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ORIGINAL ARTICLE

# Association of Celiac Disease and Inflammatory Bowel Disease: A Systematic Review and Metaanalysist

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## ABSTRACT

**Introduction:** Immune-mediated diseases such as celiac disease and inflammatory bowel disease (IBD) are still unable to be fully recognized, although the etiologic factors are multifactorial.

**Material and Method:** This meta-analysis taken literature based on full-text English journals published in the last 20-years ago (range 2002-2022). This article aims to discuss one-way or two-way connection between IBD inflammatory bowel disease and celiac disease CeD. The databases that we use in writing this article are Sage Pub, Pubmed and Google Schoolar.

**Result:** Several researches have presented that with IBD in patients, CeD is more common than the general population, although these results are inconsistent.

**Conclusion:** One of the risk factors associated with the association between IBD and CeD is genetic susceptibility, which can be clearly identified from a previous family history of the disease.

**Keyword:** Celiac Disease; Crohn's Disease; IBD (Inflammatory Bowel Disease); Ulcerative Colitis

## INTRODUCTION

Irritable bowel syndrome (IBS) and celiac disease (CD) are immune-mediated conditions are still not fully understood, while the etiologic causes are multifaceted. This is considered to involve a complicated interaction between hereditary and factors of environment. Innate and adaptive immune systems' dysregulation, which is then followed by the activation of inflammatory cascades, can cause to chronic inflammation in the intestine and the manifestation of numerous disorders. The medical symptoms of CeD and inflammatory bowl disease can be comparable.[1]

Two illnesses (Crohn's disease and ulcerative colitis) fall under the umbrella of inflammatory bowel disease (IBD) and are both characterised by persistent inflammation of the GI tract.[2] People in industrialised countries have the greatest rates of IBD, while people in developing countries have the lowest rates. IBD is more common among people who live in colder climates or in cities than in people who live in warmer climates or in rural areas.[3]

North American Crohn disease prevalence was three hundred and ninteen per one lac people, while European prevalence was 322 per 100,000 people, according to a review of IBD. There were 249 cases per 100,000 people in North America and 505 in Europe for ulcerative colitis. [4] Pathogens, such as viruses and bacteria, are normally attacked by a well-functioning immune system. Inflammation in the digestive tract can be caused by abnormalities in the immune system, such as by environmental exposures. [2,5] Gluten causes an inflammatory reaction in the body (a proteins group discovered in wheat and similar grains). The symptoms of celiac disease can be reduced by gluten-free diet , but it can take months before the full benefits of the diet are felt. [6]

There is still substantial disagreement over the connection between celiac disease and inflammatory bowel disease. The results of this meta-analysis and systematic review piqued our interest, so we decided to investigate the possibility that CeD is linked to IBD.

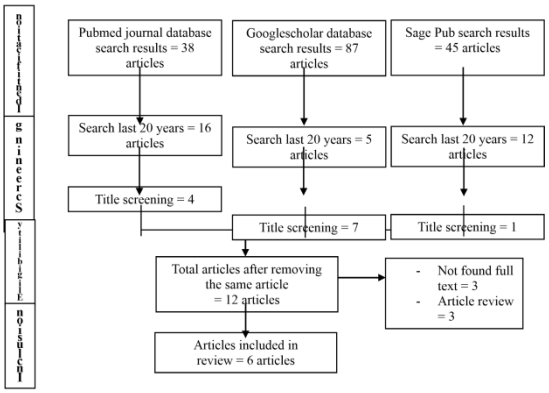


Figure 1: Article search flowchart

## MATERUAL AND METHODS

This meta-analysis taken literature based on full-text English journals published in the last 20-years ago (range 2002-2022). This article aims to discuss one-way or two-way relationship between CeD and IBD. The databases that we use in writing this article are Sage Pub, Pubmed and Google Schoolar. PICO (Patient, Index, Comparative, and Objective) analysis used in this research involved inflammatory bowel disease infected patients, the index examined was the patient's with celiac disease, and not comparisons. The desired result is one-way or two-way relationship between IBD and CeD. The studies included in the analysis were clinical trials and randomized clinical trials.

