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Reelin levels in inflammatory bowel disease: A case-control study

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Ethics Committee Approval
Ethics committee approval (TC Ministry of Health Ankara Provincial Health Directorate Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethical Committee (15.12.2014, 18/19) was obtained, and all participants gave informed consent before inclusion in the study.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Crohn's Disease (CD) and Ulcerative Colitis (UC) are grouped as Inflammatory Bowel Diseases (IBD). There are many similarities between these two diseases, and CD and UC cases cannot be separated at a rate varying between 5% and 10%. Reelin is an extracellular matrix protein first known for its vital role in neuronal migration. Studies in rodent small intestine suggested that reelin protects the organism from intestinal pathologies. In a 5-year retrospective case-control study, we aimed to detect the effectiveness of serum reelin level in patients with IBD in determining the severity and activation of the disease and compare healthy volunteers with patients in terms of inactivation and remission.
Methods: The data of all 194 IBD patients diagnosed at Beyazit Training and Research Hospital between 2011-2015 were retrospectively reviewed. The patients were matched with 30 healthy volunteers. Risk factors were assessed by multivariate logistic regression analysis.
Results: The serum reelin levels were similar between UC and CD patients, the control group, UC and CD groups (P=0.067), and those with active disease or disease in remission, and did not differ according to disease behavior or location of involvement.
Conclusions: Our study shows that Reelin cannot be used as an activation/remission marker in IBD. In addition, it does not differentiate between UC and CD.

Keywords: Reelin, Inflammatory bowel diseases, Crohn's disease, Ulcerative colitis

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Introduction

Inflammatory Bowel Diseases (IBD) refer to inflammatory diseases involving the colon and small intestine (Baumgart and Carding, 2007). These can be idiopathic and recur chronically to cause inflammation in the gastrointestinal tract. It has two main subtypes: Ulcerative Colitis (UC) and Crohn's Disease (CD), and a third subtype in the form of indeterminate colitis [1].

Clinically, UC and CD share similar symptoms such as diarrhea, hematochezia, and abdominal pain, but differ in terms of the location and depth of inflammation, as well as complications and prevalence [2].

In ulcerative colitis, submucosal tissue and inflammation of the colonic mucosa are present, and involvement is not seen in deeper parts except for the fulminant type. While it starts with rectal involvement in most patients, the lesions progress proximally without space in between, thus becoming continuous [3]. In ulcerative colitis, the target tissue is the colon. If only the rectum is involved, the disease is called hemorrhagic proctitis or ulcerative proctitis. If only the sigmoid colon and rectum are involved, it is called ulcerative colitis with distal involvement [4]. Crohn's disease, on the other hand, can involve the gastrointestinal tract from the mouth to the anus, and it is most seen in the terminal ileum. Intact mucosal areas as well as intermittent lesions can be observed. All layers of the gut are inflamed [5].

Chronic inflammatory bowel diseases, namely, Crohn's disease, and ulcerative colitis, constitute an essential part of gastrointestinal diseases in children and adults. Inflammatory bowel diseases worldwide are typical in regions such as the United States, England, and Scandinavia [6]. The age of onset of Crohn's Disease ranges between 20-30 years [7, 8]. While 5% to 15% of patients are older than 60 years of age, 25% are diagnosed before the age of 18 years [9]. Phenotype and natural disease history may differ according to the age of onset [10]. For example, pediatric-onset ulcerative colitis is characterized by a high spread rate and surgical treatment is performed in approximately 20% of children in the first ten years of follow-up after diagnosis [11]. On the other hand, although the clinical course of elderly inflammatory bowel disease patients seems mild due to a more minimal disease progression over time, they are more vulnerable, and due to the numerous side effects related to treatment, the risk of infections, malignancy, bone disease, eye disease, malnutrition, and thrombotic complications are increased [12, 13].

