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Effect of Breastfeeding on the Risk of Developing Inflammatory Bowel Disease

Anne Sütü ile Beslenmenin İnflamatuar Bağırsak Hastalığı Gelişme Riski Üzerine Etkisi

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Abstract

Aim: This study aimed to investigate whether breastfeeding in early childhood affect the risk of devoloping inflammatory bowel disease (IBD).

Material and Method: The data of patients obtained from the survey were compared to the data of their non-IBD siblings as a control group. The relationship between the demographic and clinical chararecteristics of IBD patients and breastfeeding was also analyzed.

Results: 304 IBD patients were included in the study. 182 (59.9%) of the patients were diagnosed with ulcerative colitis (UC), and 122 (40.1%) with Crohn's disease (CD). The CD patients included in the study were compared to the CD siblings group of 332, and the UC patients compared with the UC siblings group of 508. Compared to the control groups, the proportion of those who never breastfed was higher in both the CD and UC groups (7.4% vs. 2.1% for CD [p=0.017] and 3.9% vs. 0.8% for UC [p=0.01]), and the risk of disease increased in those who was not breastfed (OR= 3.70 [1.35-10.16] for CD [p=0.017] and OR= 5.07 for UC [1.47-17.53] [p=0.010]). The protective effect against CD increased as the duration of breastfeeding increased, but that the protection increased with breastfeeding for up to 12 months for UC, and breastfeeding for more than 12 months did not provide additional protection. There was no relationship between breastfeeding and demographic and behavioral chracteristics of patients

Conclusions: Not having been breastfed in infancy increases the risk of developing both UC and CD, and as the duration of breastfeeding increases, the protection against diseases risk increases.

Keywords: Crohn's disease, ulcerative colitis, breastfeeding, disease risk

Öz

Amaç: Bu çalışmanın amacı, erken çocukluk döneminde anne sütü almanın inflamatuar bağırsak hastalığı (İBH) gelişme riskini etkileyip etkilemediğini araştırmaktır.

Gereç ve Yöntem: Anketten elde edilen hasta verileri İBH olmayan kardeşlerinden oluşan kontrol grubu ile karşılaştırıldı. Annesütü alma durumu ile İBH hastalarının demografik ve klinik özellikleri arasındaki ilişki de ayrıca analiz edildi.

Bulgular: Çalışmaya 304 İBH hastası dahil edildi. Hastaların 182'si (%59,9) ülsaratif kolit (ÜK), 122'si (%40,1) Crohn hastalığı (CH) tanılıydı. Çalışmaya dahil edilen Crohn hastalarının verileri 332 kişilik CH kardeş grubu ile ve ÜK hastalarının verileri de 508 kişilik ÜK kardeş grubunun verileri ile karşılaştırıldı. Hiç anne sütü almayanların oranı hem CH hem de ÜK grubunda, kontrol grubuna göre anlamlı olarak daha yüksekti (CH için %7,4 ve %2,1 [p=0,017] ve ÜK için %3,9 ve %0,8 [p=0,010]) ve hiç anne sütü almayanlarda hastalık riski anlamlı olarak artmıştı (CH için OR= 3,70 [1,35-10,16] [p=0,017] ve ÜK için OR= 5,07 [1,47-17,53] [p=0,010]). Ayrıca anne sütü alma süresi arttıkça CH'a karşı koruyucu etkinin arttığı, ÜK için ise 12 aya kadar emzirme ile koruyucu etkinin arttığı, ancak12 aydan fazla anne sütü almanın ek koruma sağlamadığı belirlendi. Anne sütü alma ile hastaların demografik ve klinik özellikleri arasında ilişki saptanmadı.

Sonuç: Bebeklik döneminde anne sütü almamış olanlarda hem ÜK hem de CH gelişme riski artmakta ve emzirme süresi arttıkça hastalık riskinden koruyuculuk artmaktadır.

Anahtar Kelimeler: Crohn hastalığı, Ülseratif kolit, anne sütü, hastalık riski

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INTRODUCTION

Although the etiology of Crohn's disease (CD) and ulcerative colitis (UC), which are chronic inflammatory diseases of the gastrointestinal tract, is still not fully understood, genetic predisposition, environmental causes and abnormal immune response against intestinal flora are the main suggested causes. Mutations in more than 200 genes that affect immune regulation functions in IBD have been identified.[1] However, in a study conducted with monozygotic twins, an association of up to 55% for CD and 17% for UC was found.[2] This indicates that genetic predisposition alone is not effective in the pathogenesis of the disease.

