

Relationship Between Bilirubin Level and Disease Activity in Crohn's Disease

Crohn Hastalığında Bilirübin Düzeyi ile Hastalık Aktivitesi Arasında İlişki

Bilirubin Level in Crohn's Disease

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Özet

Amaç: Crohn Hastalığı (CH), gastrointestinal sistemin kronik inflamatuar bir hastalığıdır. Patogenezinde; bağırsakta trnasmural inflamasyonun geliştiği bilinmektedir. Son zamanlarda, inflamasyondan kaynaklanan oksidatif stres ve iskemi ile antoksidan kapasite arasındaki dengesizlik sonucu, bağırsak hasarının oluştuğu mekanizması üzerinde durulmaktadır. Bilirübin, Heme yıkımı sonucu oluşan metabolik üründür. Artmış oksidatif streste, iskeminin şiddetine göre değişebilen kan bilirubin düzey artışları izlenmektedir. Çalışmamızın amacı CH aktivitesinin bir göstergesi olarak serum bilirubin düzeyini değerlendirmektir. Gereç ve Yöntem: Otuz adet aktif Crohn Hastalığı olan ve 66 adet sağlıklı kontroller çalışmaya dahil edildi. Klinik aktivitesi Crohn Hastalık Aktivite İndeksi (CDAI) kullanılarak belirlenmiştir. Serum bilirubin düzeyleri hastalığın aktif ve remisyon dönemlerinde kontrol grubu ile karşılaştırılmıştır. Bulgular: Total bilirubin değerleri incelendiğinde, CH olan grupta bilirubin seviyesi kontrol grubuna göre anlamlı yüksek saptanmıştır ($p<0,05$). Total bilirubin değeri remisyon döneminde sırasında istatiksel açıdan anlamlı azalma göstermiştir ($p <0,05$). Tartışma: Çalışmamız serum bilirubin düzeyinin aktif Crohn hastalarında kontrollere göre artmış olduğunu gösterdi.

Anahtar Kelimeler

Crohn Hastalığı; Bilirubin; Crohn Hastalık Aktivite İndeksi; İnflamasyon

Abstract

Aim: Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal system. Regarding its pathogenesis, it is known that transmural inflammation develops in the bowel. In recent years, it has been considered that bowel damage occurs as a consequence of an imbalance between oxidative stress and ischaemia and antioxidant capacity. Bilirubin is the metabolic product that develops as a result of heme destruction. In oxidative stress, blood bilirubin levels increase in correlation with the intensity of ischaemia. The aim of our study was to evaluate the potential of bilirubin as a serum factor to be a marker of disease activity of CD. Material and Method: Thirty patients diagnosed with active CD and 66 healthy control subjects were involved in the study. Clinical activity was determined using the Crohn's Disease Activity Index (CDAI). Serum bilirubin levels of active disease and remission periods were compared with the control group. Results: When total bilirubin values were examined, the bilirubin level among Crohn's disease patients was significantly increased compared to the control group ($p<0.05$). The total bilirubin value exhibited significant alteration during the remission period ($p<0.05$). Discussion: Our study showed that serum bilirubin was increased in active CD patients compared to controls.

Keywords

Crohn's Disease; Bilirubin; Crohn's Disease Activity Index; Inflammation

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal system. Its etiology is multifactorial and involves genetic predisposition, immunological causes, microbial agents, and environmental factors [1]. Regarding its pathogenesis, it is known that transmural inflammation develops in the bowel. In recent years, it has been considered that bowel damage occurs as a consequence of an imbalance between oxidative stress and ischaemia and antioxidant capacity [2,3].

Bilirubin is the metabolic product that develops as a result of heme destruction. The heme-oxygenase (HO) enzyme catalyzes heme destruction, and iron, biliverdine, and carbon monoxide result as end-products [4]. Biliverdine is converted into bilirubin by being reduced in the lungs. In recent years, it has been considered that bilirubin has constructive effects in preventing oxidative alterations in many diseases, such as atherosclerosis, cancer, inflammatory, autoimmune, and degenerative diseases [5]. On the other hand, increased bilirubin levels also reflect the impact of HO, which is produced under oxidative stress conditions. In other words, in oxidative stress, blood bilirubin levels increase in correlation with the intensity of ischaemia [6].

