Celiac Disease and Obesity: Is Bariatric Surgery an Option?

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Abstract

Celiac disease (CD) is an immune-mediated enteropathy associated with malabsorptive syndrome and fat-soluble vitamin deficiencies. CD affects one percent of individuals but is largely underdiagnosed, as its multifaceted clinical presentations create challenging diagnostic scenarios. With the rise of the obesity epidemic, doctors are increasingly seeing CD patients with overweight or obesity, which raises the question of bariatric surgery. However, few studies so far have investigated bariatric surgery in this patient population. Here we provide a comprehensive review of the literature on CD, its nutritional consequences and complications, and we discuss the possible impact of bariatric surgery on weight loss, nutritional deficiencies, response to gluten-free diet, and long-term post-operative complications. We also review the effect of bariatric surgery on the incidence of CD.

Keywords: Celiac disease, bariatric surgery, obesity, gluten-free diet, Roux-en-Y bypass, sleeve gastrectomy

Introduction

Celiac disease (CD) is an autoimmune disorder that can occur in genetically predisposed people where the ingestion of gluten leads to damage in small intestine[1]. It is characterized by villous atrophy inducing a malabsorption syndrome [2]. CD was classically defined in the child as a chronic enteropathy with villous atrophy secondary to an inappropriate immune response of the intestinal mucosa to the gliadin in wheat, barley and rye. The disorder often presents with diarrhea, malabsorption of one or more nutrients, and resultant weight loss, and it involves a mucosal inflammatory response that extends from the duodenum into the more distal small intestine for variable distances.

CD is heavily underdiagnosed, due to its many variable clinical symptoms and multi-organ manifestations (Figure 1). Diagnosis of CD is based on the presence of predisposing genetic factor human leukocyte antigen (HLA) DQ2/8 haplotypes, with positive small intestine biopsy and serological antibodies upon a gluten-containing diet[3]. Histological confirmation of CD diagnosis is based on demonstrated small bowel mucosal villous atrophy, intraepithelial lymphocytosis and crypt hyperplasia in biopsy samples obtained by gastroscopy [4,5].

The spectrum of CD may present in different forms. The classical form may be diagnosed at any age of life and is often characterized by crypt hyperplasia and villous atrophy along with features of malabsorption [1,6]. Diarrhea, steatorrhea, weight loss or growth failure is required. The atypical form is characterized by positive celiac serology, limited abnormalities of the small intestinal mucosa or no intestinal symptoms, but associated extraintestinal conditions such as osteoporosis, peripheral neuropathy, anemia and infertility. The latent form is defined by presence of predisposing gene HLADQ2 and/or HLA-DQ8, normal intestinal mucosa and, possible positive serology [3]. This changing face of CD (more latent than

classical form) is accompanied by a change in diagnostic strategies but also in the whole definition of the disease itself [7].

Historically, patients with CD were more frequently underweight, but nowadays CD patients are increasingly overweight or obese [8,9]. Some who are severely obese are candidates for bariatric surgical management. Bariatric surgery is generally safe, feasible and effective in patients with autoimmune disorders [10,11]. However, in certain types of surgery, co-existing malabsorptive processes may further increase the risk of post-operative complications or nutritional deficiencies. This review provides a thorough appraisal of CD in the context of obesity, its nutritional consequences and complications, and opens discussion on the possible impact of bariatric surgery on weight loss, nutritional deficiencies, response to gluten-free diet, and long-term post-operative complications.

Epidemiology of celiac disease

The prevalence of CD has increased significantly over the past fifty years, partly due to better diagnostic tools and screening of individuals at high risk for the disorder [2]. In Western countries, the prevalence of CD is between 0.6 and 1% in the general population, but a much more prevalent 3–6% in type 1 diabetics, 5–10% in the first-degree relatives of a CD patient, from 1 to 3% in osteoporotic patients and from 3% to 15% in patients with iron-deficiency anemia [12]. The prevalence of CD varies according to ethnic origin. It is high in Caucasians compared to Blacks and Hispanics, which appears to correlate with the frequency of patients with a predisposing HLA gene. The prevalence of CD in European countries was found to be 1% (among 29,212 patients from Finland, Germany, Italy and the UK). Incidences close to those of Europe or the United States were noted in North Africa, the Middle East and India. On the other hand, CD is almost unseen in Southeast Asia and Black Africa.