Many environmental factors that increase or decrease the risk of disease have been defined in patients with IBD, such as smoking, use of antibiotics and some other drugs, breast milk, excessive hygiene, past infections, deficiencies of some vitamins, and physical activity.[3] In patients with genetic predisposition, chronic inflammation develops in the intestines as a result of an excessive immune response to abnormal intestinal flora triggered by environmental factors.[4] It is known that the decrease in species such as *Bifidobacterium*, *Clostridium*, *Lachnospiraceae* and the increase in species such as *Proteobacteria*, *E. Coli*, Fusobacterium in the intestinal flora play a role in the development of IBD by changing the innate immune response.[5] Breastfeeding not only provides protection against infections in infants, but also has important effects on the microbiome composition of the intestines and immune tolerance, and plays a protective role against atopic, allergic and autoimmune diseases.[6-9] It has been reported that human milk oligosaccharides (HMOs), which are abundant in breast milk, act as a prebiotic to increase the beneficial species, especially *Bifidobacterium*, in the intestinal flora, and to reduce harmful bacteria such as *Acinetobacter* and with its antibacterial effect.[10,11]

Studies investigating the effect of breast milk on the risk of IBD so far are quite heterogeneous. While breastfeeding was found to be protective against IBD in some of them, it was found to have no effect in others.[12-14] Identifying and eliminating the modifiable factors in the etiology of diseases is important for the prevention of diseases. In this study, we compared the breastfeeding status of IBD patients and their healthy siblings in order to minimize the effects of genetic and environmental factors.

MATERIAL AND METHOD

Patients diagnosed with inflammatory bowel disease monitored in the Gastroenterology clinic of our hospital were included in the study. After obtaining approval from the ethics committee of our hospital (No: E1-22-2744), the patients' gender, age at diagnosis, place of residence (village, town, city), disease subgroup (UC, CD), disease localization according to the Montreal Classification[15] and CD behavior (inflammatory, stricture, fistulization, perianal disease), medications used, steroid refractoriness or dependence, and history of surgery related to IBD were recorded. The data on the duration of breastfeeding of patients were obtained by face-to-face questionnaire, and, for their siblings, by contacting them and their mothers. Patients who were not known for how long they were breastfed and their siblings were excluded from the study. Only those who were known for how long they were breastfed were included in the study.

Statistical Analysis

IBM SPSS Statisticsfor Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. Descriptive statistics (frequency, mean and SD, median and minimum-maximum) were calculated. Categorical variables were summarized as percentages. Normality analysis of the data was evaluated via Kolmogorov-Smirnov and Shapiro-Wilk tests. In group comparisons, a parametric test (Student's t-test) was used for normally distributed continuous variables, where as a non-parametric test (Mann-Whitney U and Kruskal-Wallis) was used for non-normally distributed variables. A chi-squared test or Fisher's exact test (when chi-squared test assumptions do not hold due to low expected cell count) was used to compare categorical variables in different groups. In estimating the risk ratio of the duration of breastfeeding on the disease state; It was tested by calculating odds ratios adjusted with 95% confidence intervals. Spearman correlation coefficient was used to evaluate the relationship between breastfeeding and disease. Statistical significance was considered $p \leq 0.05$ with a confidence interval (CI) of 95%.

RESULTS

304 IBD patients were included in the study. Mean age was 44.53±12.26 years, 173 (56.9%) of the patients were male. 182 (59.9%) of the patients were diagnosed with UC, and 122 (40.1%) with CD. Demographic and clinical characteristics of patients CD and UC are shown in **Table 1**. The data of a total of 840 siblings of these patients (508 siblings of UC patients and 332 siblings of CD patients) were analyzed. The data of 122 CD patients included in the study were compared to the CD siblings group of 332, and the data of UC patients with the UC siblings group of 508.

Comparing the 122 CD patients to 332 siblings, it was found that the rate of those who were not breastfed in the CD group was statistically significantly higher than the sibling group (7.4% and 2.1%, p=0.017) and the risk of disease increased significantly in those who were not breastfed (p=0.01, OR= 3.70 [1.35-10.16]). In addition, when the breastfed group was analyzed separately as >3 months, >6 months and >12 months, it was found that the protective effect increased as the duration increased (**Table 2**).