The Crohn's Disease Activity Index (CDAI) is still the most common method for evaluating CD inflammatory activity [7]. In this standard examination, the clinical symptoms of the patient are the primary factors while the physical examination and laboratory findings are less considered. Disease activation intensity is determined based upon the figures calculated from the criteria. The result from this method may not give a solid assessment of the disease situation since the course and symptoms of CD may vary from patient to patient. In a recent study it was determined that the CDAI is not sufficient to distinguish the symptoms of irritable bowel syndrome from active Crohn's disease [8].

Considering that inflammation plays a crucial role in the mechanism of CD, the aim of our study was to evaluate the potential of bilirubin as a serum factor to be a marker of disease activity of CD.

Material and Method

Patients

This study was a retrospective and concentric study. Thirty patients diagnosed with active CD (14 female and 16 male, average age: 47.73±14.95) and 66 healthy control subjects (30 female and 36 male, average age: 48.42±15.08) were involved in the study from the Gastroenterology unit. Each participant signed an informed consent form in accordance with the requirements of the Declaration of Helsinki. The study was approved by the local ethics committee of Canakkale Onsekiz Mart University.

CD diagnosis was made based on endoscopic and histopathologic criteria. Clinical activity was determined using the Crohn's Disease Activity Index (CDAI). It was defined as the active phase of the disease if the CDAI was ≥ 150 and as remission if the CDAI was < 150 [7]. Subjects with elevations in any of the liver function tests (defined as alanine aminotransferase 40 U/L, aspartate aminotransferase 30 U/L, gamma glutamyl transferase 70 U/L, and alkaline phosphatase 120 U/L) were excluded from the study.

Healthy control subjects were recruited from among patients with GOR and were matched to the patients by age and sex. Patients with CD were excluded from the study when there was any documentation of abdominal abscess, bowel obstruction, active gastrointestinal bleeding, evidence of liver disease, those who had pitches on their liver function tests, or pregnancy. Control subjects were excluded from the study if there was any evidence of an acute viral or bacterial infection, presence of inflammatory disorder, or use of anti-inflammatory medications (e.g. oral corticosteroids, aminosalicylic acid, or non-steroidal anti-inflammatory agents).

Laboratory

Laboratory evaluations included routine liver biochemistry (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels, total bilirubin, albumin, alkaline phosphatase, and gamma glutamyl transpeptidase [GGT]).

Venous blood samples of the participants were collected from the antecubital vein while patients rested in a supine position after an overnight fast. Serum samples were stored at 80°C and thawed immediately before analysis. Serum ALT, AST, GGT, ALP, albumin, and bilirubin levels in fasting subjects were analyzed using the ROCHE module Cobas 6000 (C501) and kits were procured from ROCHE diagnostics.

Statistics

SPSS software (Version 19.0; IBM, Chicago, IL, USA) was used for the statistical analysis and $P<0.05$ was considered statistically significant. Adjustment to normal distribution was evaluated by the Kolmogorov–Smirnov test, and all numerical data were expressed as a mean, SD, or median (interquartile range). Differences between groups were evaluated using the Mann–Whitney U test for nonparametric data, Student's t test for parametric data and chi square test at the initial stage. Correlations between parameters were analyzed using the Pearson (for normally distributed parameters) and Spearman (for parameters without normal distribution) correlation coefficients.

Results

96 subjects in total, comprising 30 Crohn's disease patients and 66 healthy controls, were involved in the study. Age and gender distribution were not significantly different between subjects with and without CD (Table 1).

Table 1. Basic characterics of patients and controls

	Controls	Chron´s disease
n	66	30
Age, years (Mean)	49,60±13,82	48.42±15.08
Sex	36 male, 30 female	16 male, 14 female

Liver function tests were assessed within the group both in active and in remission periods, and then were compared with the control group. Albumin levels were quite low in the active period ($p<0,05$). No considerable change was observed in other liver function tests (Table 2).

