and 3.8%, respectively) and current steroid use (40% CrD, 52.7% UC).

A study on nutritional parameters of pediatric and adult populations (Marcil *et al.*, 2019) found that prevalence of undernutrition paediatric and hypoalbuminemia was similar in both paediatric and adult patients. However, anaemia and iron deficiency were more often observed in paediatric subjects, compared to adults (59.1% vs 36.9%, respectively, and 37.9% vs 25.3%). Patients with active Crohn's disease were more likely to be undernourished in both groups.

**NSAID-induced enteropathy.** The association of upper and lower GI injury with the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is well described. This injury can include bleeding, which may be severe enough to result in hospitalisation. Even a low dose of aspirin and non-aspirin-NSAIDs increases mean faecal blood loss from roughly 0.5 mL/d to 1–2 mL/d (i.e. 0.5–1.0 mg iron loss/d). Among patients treated with aspirin doses  $\geq$  1800 mg/d, 31% had a blood loss of  $\geq$  5 mL/d (i.e.  $\geq$  2.5 mg iron loss/d). Although cyclooxygenase-2 (COX-2) inhibitors are associated with fewer GI injuries than traditional NSAIDs, long-term use of a COX-2 inhibitor may also induce GI injuries and require concomitant medication for associated anaemia and small intestinal injuries. Notably, routine endoscopic examination might not reveal NSAID-induced GI injuries. Therefore, capsule endoscopy is much more preferred for small bowel injuries, especially in patients with unexplained anaemia or IDA (Lim and Yang, 2012; Goldstein and Cryer, 2015; Shin *et al.*, 2017).

In a study on 83 Korean subjects, 55 had stool with obvious blood and 28 had normal stool but presenting with iron deficiency anaemia (Song and Shim, 2016). The detection rate

of small intestine bleeding and lesions using capsule endoscopy occurred in 60 of 83 patients. A rather high number of ulcerative/erosive lesions (40 of 51) was observed in cases of inactive bleeding. As a result, only 30.1% of 83 patients had NSAID-induced enteropathy (Song and Shim, 2016).

This also demonstrated how capsule endoscopy can improve diagnostics in cases of obscure GI bleeding and should be considered for patients with unexplained bleeding, receiving aggressive therapy and unmanageable IDA (Song and Shim, 2016).

**Protein losing enteropathy.** Protein-losing enteropathy (PLE) is a condition in which there is an increased loss of protein through the gastrointestinal tract of various aetiologies (Nagra and Dang, 2021). The condition can be suspected in cases of low serum proteins and when other causes of hypoproteinemia have been eliminated (Craven and Washabau, 2019).

PLE includes three groups of disorders:

#### 1. Primary Erosive/Ulcerative Gastrointestinal Disorders

Diseases of this group cause deep or superficial mucosal damage, i.e. inflammatory bowel diseases, gastrointestinal malignancies, different kinds of erosions or ulcers of gastroduodenal area, *Clostridium difficile* colitis, graft vs. host disease etc.

#### 2. Non-Erosive/Non-Ulcerative Gastrointestinal Disorders

This group includes diseases associated with either local inflammatory process or systemic inflammation, which will change the mucosal villi, i.e. CD, Menetrier disease, tropical sprue eosinophilic gastroenteritis, intestinal parasitic infections, bacterial overgrowth, Whipple disease, collagenous colitis, mixed connective tissue diseases, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) (Akkelle *et al.*, 2018; Zubiaga *et al.*, 2019).

#### 3. Disorders Causing Increased Interstitial Pressure or Lymphatic Obstruction

Here the pathology is mostly outside the bowel itself, and includes: primary intestinal lymphangiectasia, right-sided heart failure, constrictive pericarditis, congenital heart disease, cirrhosis with portal hypertension, hepatic venous outflow obstruction, sarcoidosis, retroperitoneal fibrosis, lymphoenteric fistula, and lymphoma (Melenovsky *et al.*, 2018; Miranda *et al.*, 2019; Schumacher *et al.*, 2019).

Another possible combination to mention is IDA and PLE due to excessive cow milk intake, as there are quite many reports for this comorbidity (Hamrick, 1994; Nickerson *et al.*, 2000; Yasuda and Rufo, 2018; Michaela *et al.*, 2020).