Table 1. Demographic and clinical characteristics of patients with Chron's disease and ulcerative colitis.

Demographic and clinical characteristics	CD (n=122)	UC (n=182)
Age	41.16±11.26 (17-82)	46.89±12.44 (18-76)
Gender		
Female	56 (45.9%)	75 (41.2%)
Male	66 (54.1%)	107 (58.8%)
Age at Diagnosis*	17-62 (34.08±9.97)	12-66 (38.22±12.07)
A1 (0-16 years)	0 (0.0%)	7 (3.9%)
A2 (17-40 years old)	93 (76.2)	97 (53.6%)
A3 (>40 years)	29 (23.8)	78 (42.5%)
UC localization*		
Proctitis (E1)	-	41 (22.5%)
Left Type (E2)		106 (58.3%)
Extensive (E3)		35 (19.2%)
CD localization*		
Ileal (L1)	51 (41.8%)	
Column (L2)	16 (13.1%)	-
ileocolon (L3)	55 (45.1%)	
Isolated upper GIS (L4)	0 (0.0%)	
CD behavior*		
Inflammatory (B1)	68 (55.7%)	
Stricturan (B2)	34 (27.9%)	-
Penetrating (B3)	20 (16.4%)	
Perianal disease (p)	21 (17.2%)	
IBD-related operation		
Yes	42 (34.4%)	13 (7.1%)
No	80 (55.6%)	169 (92.9%)
Steroid refractory/dependent		
No	83 (68.0%)	168 (92.3%)
Refractory	26 (21.3%)	9(4.9%)
dependant	13 (10.7%)	5 (2.8%)
Family history of İBD		
Yes	11 (9.0%)	33 (18.1%)
No	111 (91.0)	149 (81.9%)
Place of residence		
Village	7 (5.7%)	24 (13.2%)
Town	36 (29.5%)	43 (23.7%)
City	79 (64.8%)	115 (38.1%)
Patients' mean breastfeeding duration	12.92±9.47 (0-48 ay)	14.83±8.63 (0-36 ay)
Patients who have never been breastfed	9 (7.4%)	7 (3.9%)
Number of siblings	332 (Median:4 [0-9])	508 (Median:4 [0-18])
Siblings' mean duration of breastfeeding	15.51± 7.87 (0-48 ay)	14.67±7.06 (0-54 ay)
Siblings who have never been breastfed	7 (2.1%)	4 (0.8%)

CH: Crohn's disease, UC: ulcerative colitis, IBD: inflammatory bowel disease, *Montreal Classification

Table 2. Comparison of patients with Crohn's disease and their siblings in terms of duration of breast milk intake.

Breast milk intake	Patients n (%)	Sibling n (%)	p	Odds Ratio	95% Confidence Interval
No	9	7	0,017	3.7	1.346-10.159
Yes	113	325			
≤3 month	19	20	0,001	2.88	1.478-5.602
>3 month	103	312			
≤ 6 month	38	46	0,000	2.81	1.717- 4.608
>6 month	84	286			
≤12 month	77	161	0,006	1.87	1.187-2.283
>12	45	171			

Comparing the 182 UC patients to 508 siblings, the proportion of those with UC who were not breastfed was significantly higher than the sibling group (3.9% vs. 0.8%, p=0.010), and the risk of disease was found to be significantly increased in those who were not breastfed (OR=5.07 [1.47-17.53]). In addition, when the breastfed group was analyzed separately as >3 months, >6 months and >12 months, it was found that the protective effect increased as the duration increased (p<0.05), but there was no additional protection after 12 months (p>0.05) (**Table 3**).

Table 3. Comparison of patients with ulcerative colitis and their siblings in terms of duration of breast milk intake.

Breast milk intake	Patients n (%)	Sibling n (%)	p	Odds Ratio	95% Confidence Interval
No	7	4	0.01	5.07	1.466-17.525
Yes	175	504			
≤3 month	15	21	0.03	2.1	1.056-4.160
>3 month	167	487			
≤ 6 month	36	63	0.01	1.75	1.118-2.751
>6 month	146	445			
≤12 month	102	298	0.59	0.9	0.64-1.282
>12	80	210			

There was no relationship between the status and duration of breastfeeding and gender, age at diagnosis, place of residence, UC localization, operation history, medications used, and steroid refractoriness or steroid dependence in patients with UC.