It is also quite surprising that the prevalence of inflammatory diseases differs according to age, gender, ethnicity, time, and geographical distribution [7, 14, 15]. Significant efforts have been made to determine the cause. Studies suggest that various types of bacteria, such as Heliobacter hepaticus, Pseudomonas maltophilia, Bacteroides fragilis, Bacteroides necrophorum, Blastocystis hominis, Edwardsiella tarda, Plesiomonas shigelloides, Aeromonas hydrophila, Chlamydia trachomatis, Yersinia enterocolitica, Campylobacterfetus jejuni, Aerobacter bifidobacteria, Aerobacter coprococcus, Aerobacteraerogenes, Bacillus vulgatus, Pseudomonas maltophilia, Mycobacteria kansasii, Mycobacteria paratuberculosis, Mycobacteria tuberculosis, Escherichia coli, Bacillus morgagni, Spherophorus necrophorus, Bacillus pyocyaneus, Bacillus proteus, Bacilluscoli, fungi such as Monilia and Histoplasma, viruses such as lymphopathia venereum, viruses such as Behcet virus, cytomegalovirus, paramyxovirus, Poliovirus, reovirus, coxsackie A and B, herpes, measles, influenza, rotavirus, Epstein-Barr, adenovirus, and Echo A, B, parasites and protozoans such as Escherichia histolytica, calcium phosphate, silicon oxide, titanium and aluminum microparticles from soil, dust, toothpaste, and diet, non-steroidal anti-inflammatory drugs and oral contraceptives, sugar, fat, and protein components from fast food, coke, coffee, farm products, margarine, vegetables, and fruits, glycoalkaloid compounds in potatoes, smoking, and other factors such as frozen products transported with cold chain play a role [16-23]. Despite this, the increasing incidence of inflammatory bowel diseases, especially in recent years, has led experts and researchers to view this situation as an expanding global health problem of industrial-urbanized societies [24]. In this context, it has become essential to study inflammatory bowel diseases in more detail and determine the factors that play a role in their etiology.

Reelin is an extracellular glycoprotein secreted by Cajal-Retzius cells and GABAergic interneurons in the adult brain during embryonic brain development. The full-length Reelin is about 460 kDa and has a signal peptide, an F-spondin-like domain, eight Reelin repeats (R1-R8), and a positively charged sequence at the C-terminal [25]. It modulates neuronal function and synaptic plasticity in the mature brain and regulates tau phosphorylation, axonal growth, and dendritic spine morphology [26]. Studies show that Reelin deficiency is associated with bipolar disorder and major depression, autism, epilepsy, and schizophrenia [27-30]. There are also studies suggesting that Reelin may play a role in inflammatory bowel diseases [31-33]. Additionally, studies show its function in crypto-villus homeostasis and that Reelin regulation plays a protective role against diseases such as acute colitis [31, 34]. However, no previous study directly examined the role of Reelin in inflammatory bowel diseases in the local or international literature. In this respect, this study aims to determine the role of Reelin in inflammatory bowel diseases and contribute to the literature.

Materials and methods

Design and sample

The present hospital-based case-control study retrospectively collected the data of cases and controls aged between 25-65 years who reside in Ankara.

This study was completed in the Dışkapı Yıldırım Beyazıt Training and Research Hospital Gastroenterology - IBD Clinic located in Ankara, Turkey. According to IBD clinic records between 2011-2015, the diagnoses of 194 individuals were confirmed as Crohn's Disease and Ulcerative Colitis. Using the telephone numbers included in the files, investigators contacted the individual regarding whether they wanted to be included in the study. Information about the aim and method was provided over the phone, and the individuals were invited to the IBD clinic for collection of the data. A total of 194 patients agreed to participate in this study as the case group.

Individuals with similar sociodemographic characteristics as the case group were chosen from visitors at the same hospital to be included in the control group. A total of 30 volunteers, aged 25 years and above, who were not diagnosed with IBD or any other illness, were identified as potential control group members. All those who were invited to participate in the study were informed that participation was on voluntary basis, they could withdraw at any time, and their privacy would be respected. Researchers contacted the subjects at the hospital, both the cases and the controls, and gave them questionnaires to collect data.

