

Effects of milk and fruit consumption on Crohn's disease: a systematic review.

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Abstract: **Introduction:** There are currently many studies that discuss possible relationships among the diet, the etiology of Crohn's disease and the possible improvement or worsening of its symptoms. Most of them are based on surveys that describe the dietary patterns adopted by these patients. **Objectives:** The present review will address quantitative studies comparing the consumption of certain foods (milk and fruits) by subjects diagnosed with Crohn's disease and healthy subjects. On the other hand, it will also address studies of patients who exclude these foods from their diets because they associate them with worsening symptoms of the disease. **Methodology:** This systematic review was elaborated following the PRISMA guidelines. Six studies that analyze the selected subject matter were selected. **Results:** The two foods selected for study are very often present in articles that relate diet and Crohn's disease, and both are considered by patients to be influential in the evolution of their pathology. **Conclusions:** Each study presents different results; thus, to date, there is no consensus on the best diet to follow in inflammatory bowel disease. Of course, it has not been sufficiently demonstrated that the consumption of certain foods causes or worsens the development of this disease. Therefore, further investigations are necessary.

Keywords: Crohn's disease; Milk; Fruit.

1. Introduction

Crohn's disease is a type of inflammatory bowel disease (IBD) that can affect any part of the digestive tract from the mouth to the anus [1] but most commonly affecting the last segment of the small intestine, the ileum.

The incidence of Crohn's disease has increased remarkably over the last 30 years in all developed countries, reaching a plateau in the seventies and stabilizing at between 10 and 15 cases / 100,000 / year [2]. Its presence is greater in northern Europe, Canada and the USA [3] than in southern Europe, Asia and Africa. In Spain, the incidence is approximately 5 to 10 cases per 100,000 inhabitants [4,5].

Crohn's disease usually affects the youth population, with a peak between 15 and 30 years, but new cases are observed at any age, even in children. It occurs in both men and women [6].

The causal mechanism in IBD is not entirely clear. There is no doubt that there is a genetic predisposition to the disease and that certain bacterial pathogens, environmental factors, dietary components, tobacco, or certain drugs are necessary to trigger and maintain the disease. This interaction is thought to trigger an exaggerated response of the intestinal mucosa to different antigens that favor the development of the disease [7].

There is no clear preventive strategy for the disease, but it is emphasized that breastfeeding [8,9], and eating a healthy diet [10] with adequate fiber intake [11] can act as protective factors against the development of inflammatory bowel disease.

2. Materials and Methods

PubMed, Scopus and Web of Science were searched using the broad key words "Crohn's disease,"

“milk” and “fruit”. The results were limited to human studies and those available in English. We found a total of 57 articles with these characteristics; 20 duplicates were removed. A total of 37 articles were reviewed and found to be relevant. Only 30 studies were found in full text, and 24 were excluded for different reasons. Finally, 6 studies presenting relevant and interpretable dietary data regarding fruit and milk intake were selected. (Figure 1)