For systematic reviews and meta-analyses (PRISMA) preferred reporting items were used in this investigation, which began with the researchers manually entering keywords into each database to begin the search. IBD and celiac disease were included in the search terms. (("inflammatory bowel diseases," [MeSH Terms] OR ("inflammatory," [All Fields] AND "bowel," [All Fields] AND "diseases,"[All Fields]) OR "inflammatory bowel diseases,"

[All Fields] OR ("inflammatory," [All Fields] AND "bowel," [All Fields] AND "disease"[All Fields]) OR "inflammatory bowel disease," Researchers got six articles which will then be included in the discussion (Table 1).

## RESULT

Figure 1 and Table 1 indicate the correlation between leptin levels and breast cancer risk, respectively. In a group of patients with CeD, 3.2% of the participants had IBD. Serum tests for celiac disease were positive in all of the patients. According to Marsh's classification, histology results: 1/8 M1, 2/8 M2, 3/8 M3a, 2/8 M3b. According to the Montreal classification, below is the breakdown: 4/6 individuals are B1with Crohn's disease, 2/6 indiviuals are B2 with Crohn's disease, and 2/2 patients are S2 with ulcerative colitis. Ostepenia and osteoporosis were found in 4/8 and 2/8 of the patients, respectively. [7]

Table 1: The litelature include in this study

| Author | Origin | Method | Sample Size and Population | Period | Result | Outcome |
|---|---|---|---|---|---|---|
| Bengi, 2019[8] | Turkish | Retrospective study | 959 patients (396 ulcerative colitis (UC), 363 Crohn's disease (CrD) | January 2009 and July 2016 | CeD was investigated in 79 (%10.4) IBD patients, and in 5.06% (n = 4) of them, we diagnosed CD | Did not an increased prevalance of CeD in IBD patients. |
| Yang, 2005[9] | USA | Retrospective study | 455 patients with celiac disease, IBD was identified in 10 (5 UC and 5 had CD) | Between 1981 and 2002 | IBD was identified in 10/455 patient CeD (5 had ulcerative colitis and 5 had Crohn's disease). This represented an age- and sex-adjusted prevalence rate ratio for UC of 3.56 (95% confidence interval, 1.48-8.56) and for CD of 8.49 (95% CI, 3.53-20.42). | IBD was significantly more common in CeD patients than in the general population with prevalence of IBD to be 2,20% in CeD patients |
| Kocsis, 2015[7] | Hungary | Cohort prospective study | 245 patients with IBD | November of 1997 till November of 2013 | Montreal classification: 4/6 Crohn's disease patients are B1, 2/6 Crohn's disease patients are B2, 2/2 ulcerative colitis patients are S2. Normal bone mineral density was detected in 2/8 case, osteopenia in 4/8 and osteoporosis in 2/8 patients. | IBD was significantly more common (3.2%) in CeD patients than in the general population |
| Author | Origin | Method | Sample Size and Population | Period | Result | Outcome |
| Leeds, 2007[10] | UK | Cross sectional | The study included 305 patients with coeliac disease, 354 with IBD and 601 healthy controls. | No date | The prevalence of IBD in coeliac disease was increased 10-fold compared with that in controls (OR 9.98, 95% CI 2.8-45.9, p=0.0006), while the prevalence of CeD in IBD was comparable with that in controls (OR 1.02, 95% CI, 0.24-4.29, p=1.0). | IBD prevalence of 3,30 % among 305 CeD patients, however the prevalence of CeD among IBD patients was comparable with that of the controls |
| Casella, 2010[11] | Italy | Cross sectional | 1711 consecutive outpatients with inflammatory bowel disease | Between January 2002 and December 2004 | 860 (50.2%) had CD, 791 (46.2%) had UC (371 females, mean age 40, range 18-80), and 60 (3.5%) had indeterminate colitis | 9/ 1711 patients (0.5%) had serological and histological findings compatible with CeD; six of them had UC and three had CD. |
| Chung, 2018[12] | USA | Retrospective matched case-control study | 342 inflammatory bowel disease patients | Between 1997 and 2016 | Patients with IBD + CeD had higher rates of primary sclerosing cholangitis [19.3% vs 5.7%; OR, 4.4; 95% CI, 2.1–9.4; p <0.001], extensive ulcerative colitis [78.1% vs 59.0%; OR, 2.8; 95% CI, 1.5–5.5; p =0.002], and family history of CeD [10.5% vs 3.5%; OR 3.2; 95% CI, 1.3–8.2; p =0.01], compared with patients without concomitant celiac disease. | IBD patients with concomitant CeD have unique phenotypic features compared with non-celiac IBD, with higher risks for colitis-related hospitalisations, extensive colitis, and primary sclerosing cholangitis. |