Data were collected from patient files and the hospital's information processing system. CD Activity Index "CDAI" and the Truelove activity index were calculated for Ulcerative Colitis, and serum Reelin levels were determined in the hospital's biochemistry laboratory.

Data collection

Researchers conducted face-to-face interviews with both the case and control groups at the hospital. The investigators introduced themselves, explained the study's purpose, and obtained informed consent from all subjects before the interview. A customized questionnaire and personal interviews were used to collect demographic and risk factor data from each participant.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the chi-square test and logistic regression analysis with the SPSS 22.0 software. The chi-square test was used to compare Reelin levels. The non-paired student t-test was used to analyze parametric data. The relationship between blood Reelin concentration and clinical parameters was assessed with Spearman's correlation analysis. Statistical significance was defined as a probability (p) value of less than 0.05. Power analysis was performed using the computer-aided statistics program G-power. According to previous studies [27, 28] in the literature, the smallest sample size to represent the population with 95% strength was 52 participants at 0.8 power and a 5% alpha error margin.

Ethical considerations

Ethics committee approval (TC Ministry of Health Ankara Provincial Health Directorate Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethical Committee (15.12.2014, 18/19) was obtained, and all participants gave informed consent before inclusion in the study. This study complied with the principles of the Declaration of Helsinki.

Results

General characteristics and demographic data of the participants in the study are presented in Table 1. Ninety-nine of 194 patients had UC and 89 had CD. The mean ages of the UC and CD patients were 41.77 (7.77) years and 39.63 (15.55) years, respectively. There were 40 females and 59 males in the UC group, and 36 females and 43 males in the CD group.

The serum Reelin levels were similar between the UC and CD groups (P=0.419), and between UC, CD, and control groups (P=0.059) (Table 2, 3). There were no significant differences in terms of serum Reelin levels when the UC and CD groups were compared with the control group separately (P=0.910, P=0.436, respectively) (Table 3).

Table 1: Demographic features of study group

	Ulcerative colitis (UC)	Crohn's disease (CD)	Control group
Age (SD)	41.77(7.77)	39.63(15.55)	28(6.3)
Female	40	36	15
Male	59	59	15
Active	50	49	
Remission	49	46	
Localization			
Proctitis	22		
Left Side Involvement	48		
Extensive	29		
Ileal		32	
Colonic		9	
Ileocolonic		51	
Disease behavior			
Inflammatory		64	
Stricturing		3	
Penetrant		10	
Inflammatory + Perianal		7	
Inflammatory + Stricturing		6	

Table 2: Average reelin level in all groups

	n	Reelin ng/ml
Total of UC	97	0.6216(1.0835)
Total of CD	92	0.3993(0.5101)
Control group	30	0.5576(0.6142)
Active CD	49	0.3675(0.5789)
Active UC	48	0.3846(0.4850)
CD in Remission	43	0.4354(0.5789)
UC in Remission	49	0.8538(1.4161)

Table 3: Comparison of all groups

Total	UC	CD	*P*-value UC + CD vs. control group	*P*-value UC vs. control group	*P*-value CD vs. control group
n=189	n=97	n=92	0.419	0.910	0.436

The serum Reelin levels of 49 CD patients who were in active disease period and 46 who were in remission were similar (P=0.518) (Table 4). Serum Reelin levels according to disease location of all CD patients, and those with active CD and CD at remission are shown in Table 5. Table 5 shows that Reelin levels do not differ significantly according to the location of involvement among all patients with CD (X^2=0.109; P=0.947), or among those with active CD (X^2=0.299; P=0.861) and CD in remission (X^2=0.653; P=0.721).