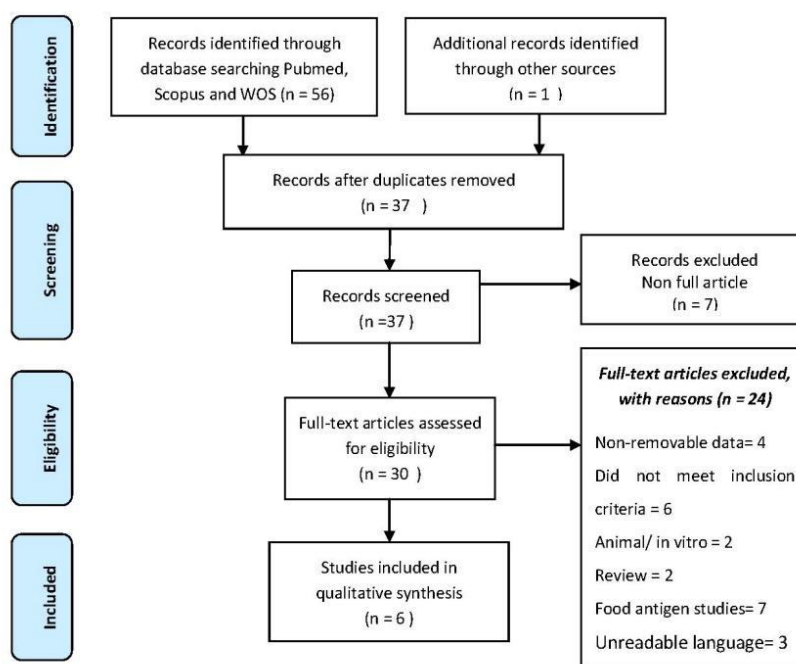


Figure 1. PRISMA flow diagram

3. Results and discussion

3.1. Dietary tolerance studies

In one study performed on a sample of New Zealand Caucasian patients with CD [12] (only subjects with self-reported European ancestry were included), a dietary questionnaire was used for evaluation. The dietary questionnaires were composed of 15 food and beverages categories, each with 6-40 specific food options or 257 total individual food items.

The responses from a sample of 30 patients with CD were considered to assess overall fruit consumption. A total of 5% of these patients reported that fruit consumption improved the symptoms of their disease; however, 17.8% reported that consuming fruit worsened their symptoms. Thus, it is clear that a greater number of people identified the fruit as detrimental in the evolution of their disease. Specifically, banana was reported to have the most beneficial effects, whereas grapefruit was reported to have the worst effects.

In general, this study discourages fruit consumption based on the responses of the subjects surveyed. From our point of view, this conclusion would not be valid because the size of the sample that responded to the fruit item is too small ($n = 30$) to produce significant data and to be able to extrapolate to the population.

Regarding the consumption of dairy products, just under 30% of subjects reported that they had been advised not to eat dairy foods, so they avoided them on this basis. These subjects were excluded from analysis. A small sample of responses was taken into account ($n = 11$). Of these patients, an average of 20.5% stated that the consumption of these products worsened their symptoms, whereas 5.6% reported

otherwise. Goat's milk was substantially better tolerated than cow's milk, yet both were identified by a higher percentage of subjects as more harmful than beneficial.

In conclusion, dairy products in general are considered detrimental in the evolution of the symptomatology. In our opinion, the data are inconclusive for the same reason: the sample is too small.

In the article by TJ Green *et al.*, patients' diets and preferences in a pediatric population with inflammatory bowel disease [13] were evaluated. Of the 153 questionnaires mailed, 125 were returned. Sixty-one percent of respondents had CD (n = 76), and ninety percent of CD respondents indicated that they had made at least one dietary modification since diagnosis. Specifically, 11.8% of the respondents had restricted their consumption of fruit juice because they noticed worsening symptoms of their disease. Considering that we started from a sample of pediatric patients in whom the incidence of Crohn's disease differs from that of adults, we can be sure that the restriction of fruit juice intake by nine respondents is insufficient to conclude that this food has a detrimental effect on the symptomatology. With a limited initial sample (n = 76), it is risky to draw conclusions and extrapolate them to the rest of the pediatric population.

If we look at dietary restrictions with respect to milk consumption, in this study, 30.3% of respondents said that they had stopped consuming this product because it worsened their symptoms. Responses from 23 children could be considered more significant than the previous results, but failing to compare their consumption with that of healthy children, it is difficult to conclude that lower milk consumption has beneficial effects. Compared with the restriction that make of this product children with ulcerative colitis, there is no statistically significant difference between both.