Note that 30% of Caucasian populations carry HLA-DQ2, and most will eat wheat, while only 1 in 100 will develop the disease. The remaining susceptibility is thought to be due to a combination of genetic and environmental factors [3]. Overall, the HLA-DQ2 haplotype confers the highest genetic risk for developing CD. There is also a general consensus that female gender and a family history of CD are also risk factors. In a recent publication, higher gluten intake during the first 5 years of life was associated with increased risk of CD autoimmunity and CD among genetically predisposed children carrying HLA antigen genotypes associated with type 1 diabetes and CD [13].

The incidence of CD has increased significantly over the last 30 years, from 2–3 to 9 or 13 new cases per 100,000 inhabitants per year [14–16]. This increase in incidence over time probably reflects more recognition of atypical and latent forms through serological testing. Differences in the prevalence of predisposition genes and food diversification practices (gluten introduced earlier or later in life) could also explain the geographical variations and—over time—incidence of the disease. However, the majority of patients with CD remain undetected worldwide, and several reports have suggested that upper gastrointestinal surgeries may unmask undiagnosed CD [2].

Nutritional consequences of celiac disease

There are two types of intestinal mucosal damage: first a reduction in the number of mature absorptive cells, and second a dysfunction of the remaining cells characterized by villous atrophy (flattening of the mucosa and reduction of the absorptive surface).

Reduced levels of iron, folate, vitamin B12, vitamin D, zinc and magnesium are common in untreated CD patients, probably due to a loss of brush border proteins and enzymes needed for the absorption of these nutrients. In a majority of patients, removing gluten from the diet

leads to histological recovery and normalization of iron, vitamin and mineral levels. Iron-deficiency anemia is the most common extra-intestinal sign of CD and usually resolves with adherence to a gluten-free diet. However, deficiencies of both folate and vitamin B12 may persist in some patients on a gluten-free diet, thus requiring vitamin supplementation to improve health status. Similarly, bone mineral density does not always normalize after excluding gluten from the diet, and in these cases vitamin D and calcium supplementation is recommended. Furthermore, resolution of mucosal inflammation may not be enough to abrogate magnesium deficiency. Since gluten-free cereal products have a lower magnesium content than their gluten-containing counterparts, a magnesium-enriched diet should be encouraged in CD patients [17]. **Table 1** summarizes the nutritional deficiencies frequently reported with a gluten-free diet (GFD) [18–21].

In a study of 80 patients assessing the nutritional and vitamin/mineral status of current 'early diagnosed' but untreated adult CD patients in the Netherlands, Wierdsma *et al.*[22] showed that compared to healthy individuals, CD patients were most frequently deficient in folic acid (20%, 16/80), followed by vitamin B12 (19%, 15/79), vitamin B6 (14.5%, 9/62), vitamin A (7.5%, 4/53) and vitamin (25-hydroxy) D (4.5%, 1/21). Approximately 67% (26/39) of the patients had zinc deficiency, 32.4% (23/71) had anemia, 46.2% (18/39) had insufficient iron stores evidenced by low ferritin, and 25% (8/40) had iron-deficiency anemia. CD patients had lower vitamin A and folic acid than healthy controls. Overall, 17% were malnourished (>10% undesired weight loss), 22% of the women were underweight (BMI<18.5), and 29% of all patients were overweight (BMI>25). Vitamin deficiencies were barely seen in healthy controls, with the exception of vitamin B deficiency [22].

In a study of 39 biopsy-proven CD patients, 16 (41%) patients were vitamin B12-deficient (<220 ng/L) and 16 (41%) patients (11 women and five men) were anemic [18]. Only 5/16 (31%) of the vitamin B12-deficient patients were also folate-deficient. The Schilling test,

performed in 10 of the vitamin B12-deficient patients, showed five low and five normal results. Although only five patients received parenteral vitamin B12, the vitamin B12 levels had normalized in all patients at follow-up. Three vitamin B12-deficient patients had acral paresthesia at presentation that resolved after vitamin B12 replacement [18].