Again, no relationship was found between the status and duration of breastfeeding and gender, age at diagnosis, place of residence, CD localization, CD behavior, perianal disease, operation history, medications used, and steroid addiction and refractoriness in patients with CD.

DISCUSSION

Many environmental factors along with genetic predisposition are blamed in the etiology of IBD, and the immune response against abnormal intestinal flora is mostly emphasized.[5] It has been reported that breast milk intake in the first period of life contributes to the formation of favorable intestinal flora and immunity.[10]

In a study conducted by the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) Group, they showed that breast milk is protective against IBD.[16] Similarly, in a meta-analysis of 35 studies by Xu et al.[13] it was found that the risk of both UC and CD was lower in those who received any amount of breast milk compared to those who did not receive any breast milk, and this effect was clearer in Asian populations than in European populations. In another meta-analysis, breast milk was found to be associated with a lower risk of CD and UC, while this relationship was found to be strong in studies with high methodological quality.[17] Contrary to these studies, it was reported that no relationship was found between breast milk and the risk of UC and CD in a prospective study including 146,681 women

in the National Health Survey I and II cohorts published in 2013.[14] Again, in different studies investigating the protectiveness of breast milk in patients with CD and UC, the effectiveness of breast milk could not be demonstrated.[18-21] Interestingly, Baron et al.[22] found that breast milk intake increased the risk of CD in their study in pediatric population. In our study, however, we found that having never been breastfed significantly increased the risk of developing both UC and CD, and even when the duration of breastfeeding was compared, the highest risk increase was seen in those who were never breastfed. Since siblings of the patients were taken as the control group in our study, the effect of genetic and environmental factors was minimized, and the effectiveness of breast milk was demonstrated. Considering the previous studies on colostrum, which is the milk secreted in the first days after birth, which reported that colostrum increases immunity, provides protection against harmful pathogens, and helps the development of the newborn immune system, this was thought to be no surprise.[23-25] We think that the reason why only less than 5% of the patients in our study were not breastfed, and that the rate of not receiving breast milk at all in studies in other countries was more than 20%[18-21] is due to the different patient populations studied, environmental factors and differences in local nutritional behaviors.

In addition to the protective effect of breast milk in CD and UC, the protective effect of the duration of breastfeeding against the disease has been investigated in different studies. In a meta-analysis, it was reported that the protective effect increased as the duration of breastfeeding increased.[13] Similarly, in another study, it was reported that the protective effect was clearer in those who were breastfed for longer than 12 months.[16] Ko et al.[26] analyzed separately the immigrants from the Middle East to Australia and the native Caucasian race and reported that having been breastfed for more than 3 months reduces the probability of developing CD, and that having been breastfed for more than 6 months reduces the likelihood of developing UC. In other studies, it has been reported that having been breastfed for more than 6 months reduces the risk of CD and UC.[27-29] Gearry et al.[30] on the other hand, reported that it is necessary to have been breastfed for at least 3 months for a protective effect. Differently, Sonntag et al.[18] found no significant difference in terms of breastfeeding duration in both CD and UC groups, while Striscioglio et al.[31] claimed that having been breastfed for longer than 3 months increases the risk of CD in their study on pediatric patients. In our study, we found that the protective effect of breast milk starts from the first months and the protective effect increases in parallel with long-term breastfeeding, however, having been breastfed for more than 12 months does not provide additional protection in UC patients. We think that different results may be caused by diet, medications used in childhood, immunization, environmental factors and variability in different populations in the etiology of the disease.

Siblings of the patients were taken as the control group in order to reduce environmental and genetic effects, and the main limitations of this study are that it is a study conducted with the questionnaire and where the information was questioned retrospectively, and that the smoking status of the patients and their siblings, the time of supplementary food initiation, diet, childhood infections, vaccination, and hygiene conditions that may be associated with the risk of disease are not known.

CONCLUSION

Not having been breastfed in infancy increases the risk of developing both CD and UC, the protective effect of breast milk starts from the first months and the protective effectiveness increases in parallel with long-term breastfeeding.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 29/06/2022, Decision No: E1-22-2744).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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