Examining the article by Aaron B. Cohen *et al* [14], we observe that the patients interviewed reported significantly more avoidance of milk than consumption. Of an initial sample of 1121 patients with CD, 105 patients responded that they avoided milk consumption because they considered it detrimental, whereas 6 patients classified it as beneficial. On this occasion, we have more relevant data (P <0.05). With respect to the sample of respondents, 9.36% of the patients responded negatively to milk, which is not a conclusive percentage; therefore, investigations in this area should continue. However, only 0.53% of respondents reported that milk consumption was beneficial. In this case, we could say that the consumption of milk does not produce beneficial effects, but we cannot deduce that it is harmful. Indeed, this food may simply not produce any changes in the evolution of the patient's illness. Regarding fruit consumption, 136 patients reported feeling worse with fruit consumption, whereas 50 reported benefits. The conclusion we can draw is similar to that for milk consumption.

Lower consumption of fruits (57%) and milk (22%) is observed among patients with active Crohn's disease compared to patients with inactive disease. Given this high percentage, we could end by saying that fruit considerably worsens symptoms during active periods of disease. This conclusion is supported by the OR of an ostomy among patients with active Crohn's disease, where 81% confirmed that the consumption of this food worsened their condition.

Reviewed studies are summarized in table 1.

Table 1. Dietary tolerance studies summary.

Study (year)	Subject	Design	Method	Duration	Measurable outcomes
Christopher M. Triggs, et al. (2010) [12]	4046 New Zealand Caucasian patients with CD	??	Dietary questionnaires	??	<p>A summary of the statistics associated with food tolerance data. Fruits (N= 30) Beneficial = 5.0%, Detrimental: 17.8%, No difference = 52.4%, No response = 24.8%</p> <p>Bananas stand out as having the most marked beneficial effects and, indeed, are one of the few foods that are more often associated with a reduction in symptoms (20%) than with symptom exacerbation (approximately 10% of reports).</p> <p>On the extreme right-hand side, grapefruit stands out as profoundly negative, with approximately 40% of subjects claiming exacerbation of symptoms and only approximately 3% of subjects being able to tolerate it.</p>
TJ Green, et al. (1998) [13]	76 of respondents with CD.	??	self-administered questionnaire	??	<p>Percentage of respondents with Crohn's disease restricting their consumption of a particular food or food group since diagnosis</p> <p>Milk 30.3 % (n=23) Fruit juice 11.8% (n=9)</p>
Aaron B. Cohen, et al. (2013)[14]	1,121 respondents with CD, 405 respondents with CD-related ostomy.	cohort study of patients with IBD	semiquantitative food frequency questionnaire	June 2011-October 2011	<p>Frequency of patient-reported foods that improve or worsen symptoms</p> <p>N = 6 Patients with CD reported that milk made them feel better. N = 105 Patients with CD reported that milk made them feel worse. P< 0.05 (0.00039).</p> <p>N = 50 Patients with CD reported that fruit made them feel better. N = 136 Patients with CD reported that fruit made them feel worse. P< 0.05.</p> <p>Patients with active CD reported consuming significantly less fruit (OR 0.43, 95% CI 0.33–0.57) and milk (OR 0.78, 95% CI 0.62–0.97) than those without active disease.</p> <p>Compared to CD patients, CD ostomy patients reported significantly greater consumption of milk (OR 1.84, 95 %CI 1.35–2.52).</p> <p>CD ostomy patients with active disease reported consuming significantly less fruit (OR 0.19, 95 % CI 0.05–0.64) than those without active disease.</p> <p>Patients identified foods that they believe worsen symptoms and restricted their diet.</p>

3.2. Consumption studies

In the study by Ibrahim Abubakar *et al* [15], the following results are presented. The consumption of pasteurized milk reduces the risk of Crohn's disease by 18%. According to their data, there is greater consumption of milk in the control group (26.01 liters) than in the patient group (22.77 liters / month). We must emphasize that these numbers correspond to 218 respondents with CD and 812 controls. We argue that given the greater number of individuals in the control group, it is very probable that this group would have higher consumption of this product. Since more people are surveyed, average consumption may rise. This study further hypothesizes that milk could be contaminated with *Mycobacterium avium paratuberculosis* (MAP), a microorganism that is present in the feces of cattle. Studies have demonstrated the presence of this microorganism in pasteurized milk. The conclusion we reached can be summarized as follows: more milk consumption could lead to contamination with disease-causing mycobacteria; however, the case group reported less milk consumption than the healthy controls. Thus, we can deduce that the initial hypothesis is not supported, since greater consumption of milk should occur among patients with CD and not vice versa.