A well-led gluten-free diet will correct most vitamin and trace element deficits.

Deora *et al*.[23] evaluated the prevalence of micronutrient deficiencies in 140 CD patients under 17 years old and measured serum micronutrient levels and IgA-class anti-transglutaminase antibodies at diagnosis, 6 months and 18 months after starting a GFD. At diagnosis, serum vitamin D was the most commonly deficient vitamin in 70% of children. Serum ferritin was subnormal in 34.5% along with zinc in 18.6% of children, and remarkably, only 12 (10.9%) children had iron-deficiency anemia. There was no correlation between micronutrient deficiencies at diagnosis and serum transglutaminase IgA antibody or degree of villous atrophy. Reassuringly, the measured serum micronutrient levels had mostly normalized at 6 months after starting GFD, except for vitamin D which improved but remained subnormal [23].

Nevertheless, the GFD remains a difficult diet to follow, with compliance problems, that may lead to the exclusion of certain foods and therefore other nutritional deficiencies. CD is a life-long disorder, and effective treatment with a strict GFD is difficult and usually time-consuming for the patient.

Severe complications of celiac disease

The two main serious and feared complications of CD are intestinal lymphoma and small bowel adenocarcinoma [1,2].

Lymphoma complications of CD are rare, with an incidence of less than 3 per 100,000 inhabitants per year, but serious. One identified lymphoma complication is clonal refractory

sprue, known as type II (SR II). SR II is an intra-epithelial lymphoma with a low degree of malignancy that is associated with CD and characterized by an expansion of small intraepithelial lymphocytes of abnormal phenotype. It's course can evolve into high-malignancy T-lymphoma in 30 to 50% of cases at 5 years, and its prognosis is bleak, with less than 45% of patients alive 5 years after diagnosis [24,25]. Diagnosis is difficult and requires specific immunohistochemical, phenotyping and molecular studies. Emerging from the small intestine, the abnormal intraepithelial lymphocytes can spread through the entire digestive tract (distal small intestine, stomach, and colon), circulate in the blood, and invade the bone marrow and various epithelia such as the epitheliotropic skin and lungs. More recently, granular leukemias (like large granular lymphocytic leukemia) have been identified which, from the periphery, invade the intestine of CD patients, often leading to GFD resistance.

These high-malignancy T-lymphomas (enteropathy-associated T-lymphoma; EATL) are rare (incidence estimated between 0.22 and 1.9 per 100,000 inhabitants) but with a bleak outcome. EATL may be diagnosed through surgery revealing CD, but when CD is already diagnosed, it is important to screen for lymphoma in case of resistance to GFD, whereas diagnosis after roux-en-Y gastric bypass (RYGB) can prove complex due to the excluded jejunum.

There is a reported increase in the risk of small bowel adenocarcinoma in patients with CD (odds ratio ranges between 4.3 to 60.0) that is usually detectable in the jejunum [26]. Indeed, in a study that evaluated the frequency of small-bowel malignancy in the UK and its relationship to the presence of CD, the authors found a diagnosis of CD in 13% of adenocarcinoma cases and in 39% of lymphomas, which highlights the fact that CD confers susceptibility to small bowel adenocarcinoma as well as lymphoma [27]. Unlike intestinal lymphoma, small bowel adenocarcinoma is not preceded by refractory CD and should be suspected in cases of sudden intestinal (sub)occlusion and/or anemia [1]. In their retrospective

study, Sharma *et al.* found no increase in intestinal lymphoma (p=0.99) nor an increase in small intestine adenocarcinoma in CD patients given bariatric surgery [28].