The connection between PLE and IDA is unknown, but likely arises from a combination of either increased lymphatic pressure or ongoing inflammatory, erosive, or exudative process (Levitt and Levitt, 2017). Here again the most

likely explanation would be that there are multiple mechanisms overlapping.

One explanation could be that iron deficiency impairs epithelial junction regulation leading to increased permeability of the mucosal layer, and therefore increasing protein efflux to bowel lumen (MohanKumar *et al.*, 2020). Another explanation could be associated with the hypothesis that excessive cow milk damages the mucosal layer directly and leads to protein loss as well as iron loss, considering what has been described above about the physiological mechanisms of iron absorption in neonates that lead to IDA (Eastham and Walker, 1977).

Yet the correlation and mechanisms between IDA and PLE has to be uncovered, for now there are only reports of this phenomenon (Michaela *et al.*, 2020).

## CONCLUSIONS

Many discoveries have been made in the field of understanding iron absorption and regulation. Unfortunately, some questions still remain. The main questions are associated with our understanding of iron regulation beyond the FPN-HEPC axis, and the mechanism behind changes of epithelium in different conditions.

The studies on enteropathies indicate that IDA is a quite frequent finding. Depending on the study, almost half of the studied patients had IDA. However, in all enteropathies, IDA was more an additional finding or as an additional symptom that needed further investigation. That is why many authors consider that IDA is caused by secondary mechanisms and not enteropathy per se, and should be associated with undernourishment, severe mucosal atrophy, malabsorption, bleeding.

Another important issue is that IDA or latent iron deficiency can be associated with presence of mucosal changes of duodenum and/or jejunum described by endoscopy, particularly capsule endoscopy, but without any of specific enteropathy diagnosis, as discussed in our article. In such a scenario, visual mucosal changes have been described as congestion enteropathy, erosive enteropathy, haemorrhagic enteropathy, segmental enteropathy, and erythematous enteropathy. However, there is no or very limited quality data in the literature about its correlation with IDA or latent iron deficiency. Future studies should be focused on these important questions, since the methods of visual diagnostic are becoming more and more available worldwide.

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## DZELZS DEFICĪTA ANĒMIJA UN IEKAISUMA ANĒMIJA ENTEROPĀTIJU GADĪJUMĀ, KO IZRAISA BIEŽĀKĀS TIEVĀS ZARNAS SLIMĪBAS: ŠĪBRĪŽA SITUĀCIJA

Nav noslēpums, ka dzelzs deficīts ir biežākais anēmijas cēlonis pasaulē, un vairāki pētījumi ir parādījuši, ka anēmija ir galvenais faktors, kas samazina dzīves kvalitāti (QoL). Mūsu raksta uzmanības centrā ir dažādu enteropātiju apskats, ko izraisa specifiski traucējumi un dzelzs deficīta anēmijas izplatība, sākot ar līdz šim zināmo izpratni par dzelzs uzsūkšanās un regulēšanas fizioloģiju zarnās. Patoloģijas, kuras mēģinājām aptvert, bija celiakija, Krona slimība, NPL izraisīta enteropātija un proteīnu zaudēšanas enteropātija. Diemžēl ne viss vēl ir skaidrs, joprojām paliek jautājumi, galvenokārt saistībā ar mūsu izpratni par dzelzs regulēšanu ārpus FPN-HEPC ass un to, kāds mehānisms ir aiz epitēlija izmaiņām dažādos apstākļos. Atkarībā no enteropātijas pētījuma un patoloģijas gandrīz pusei pētīto pacientu bija dzelzs deficīta anēmija (IDA). Tomēr visās enteropātijās IDA ir vairāk nekā papildu atradums vai kā papildu simptoms, kam nepieciešama turpmāka izmeklēšana. Tāpēc daudzi autori uzskata, ka IDA izraisa sekundāri mehānismi, nevis enteropātija *per se*, un tam vajadzētu būt saistītam ar nepietiekamu uzturu, smagu gļotādas atrofiju, malabsorbciju, asiņošanu.