It would be very risky to conclude that the higher the consumption of pasteurized milk, the lower the risk of Crohn's disease, and this connection should be investigated further. We cannot assume that a statistically significant $p = 0.01$ implies that 100% of a population should ingest more milk to prevent this disease, as this study does not have a homogeneous sample as far as the number of participants is concerned. Would they have obtained the same results if as many patients had been included as health controls?

With regard to fruit consumption, this study suggests that its consumption decreases the risk of developing Crohn's disease by 22%. Mean fruit consumption was 6.63 kg / month in the case group and 8.12 kg / month in the control group. They suggest, therefore, that the greater consumption of fruit by the control group had a protective effect, since these individuals had not developed the disease. We reach the same conclusion as in the previous case, since the samples are not the same size, and finding these results seems likely. In our opinion, the ingested food averages differed because of the question, and it would be interesting to expand the number of patients included.

According to a study by S Reif *et al* [16] based on the distribution of the combined population of cases plus controls, they establish three levels of intake (low (<165 g/day), median (165-306 g/day), and high (>306 g/day). The median consumption of fruit by patients with Crohn's disease was 35% lower than that in the control group, but since the confidence interval included the figure 1, the difference was not statistically significant. Thus, no conclusive results were obtained regarding median fruit consumption. If we look at the high fruit consumption data, patients with CD consumed 58% less fruit than the control group, but the results were not statistically significant for the same reason as in the previous case. This study found markedly lower consumption of fruit by patients with Crohn's disease, which could suggest that low consumption of fruit increases the risk of Crohn's disease, since the healthy controls consumed considerably more fruit. However, we cannot make such claims because the differences were not statistically significant.

Finally, we examine the study by Giovanni Maconi *et al* [17]. This case-control study reports data on the high consumption of milk and fruit. If we look at the data on high milk consumption, we can see that more patients with Crohn's disease consume this product (specifically, patients, 64% vs. controls, 49.38%), but if we look at the confidence interval of the OR, the difference is not statistically significant. Regarding the high consumption of fruit, we find that both study groups report similar consumption from which we could conclude that fruit consumption does not affect positively or negatively the risk of developing Crohn's disease. It is true that the confidence interval of the OR shows that the difference is not statistically significant, but we also have to consider that the samples of subjects is quite small. Thus, we should consider it normal to find inconclusive data.

Reviewed studies are summarized in table 2.

Table 2. Daily consumption studies summary.

Study (year)	Subject	Design	Method	Duration	Measurable outcomes
Ibrahim Abubakar, et al. (2007) [15]	218 patients diagnosed with Crohn's disease. 812 controls	Case-Control Study	Validated self-administered questionnaire	December 1998 - December 2003.	<p>Consumption of pasteurized milk (per kg/month: odds ratio (OR) =0.82, 95% confidence interval (CI): 0.69, 0.97; p =0.01)) was associated with a reduced risk of Crohn's.</p> <p>The mean pasteurized milk intake among patients with CD was 22.77 liters (SD, 16.59) compared with 26.01 liters (SD, 15.81) among controls.</p> <p>Fruit consumption (per kg per month, OR =0.78, 95% CI: 0.67, 0.92; p =0.002) was associated with a reduced risk of CD.</p> <p>The mean fruit intake among patients with CD was 6.63 kg (SD, 5.99) compared with 8.12 kg (SD, 6.54) among controls.</p>
S Reif et al. (1997)[16]	Newly diagnosed patients with CD (n=33) "Healthy" population controls (n=76) Out- patient clinic control (n=68)	Case-Control Study	Personal telephone interview	1992-1993	<p>Median level of fruit consumption (g/day): OR=0.65, 95% confidence interval (CI): 0.13-1.38) patients with CD vs. controls</p> <p>High consumption of fruit (g/day): OR=0.42, 95% confidence interval (CI): 0.13-1.38) patients with CD vs. controls</p>
Giovanni Maconi, et al. (2010) [17]	25 patients with CD 160 sex- and age-matched healthy controls	Case-Control Study	Personal interviews (30 min)	June-September 2003 September 2007-June 2008	<p>Association between pre-illness intake of foods and beverages and the risk of Crohn's disease in patients who did not modify their diets before diagnosis</p> <p>High consumption of milk in patients with CD (64%) vs. controls (49,38%): OR=1.55, 95% confidence interval (CI): 0.57-4.19</p> <p>High consumption of fruit in patients with CD (32%) vs. controls (31.88%): OR=0.76, 95% confidence interval (CI): 0.26-2.21</p>