Prevalence of obesity in celiac disease and effect of gluten-free diet on weight

The worldwide surge in number of obese individuals is also increasing the number of CD patients who are overweight or obese. CD had historically been diagnosed in underweight patients, but the trends seem to be reversing. Overall, the majority of CD patients have a normal BMI: the prevalence of underweight varies from 3% to 36%, and the prevalence of overweight and obesity varies from 6% to 39% and from 3% to 13%, respectively [29–33]. Table 2 summarizes the prevalence of underweight, normal, overweight, and obese patients among patients with CD. Comparative analysis versus general population data found that CD women had a significantly lower BMI (21.9 *vs* 24.2 kg/m², p<0.0001) and fewer of them were overweight (11% *vs* 21%, p<0.0001). More CD men had normal BMI (59.5% *vs* 34%, p <0.0001), and fewer CD men were underweight (9.1% *vs* 26.7%, p<0.0001).

After 2.8 years of well-monitored GFD), 66% of underweight patients gained weight, while 54% of overweight patients and 47% of obese patients lost weight [31].

Many studies have found weight loss or stable weight in overweight or obese CD patients under a well-conducted GFD [21,29,31,34]. Ukkola *et al.* [32] prospectively investigated weight and disease-related issues in 698 newly-detected CD adults at diagnosis and after one year on a GFD and compared the findings with figures for the general population. At diagnosis, 4% of subjects were underweight, 57% normal, 28% overweight and 11% obese. On a GFD, 69% of underweight patients gained weight and 18% of overweight and 42% of obese lost weight; in the rest, BMI remained stable. Changes were similar in both symptom- and screen-detected patients (23). Another team compared BMI at diagnosis and after 2 years of treatment in patients with serological support for dietary compliance. Of GFD-compliant

patients, 81% had gained weight after 2 years, including 82% of initially overweight patients [29]. In a study on more than 1000 patients over three years, 22% of GFD-compliant patients gained weight, increasing their BMI by >2 pts [34]. Interestingly, when overweight or obese children adhere to a GFD, they may actually improve or normalize their BMI, whereas children of normal weight at the time of diagnosis are seemingly at risk for becoming overweight when starting a GFD [35]. Table 3 recaps the effect of GFD on weight gain or loss in adults, as reported to date.

Bariatric surgery and celiac disease

Bariatric surgery

Bariatric surgery (BS) is currently the most effective treatment for severe obesity. It has developed exponentially in industrialized countries as it enables sustained weight loss, improves comorbidities, and reduces cardiovascular and general mortality [36]. A recent large database study found that sleeve gastrectomy (SG) accounted for 63% of procedures performed, compared to 30% for Roux-en-Y gastric bypass (RYGB) and just 2% for laparoscopic adjustable gastric banding (LAGB) [37]. However, it also has side effects including nutritional deficiencies. Some of these deficiencies have demonstrated clinical impact that is sometimes severe, such as neurological complications due to vitamin B12 or B1 deficiency, iron-deficiency anemia, and bone demineralization with risk of fracture due to vitamin D and/or calcium deficiency.

There is growing consensus that BS leads to effective weight loss depending on type of surgery performed. Weight loss can reach up to 40% of initial weight and increases with malabsorptive procedures [38]. Percentage of excess weight loss varies from 47% for LAGB to more than 60% with RYGB and 70% for biliopancreatic diversion or duodenal switch [39].

Patients who undergo BS are monitored by a multidisciplinary team that is especially attentive to early and late complications. Restrictive and/or malabsorptive interventions frequently cause nutritional deficiencies. The main origins of these deficiencies are a lack of digestive assimilation and a lack of dietary intake due to drastic reduction of caloric intake, and possible intolerance to certain foods (fibers, proteins). The main nutritional deficiencies following BS concern proteins and certain functional amino acids, iron, zinc, calcium, vitamin D and other liposoluble vitamins, folate, vitamin B12, and polyunsaturated fatty acids [40].

The American Society for Metabolic and Bariatric Surgery Integrated Health has updated its 'nutritional guidelines for the surgical weight loss patient on micronutrients' [38,41]. According to these guidelines, all types of surgery should systematically require thiamin, vitamin B12, folate, iron, calcium and vitamin D supplementation. Vitamin D deficiency is reported to occur in up to 100% of post-weight-loss surgery patients and folate deficiency in up to 65%. These guidelines also state that the prevalence of micronutrient deficiencies is increasing while patient monitoring at follow-up is decreasing, thus justifying a multidisciplinary approach and life-long follow-up. In the Practical Recommendations of the *Obesity Management Task Force* of *the European Association for the Study of Obesity* for post-bariatric surgery medical management, Busetto *et al.* [42] state that long-term mineral and multivitamin supplementation should be prescribed to every bariatric patient with medication doses adapted to the procedure. Periodic laboratory surveillance for nutritional deficiencies is recommended and supplementation should be individualized accordingly in patients with demonstrated micronutrient deficiencies [42]. While nutritional deficiencies are uncommon after purely gastric restrictive procedures not altering intestinal continuity, they become very common after surgical procedures inducing malabsorption. However, the