Table 4: Relationship between groups and Reelin level

	n	*P*-value
Active UC	48	
UC in remission	49	0.618
Active CD	49	
CD in remission	43	0.518
UC+ proctitis	22	
UC+ left segment involvement	48	0.266
UC+ extensive	29	
CD, ileal	32	
CD, colonic	9	0.947
CD, ileocolonic	51	
CD, inflammatory	64	
CD, stricturing	3	
CD, penetrating	10	0.741
CD, penetrating, inflammatory	7	
CD, stricturing, inflammatory	6	

Table 5: Disease localization of Reelin level

Location		n	X^2	*P*-value
CD	Ileal	32	0.109	0.947
	Colonic	9		
	Ileocolonic	51		
CD+ active	Ileal	16	0.299	0.861
	Colonic	6		
	Ileocolonic	26		
CD+ remission	Ileal	16	0.653	0.721
	Colonic	3		
	Ileocolonic	25		

The Kruskal Wallis H test results according to the behavior of the disease in patients with CD, patients with active CD, and patients with CD in remission are shown in Table 6. As seen in Table 6, Reelin levels do not significantly differ with behavior of the disease among all CD patients (X^2=1.971;

P=0.741), or among those with active CD (X^2=1.845; P=0.764) or CD in remission (X^2=1.986; P=0.738).

The Kruskal Wallis H test results of Reelin levels in patients with UC, active UC, and UC in remission according to the disease location are seen in Table 7. Among the 97 UC patients included in the study, 48 were in their active period, and 49 were in remission. The serum Reelin levels did not significantly differ according to disease state (P=0.359). Also, no difference was found between the Reelin values of the patients with active UC and the control group (P=0.618).

Table 6: Reelin levels of type of disease behavior

	Type of disease behavior	n	X^2	P-value
CD	Inflammatory	64		
	Stricturing	3		
	Penetrating	10	1.971	0.741
	Inflammatory + Perianal Disease	7		
	Inflammatory+ Stricturing	6		
CD+ active	Inflammatory	32		
	Stricturing	2		
	Penetrating	5	1.845	0.764
	Inflammatory + Perianal Disease	4		
	Inflammatory+ Stricturing	4		
CD+ remission	Inflammatory	32		
	Stricturing	1		
	Penetrating	5	1.986	0.738
	Inflammatory + Perianal Disease	3		
	Inflammatory+ Stricturing	4		

Table 7: Disease localization of Reelin levels in patients

Location		n	X^2	P-value
UC	Proctitis	21	2.647	0.266
	Left Type	48		
	Extensive	28		
Active UC	Proctitis	10	0.820	0.664
	Left Type	24		
	Extensive	14		
UC in remission	Proctitis	11	1.978	0.372
	Left Type	24		
	Extensive	14		

According to the segment of involvement, the serum Reelin levels were similar between all UC patients (X^2=0.109; P=0.055), in those with active UC (X^2=0.820; P=0.072), and in patients with UC in remission (X^2=1.978; P=0.065).

ANOVA test revealed no significant differences in terms of serum Reelin levels between CD and UC patients and the healthy control group (X^2=1.007, P=0.605) according to involved segments (Table 8).

Table 8: Results of Reelin level of group

Group	n	X^2	P-value
CD	94	1.007	0.605
UC	97		
Control group	30		

Discussion

The entire surface area of the human intestine reaches 200-400 m^2 [35]. As well as being the barrier of the innate immune system, the inner cell lining of the intestines is also where interactions with commensal microorganisms occur. These interactions are precisely modulated by the intestinal immune system and contribute to immune homeostasis [36, 37].

The epithelium of the mammalian gastrointestinal tract has the fastest turnover rate of any tissue in the body and requires precisely modulated homeostasis, carefully regulated cell proliferation, growth arrest, migration/differentiation, and apoptosis programs to contribute to the immune system. In rodents, the epithelium of the small intestine is completely replaced every 2-3 days. Cell proliferation is confined to crypts of Lieberkühn, where stem cells lead to progenitor cells amplified by continuous division across the lower two-thirds of the crypts. Cell involvement and differentiation occur when the cell progenitors reach the crypt-villi junction, and the villi differentiate and form the functional compartment. Absorptive enterocytes, hormone-secreting enteroendocrine cells, opioid-producing brush cells, microfold cells, and mucus-producing Goblet cells emerge from the crypts and complete the differentiation of adjacent villi in the consistent vertical columns [38]. When mature cells approach the apical extrusion site of the villi, they undergo apoptosis and are dumped into the intestinal lumen; thus, the continuous production of new cells is balanced [39].