Bengi et al. (2019) examined 759 patients with IBD in their study. In 79 (10.1 percent) patients with inflammatory bowel illness, CD was evaluated based on symptoms. The celiac disease prevalence was not discovered to be higher in Turkish IBD patients in this investigation. [8] Cerebrovascular disease (CeD) was shown to be lower in IBD patients than in the general population, according to Casella and colleagues. [11]

Table 2: Comparison of proportion, OR, and significance between the incidence of CeD and IBS

| Author | Result | OR | p |
|---|---|---|---|
| Bengi, 2019[8] | CeD in 10.4% IBD patients | - | >0,05 |
| Yang, 2005[9] | IBD in 2,5% CeD patient | 3,35 | <0,05 |
| Kocsis, 2015[7] | IBD in 3.2% CeD patients | - | <0,05 |
| Leeds, 2007[10] | IBD in 3.3% CeD patients | 10 | <0,05 |
| Casella, 2010[11] | IBD in 0,5% CeD patients | - | <0,05 |

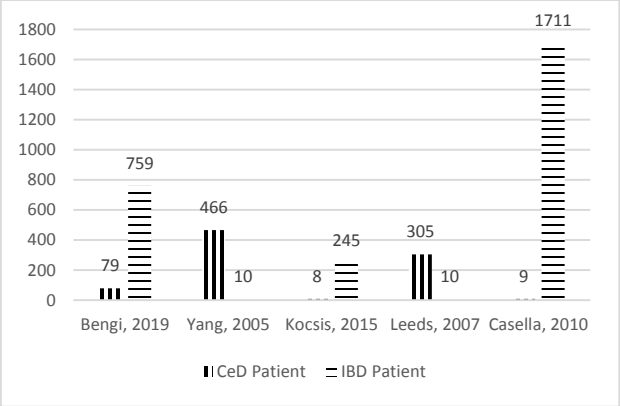


Figure 2: Comparison of IBD and CeD cases per study

Patients with celiac disease are found in the database between 1981 and 2002 were evaluated in a separate investigation. Five of the 455 celiac disease patients evaluated had ulcerative colitis, and five had Crohn's disease. Crohn's disease has a prevalence rate ratio of 8.49 and ulcerative colitis has a rate ratio of 3.56 (with a 95% confidence interval of 1.48-8.56). (95 percent confidence interval, 3.53-20.42). 9

There were 305 celiac disease sufferers, 354 people with IBD, and 601 healthy participants in the Leeds trial. Crohn's disease, indeterminate colitis and Ulcerative colitis (UC) were all found in the IBD group, with 154, 173, and 18 cases each, respectively. Villous atrophy was detected in three of the 47 patients who tested positive for antibodies following a biopsy. Endomysial antibodies (EMA) were found in just two of the three individuals, although all three had positive anti-tissue transglutaminase antibodies. Ten people with celiac disease had IBD (5 UC and 5 lymphocytic colitis). People with CeD and irritable bowel syndrome (IBD) were included in the control group (1 CD and 1 UC). In a statistically meaningful study, only antibody positivity was found (p 0.0001). [10]