occurrence of nutritional deficits is also influenced by factors independent of surgical technique, such as regular and nutrient-dense food intake and adherence with post-operative vitamin and mineral supplementation, which is far from guaranteed.

Celiac disease and bariatric surgery: reported outcomes and response to gluten-free diet

CD patients who fail to properly adhere to the GFD are exposed to a panel of vitamin deficiencies due to malabsorption syndrome. However, BS, and especially gastric bypass, also increases the risk of deficiencies.

The literature suggests that BS is safe and feasible in patients with concomitant autoimmune, inflammatory and intestinal pathologies including systemic lupus erythematosus and inflammatory bowel disease [10,11]. However, the role of BS in obese CD patients is less well defined. Combining a malabsorptive state such as CD with a restrictive and/or additional malabsorptive procedure may further increase the risk of post-operative complications or nutritional deficiencies.

Does the risk of malnutrition and complications secondary to vitamin deficiency compromise surgery? Should patients with CD be offered a purely restrictive bariatric procedure, as some have suggested?

The prevalence of CD in BS populations is relatively low, and few CD patients have undergone BS [28,43]. A study retrospectively reviewed 12,000 RYGB patients for either diagnosis (American Gastroenterological Association diagnostic criteria) or serum testing for CD [43]. Of these 12,000 patients, 342 had abnormal serology, only 3 patients (0.8%) were confirmed with CD diagnosed before the procedure, and only two followed a GFD. All were female, with an average age of 33 years and a mean BMI of 44.07 kg/m². Interestingly, there was no significant difference in terms of weight loss or excess weight loss between CD and

non-CD bariatric patients. No patients were anemic nor had vitamin B12 or iron deficiencies at 12-month follow-up. However, two patients had vitamin D insufficiencies that responded to daily oral supplementation [43]. In a nationwide inpatient sample analysis between 2004 and 2014, Sharma *et al*. [28] identified 126 patients with CD that had undergone bariatric surgery. BS did not increase in mortality, but CD patients with obesity and prior BS were three times more likely to have vitamin D deficiency (IRR 3.5; 95%CI 1.6–7.7; p=0.002) or post-operative strictures (IRR 3.3; 95%CI 1.5–7.5; p=0.004)[28].

The effect of GFD on weight (in patients who benefited from BS) is a hugely controversial topic. Some teams consider that it leads to weight gain in obese patients. An Italian team reported the case of a patient incidentally diagnosed with the silent form of CD 5 years after BS and who had changed his BMI from 35.2 to 38.4 after 12 months of GFD [44]. Their paper reports complete restoration of the intestinal mucosa within 12 months after starting GFD after BS (vertical banded gastroplasty) had been performed 5 years earlier [44].

On the other hand, cases where symptoms persist despite a well-followed GFD are defined as refractory sprue, which is a condition that leads to a risk of T-cell lymphoma (EATL) requiring endoscopic monitoring with duodenojejunal biopsies [25]. However, the realization of a gastric bypass would result in a more difficult endoscopic follow-up in these patients[45].

Moreover, it is difficult to differentiate the usual post-surgery digestive symptoms from the persistence of symptoms related to a refractory disease like diarrhea.

As recommended by The *American College of Gastroenterology* [14] and the *European Society for the Study of Coeliac Disease* [2] recommend testing for CD in certain settings, especially before BS:

– Patients with symptoms, signs or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain and bloating, or elevated serum aminotransferase levels when no other etiology is found

– Patients with a first-degree relative who has a confirmed diagnosis of CD should be tested

– Patients with type 1 diabetes mellitus should be screened regularly for CD, notably if there are any digestive symptoms, or signs or laboratory evidence suggestive of CD.