When total bilirubin values were examined, the bilirubin level among Crohn's disease patients was significantly increased compared to the control group ($p<0,05$). The albumin level was increased in liver functions tests during the remission period,

Table 2. Liver fonctions tests in Crohn´s Disease (active and remission periods) and control group

	Active period	Remission period	Controls
AST (U/L)	20.30±5.86	19.91±7.35	18.38±5.31
ALT (U/L)	22.13±12.86	19.56±11.04	19.71±8.06
GGT (U/L)	22.79±10.80	27.41±18.99	17.55±6.87
ALP (U/L)	72.38±18.27	72.64±19.32	65.22±15.99
ALB (mg/dl)	4.40±0.39	4.56±0.39	4.73±0.39
T. Bilirubine (mg/dl)	0.55±0.22	0.39±0.14	0.44±0.18

while no change was observed in other function tests. However, the total bilirubin value exhibited significant alteration during the remission period.

Discussion

Our study showed that bilirubin increased as a result of chronic inflammation in Crohn's disease and that this increase was more obvious during the activation period. We determined that this increase in bilirubin level in the course of Crohn's disease, particularly during the activation period, was statistically significant and was not correlated with CDAI.

It is known that inflammation plays a critical role in CD pathogenesis [9]. During inflammation, activated neutrophils produce ROS and induce tissue damage.

The ROS attack double bonds within polyunsaturated fatty acids, are able to stimulate lipid peroxidation and as a result cause oxidative damage [10]. Increased ROS affects intracellular signals that regulate processes such as cell growth, differentiation and cell death, and increases oxidative stress [11,12]. In studies conducted in Crohn's disease patients it has been shown that oxidative stress is increased by ROS during the activation period [13,14]. In another study done by Maor et al., it was found that oxidative stress increases while the antioxidant capacity decreases during the activation period of Crohn's disease [13].

Bilirubin is a product of HEM destruction, which is catalyzed by the HO enzyme. There are two subtypes of HO enzyme identified in humans. HO-1 is activated by a very large number of factors, including oxidative stress, and is mostly expressed in tissues [4]. It is known that induction of HO-1 enzyme occurs under stress conditions such as ischaemia, hemorrhagic shock, heat shock, hypoxia, and ROS [15]. Bilirubin production increases as a result of increased activation of the HO enzyme. Our study has shown that there is a significant level of bilirubin in CD patients where inflammation is present compared to the healthy control group. In addition, we identified a statistically significant pitch when we compared bilirubin levels during the activation period with those during the remission period. These results show that bilirubin production is increased as a result of oxidative stress under conditions where inflammation is present.

CDAI is a standard evaluation method used for identifying activation of Crohn's disease. From studies conducted in recent years, it is known that its sensitivity decreases in the presence of irritable bowel syndrome. In recent years, different activation indicators that could be used alongside the CDAI have been studied. It is known that CRP and sedimentation rate, which are used as inflammation indicators, are not specific for CD and cannot be used as activation indicators [16]. Solem et al. observed that the CRP test had 54% sensitivity and 75% specificity for CD in 105 patients [17]. In the study conducted by Yan Lu et al., a decrease in the serum level of omentin-1, which has an adipokine anti-inflammatory role, was significant among Crohn's disease patients during the activation period. In addition, this was better correlated than serum CRP level [18]. In another study, it is stated that granulocyte macrophage colony-stimulating factor antibody, which suppresses the inflammation response, is a parameter that can be used for monitoring disease activation [19]. Our work has shown that serum bilirubin measurement in CD involving inflammation can be a marker that can be used to evaluate disease activity. In addition to this, the bilirubin measurement is more easily accessible and more cost effective compared to other parameters. This parameter can easily be put to use in daily practice.

Conclusion

In summary, our study showed that serum bilirubin was increased in active CD patients compared to controls. There was a correlation of serum bilirubin with disease activity in CD. Serum bilirubin is thus a biomarker for CD disease activity. These findings should be further validated in long-term prospective studies.

Competing interests

The authors declare that they have no competing interests.

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