Epithelial cell regeneration is tightly controlled by cell-cell and cell-extracellular matrix interactions [40]. A thin and continuous cell-extracellular matrix layer separates the basement membrane epithelial cells from the interstitial connective tissue, and its composition defines the requirements. Mutual interactions between the epithelium and the underlying basement membrane regulate proliferation, migration, differentiation, apoptosis, morphogenesis, tissue repair, inflammation, and immune response [31]. Many receptors have been identified for cell-extracellular matrix molecules in intestinal epithelial cells, many of which are integrins [32]. However, the nature of cell-basement membrane interactions and their intracellular processing is largely undefined. Various components, such as myofibroblasts, cytokines, growth factors, chemokines, hormones, neurotransmitters, inflammatory mediators, and adhesion proteins, are expressed and secreted under the epithelium in the cell-extracellular matrix. Express receptors for many of these ligands allow information flow in both directions to the gut epithelium and the cell-extracellular matrix. Consequently, myofibroblasts are considered to regulate functions ranging from peripheral immune tolerance to the control of epithelial regeneration processes and provide immune homeostasis [31, 41]. Idiopathic intestinal inflammations such as inflammatory bowel diseases can occur when this homeostasis deteriorates for various reasons [36, 37].

Many markers that correlate with the clinical picture of IBD have been identified and are still being studied. In the literature, increased ADA levels were found in IBD patients compared to healthy controls [42]. In another study, it was shown that PTX3 value workup would be appropriate during the follow-up of UC patients [43].

In the studies conducted, it was determined that the expressions of Reelin among Reelin receptors, apolipoprotein E receptor (ApoER2), very low-density lipoprotein receptor (VLDLR), and effector protein Disabled-1 (DAB1) in the mucosa of the rat small intestine are limited to myofibroblasts [31, 38]. It is also known that Reelin secreted by Cajal-Retzius cells in the brain is critical for the positioning of migrating neurons during the development of the nervous system [41]. The reason is that the differentiation of the intestinal epithelium requires the migration of cells along the crypt-villus axis [31]. This suggests that Reelin, which plays a vital role in intestinal epithelial dynamics, also plays an essential role in inflammatory bowel diseases.

Based on the result of our study, we concluded that serum Reelin levels did not significantly differ between UC and CD, their active or remission periods, between the patients and the control group or according to segment of involvement. There

was no relationship between Reelin levels of the participants in the study and their diseases.

Limitations

The findings of this study must be viewed in the context of some limitations. First, the study was conducted over five years in a small group of 194 cases. Another study limitation is that all the data came from a single center and one nationality. Furthermore, no reference values for serum RELN concentrations were established. Therefore, we cannot verify our findings or compare them to those found in the international literature. However, at this stage of research, where case-control studies are the method of choice for increasing our knowledge of this intriguing signal, this is not a critical point. The study's findings and limitations are instrumental in contributing to the advancement of research in this field. Furthermore, because this research was conducted in a developing country, lifestyle changes may reveal important information about IBD. Widespread future studies are warranted to explore significant differences in clinical scores or intestinal inflammation depending on the level of RELN.

Conclusions

The study showed that Reelin could not be used as a marker of activation/remission in inflammatory bowel diseases and that there is no marker in the differential diagnosis between UC and CD. Although its routine use is not yet recommended, ADA level helps determine the clinical activity of IBD and can be preferred in selected cases. Additionally, before the widespread use of ADA levels is recommended, it should be ensured that it is easily applicable in larger populations.

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