## DISCUSSION

Some genetic, immunological, and environmental variables are shared by Celiac disease, Crohn's disease, and ulcerative colitis in their aetiology. Patients with celiac disease are more likely than the general population to develop inflammatory bowel disease, according to several studies. 2 CeD has been linked to a number of autoimmune disorders. [13]

It's still not clear if gluten consumption is a mediator in the connection between celiac disease and autoimmune illnesses or if the two can co-occur owing to other factors, such as damage to the intestinal barrier function or a shared genetic background. 14 CeD is more prevalent among IBD patients than the general population, according to several studies. The frequency of CeD (1:100) in the general population was found to be significantly higher than the prevalence of IBD (CD 0.1–16:104, UC 0.5–25:104) in the general population. [13]

However, in the Bengi research, there was no higher risk of acquiring celiac disease during follow-up in individuals with IBD compared to those without. 8 Another study by Yang et al9, which included the biggest number of patients, found that 27 of 455 individuals with CD had IBD, a prevalence of 5.9 percent (5 UC, 5 CrD, 17 microscopic colitis). Patients with IBD had a greater mortality rate than those with colon cancer or lymphoma, according to a large Swedish mortality research (70.9, 95 percent CI, 36.6-123.9). 15

Not only did their research indicate a link between IBD and celiac disease, however it also revealed that the clinical picture of thepatient was more significant and that even a colectomy was required in cases where the two conditions existed in conjunction. 9 The relationship between CD and IBD has yet to be fully explained in terms of pathophysiology. However, while the CD and HLA-DQ2 and HLA-DQ8 alleles have a strong link, IBD does not. 16,17 For example, PTPN2, TAGAP, and PUS10 have been shown to be genetically linked to both disorders by other investigations. [18]

There are two alleles of HLA-DQ2 or HLA-DQ8 in CDs produced in CeD: It is necessary, then, to look for other possible hereditary variables that contribute to the development of both disorders. First-degree relatives of celiac patients are more likely to develop UC, according to Cottone and Capello. [19]

Lopez-Vasquez et al[20] on the other hand have presented that the MICA gene is overexpressed from the gastrointestinal epithelium in CDs with IBD-transformative alterations. New research shows that the MYO IXB gene, previously linked to CD, is also altered in people with IBD. [21]

The myosin superfamily of proteins encoded by these genes helps maintain cell polarity, tight junctions and cellular skeleton's integrity. Intestinal mucosal barrier abnormalities, such as increase in the permeability at tight junctions, have been reported in celiac disease and inflammatory bowl disease as a result of mutations in this gene. Antigen presentation, autoantibody production, and bacterial translocation are all influenced by increased intestinal permeability in IBD pathogenesis. [22–24]

Some researchers believe that the Th1-mediated immune responses that lead to CD development may be caused by increased intestinal permeability in response to CrD. This may be the case because many bacteria mimic the gliadin sequences fifty seven to sixty eight and sixty two to seventy five. These bacteria then initiate the cytokine cascade (IL–15, IL–2, TNF– and IFN–). Observations of substantial levels of seroreactivity against Saccharomyces cerevisiae on both CrD and CD recently supported this notion. CD is caused by more than just the DQ2 and DQ8 alleles and enhanced gliadin presentation.25

This may help us understand why IBD is more common in people with CD but not in people with CD who have IBD. Antibody production and the development of autoimmune disorders may also result from the usage of biologic medicines. 26 According to Leeds et al, patients using infliximab had higher antibody levels than those not taking the drug, however no one in our study who was receiving anti-TNF was identified to have CD-IBD. 10 Patients with IBD and CeD were reported to be more likely to develop primary sclerosis cholangitis, severe ulcerative colitis and a family history of celiac disease. 12

## CONCLUSION

One of the risk factors associated with the association between IBD and CeD is genetic susceptibility, which can be clearly identified from a previous family history of the disease.

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