Diarrhea is classically predominant in CD, but CD should be part of the differential diagnosis in cases of post-BS diarrhea so as not to misread a diagnosis.

Is there increased incidence of CD after bariatric surgery?

A recent study reported the first case of CD diagnosed in the follow-up of duodenal switch in a woman with severe diarrhea shortly after surgery. Final diagnosis was later made based on anti-transglutaminase antibodies. The authors suggest that CD should be ruled out in patients with typical or atypical symptoms after BS regardless of the latency of onset [46]. Another asymptomatic case reported after vertical banded gastroplasty was due to familial history [44]. The mechanism by which BS can unmask latent CD is still unknown. It is thought that transient bowel hyperpermeability following such procedures could lead to an antigenic overload, but altered nutrient absorption, motility, perioperative stress and hormone variations could also be implicated [2]. In susceptible patients, the heightened gluten challenge might then sufficiently stimulate the immune response to result in clinically apparent enteropathy [47].

Discussion

CD has traditionally been associated with malabsorption and insufficient body weight, but approximately 10% of CD patients are obese at diagnosis. They could, therefore, be potential

candidates for BS. With the current obesity epidemic and the increasing incidence of CD, this situation is set to become more frequent in the near future, which raises issues concerning the specific diagnosis, choice of bariatric procedure, and specific follow-up or complications. If a malabsorptive procedure is decided, it may add to the complexity of diagnosing CD complications. Furthermore, starting a GFD after BS could increase the risk of weight regain, and so weight maintenance counselling should be an integral part of celiac dietary education[34]. In addition, many processed gluten-free products have an increased glycemic index with increased fat and lower proteins than gluten-containing meals, which raises the challenge of achieving sufficient protein intake post-operatively [2,38].

Several teams have suggested a preoperative work-up of specific CD tests (anti-endomysial and anti-transglutaminase antibodies and total IgA) before bariatric procedures. After malabsorptive surgery, diagnosis of CD by duodenal biopsies during endoscopy is technically more difficult in non-expert centers due to the excluded jejunum. In these cases, testing exclusively by serology remains an option. Indeed, a negative CD-specific serology does not completely rule out a diagnosis of CD, though it does make it much less likely.

The standard treatment of CD implementing a GFD is also successful in BS patients. However, apart from a few case reports, little is known about onset, course, diagnosis and management of CD following BS, particularly after sleeve gastrectomy and RYGB.

Should this type of surgery be indicated in patients with CD, including gastric bypass?

Should patients be screened pre-operatively in order to not miss the diagnosis and avoid the increased risk of malabsorption deficiencies? Figure 1 recaps the clinical manifestations of CD and the possible impact of BS on this protein-losing enteropathy.

This was argued in a recent study that reported 5 cases of patients diagnosed preoperatively. Four of them were asymptomatic and one had chronic diarrhea and anemia. Three of them

underwent sleeve gastrectomy. The authors suggest that, given the increasing number of asymptomatic obese patients with CD, all patients should be screened preoperatively to adapt the surgical strategy accordingly [48]. The authoritative international societies have not yet defined a specific surgical strategy according to CD screening results.

To sum up, the literature and the experience of leading groups converge to show that BS is possible and clearly an option in severe obese patients with CD as long as they are compliant with the GFD and do not have preoperative vitamin deficiencies. However, multidisciplinary teams should carry out strengthened monitoring of vitamin status and protein intake and better frame the management of weight loss.

Based on the current state of the art, systematic preoperative screening for CD in bariatric patients cannot be recommended as it carries a cost and CD in BS is still rare. Nevertheless, it should be part of the conversation with genetically-predisposed patients such as type 1 diabetics or patients with a family history of CD. More extensive studies in large populations with long-term follow-up are now needed to definitively answer these questions.