3.3. Discussion of systematic reviews

There are several systematic reviews that address the issue of Crohn's disease and its relationship to diet. In the systematic review by Rajendran N *et al* [18], they conclude that "IBD has a multifactorial etiology but food sensitivity / intolerance appears to play a role, and the culpable foods vary on an individual basis. Progress has been made by looking at factors such as IgG4 responses to food antigens."

On the other hand, a series of studies argues that allergy to milk proteins remains a possible cause of dairy sensitivity or milk intolerance in a small percentage of IBD patients. Glassman *et al* [19] note that increased prevalence of cow's milk sensitivity during infancy among children and adolescents with IBD suggests that antigenic stimuli at an early age play a role in the development of IBD [20].

Other reviews refer to evidence of intestinal malabsorption of lactose [21] and fructose [22] among the Black South African population and the corresponding lower risk of Crohn's disease compared to the white South African population. This fact could be explained by lower exposure to these carbohydrates in their traditional diet since childhood and to a high consumption of fiber. However, despite adopting the dietary habits of the white population, Black South Africans have maintained a lower incidence of IBD [23].

In the article by Barrett JS, *et al* [24], the following results are obtained: "Fructose malabsorption was more frequent in Crohn's disease (61%) than other groups (33-44%, $P < 0.05$). Lactose malabsorption was most common in Crohn's disease (42%) and ulcerative colitis (40%) and uncommon (10%) in 79 patients with newly diagnosed coeliac disease. In Crohn's disease, concurrent Fructose malabsorption and lactose malabsorption was most common (29%)". As they conclude, "The abnormal patterns observed in Crohn's disease may have pathogenic importance."

Parallel to these investigations, others focus on the response of the intestinal mucosa to food antigens. In the article by Van Den Bogaerde J *et al* [25], ten patients with Crohn's disease and 10 healthy controls were studied. The Crohn's disease group demonstrated higher rectal blood flow than controls in response to all food antigens, and this was significantly different in response to citrus fruits ($P = 0.038$). In conclusion, patients with Crohn's disease demonstrate *in vivo* and *in vitro* sensitization to food antigens.

In another article, Van Den Bogaerde J *et al* [26] assert that complex food proteins and enteric flora may act as antigenic stimuli in Crohn's disease. This study assessed the prevalence and magnitude of lymphocyte priming to these antigens in Crohn's disease. The antigens tested included cow's milk and citrus fruit, among others. The mean proliferation to antigens was not above background in controls, but in patients with Crohn's disease, proliferative responses to all food and bacterial antigens were significantly higher than background values. They conclude that the reactivity of peripheral lymphocytes to food, yeast and bacterial antigens, especially multiple antigens, is common in Crohn's disease. These sensitized lymphocytes may contribute to the inflammatory process.

4. Conclusions

Many articles that cover dietary factors and their relationships with Crohn's disease, but the results remain inconclusive. Several studies find detrimental effects of milk and fruits consumption relating to Crohn's disease, while others show benefits of their consumption. It is therefore impossible to determine whether restrictive diets are suitable for the population. It is necessary to expand research in certain specific aspects or even to consider new approaches in other fields.

Conflict of Interest: The authors declare no conflict of interest.

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