Conclusion

Currently, almost 10% of celiac patients are obese at diagnosis, and could therefore be potential candidates for BS depending on their BMI and comorbidities. In addition, in the case of latent CD, symptoms may be precipitated by gastrointestinal aggression such as BS. The issues of whether potential bariatric patients should systematically be screened for CD before surgery and whether the diagnosis of CD would influence the type of procedure merit further evaluation.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Figure legends

Figure 1. Clinical manifestations of celiac disease (gastrointestinal in green) and possible impact of bariatric surgery

520

Table 1: Frequency and consequences of nutrient deficiencies in celiac disease

Absorption site	Nutrient	Frequency of nutrient deficiencies in symptomatic forms	Main clinical signs of nutrient deficiency reported
Duodenum-jejunum	Proteins Carbohydrates Lipids	60–100%	Weight loss, amyotrophy, hypoalbuminemia, undernutrition
	Iron	40–60%	Microcytic anemia, hair loss
	Calcium	25–45%	Osteopenia, tetany, secondary hyperparathyroidism
	Magnesium	15%	Muscular cramps, tetany
	Vitamin A	15%	Night vision disorders, infection
	Vitamin B1	-	Peripheral neuropathy, Wernicke encephalopathy
	Vitamin B6	-	Normocytic anemia
	Vitamin B9	10–90%	Macrocytic anemia
	Vitamin D	10–60%	Osteopenia, tetany, secondary hyperparathyroidism, bone loss, osteomalacia
	Vitamin K	30%	Bruising, coagulopathy
	Zinc	30–50%	Anorexia, hypoguesia, delayed growth, impaired wound healing
Ileum	Vitamin B12	15–40%	Macrocytic anemia, peripheral neuropathy

Table 2. Prevalence of underweight, normal weight, overweight and obesity in CD as assessed with BMI

Study	Number of patients	Underweight	Normal	Overweight	Obese
Am J Gastroenterol 2006 [38]	371	5%	57%	39%	13%
Indian J gastroenterol 2016 [30]	210	36%	54.8%	6.2%	2.9%
J Clin Gastroenterol 2010 [31]	369	17.3%	60.7%	15.2%	6.8%
Eur J Intern Med 2012 [32]	698	4%	57%	28%	11%
J Gastrointestin Liver Dis 2012 [33]	187	3%	53%	31%	13%

Table 3. **Changes in weight category before and after initiation of a gluten-free diet (reported as % of total cohort).**

Study	n	Duration of GFD (months)	UW before GFD	NW before GFD	OW before GFD	Obese before GFD
Barone et al. [49]	39	24.3	Gained weight: 50% Lost weight: 0%	Gained weight: 0% Lost weight: 0%	Gained weight: 0% Lost weight: 11%	Gained weight: 0% Lost weight: 0%
Tortora et al. [50]	98	12	Gained weight: 60% Lost weight: 0%	Gained weight: 12% Lost weight: 0%	Gained weight: 0% Lost weight: 0%	Gained weight: 0% Lost weight: 0%
Kabbani et al. [34]	679	39.5	N=46 Gained weight*: 52% Lost weight**: 2%	N=416 Gained weight*: 21% Lost weight**: 5%	N=139 Gained weight*: 22% Lost weight**: 18%	N= 8 Gained weight*: 22% Lost weight**: 23%
Ukkola et al. [32]	698	12	N=28 Gained weight: 69% Lost weight: 0%	N=398 Gained weight: 38% Lost weight: 10%	N=195 Gained weight: 22% Lost weight: 18%	N=77 Gained weight: 16% Lost weight: 42%
Cheng et al. [31]	369	33.6	N=64 Gained weight: 66% Lost weight: 27%	N=224 Gained weight: 58% Lost weight: 37%	N=56 Gained weight: 40% Lost weight: 54%	N=25 Gained weight: 18% Lost weight: 47%
Dickey et al. [29]	188	24	N=27 Gained weight: 93% Lost weight: NA	N=94 Gained weight: 77% Lost weight: NA	N=67 Gained weight: 82% Lost weight: NA	NA

UW = Underweight (BMI < 18.5 kg/m²)

NW = Normal weight (BMI 18.6–24.9 kg/m²)

OW = Overweight (BMI 25–29.9 kg/m²)

NA = not available

* defined as a BMI increase of 2 points or more; ** defined as a BMI of 2 points or more