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The clinic importance of bilirubin parameters in ankylosing spondylitis: Case control study

Ankilozan spondilitte bilirubin parametrelerinin klinik önemi: Vaka kontrol çalışması

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Abstract

Aim: Ankylosing spondylitis (AS) is a chronic disease featuring axial changes, peripheral arthritis and systemic involvement. AS is not only characterized by the strongest genetic contribution for any complex rheumatological disease but is also influenced by environmental and immunological factors. Various proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin- (IL-) 1, IL-6, IL17/28 are probably involved in AS pathogenesis. Recent years IL -23 / IL-17 pathway in the disease pathogenesis has been shown. Bilirubin (Bb) was known to be the end product of hem catabolic pathway, but it was the subject of various studies with antioxidant, anti-inflammatory and immunomodulatory properties in the last decade. Here, the clinic importance of serum Bb parameters in AS patients has been analyzed.

Methods: The study designed as case-control. One hundred (N=100) patients with axial AS diagnosed by 2010 Assesment in Ankylosing Spondylitis International Society (ASAS) Classification Criteria were included to the study. Control group was consisted of 75 patients of similar age, gender and BMI. Participants' age, gender, body mass index (BMI), disease acitivity scores and laboratory data were recorded from the hospital data. Disease activity evaluated by Bath Ankylosing spondylitis disease activity index (BASDAI), Bath Ankylosing spondylitis functional index (BASFI) and Ankylosing spondylitis disease activity score-C-reactive protein (ASDAS_CRP). For these three scores, automatic calculation formulas were used on Internet. ASDAS_CRP>3.5 were accepted as cut-off value for high disease activity. Serum direct Bb, indirect Bb, total Bb, aspartat aminotransferase (AST), alanin aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), amylase, lipase, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were recorded from the hospital records.

Results: The study included 100 AS patients at mean age of 37.9 ± 12 years, 75 controls at mean age of 39.2 ± 5.2 years. There was no significant difference between the two groups in terms of age ($p = 0.12$), gender ($p = 0.32$), and BMI ($p = 0.067$). In the AS group, ESR ($p< 0.001$), CRP ($p < 0.001$), uric acid ($p<0.001$) was significantly higher whereas direct Bb ($P = 0.016$) were significantly lower than controls. In correlation analysis, Bb parameters and disease activity parameters were negatively correlated with each other. When we divided the group according to ASDAS_CRP> 3.5, direct Bb ($p = 0.020$), total Bb ($p = 0.029$) and AST ($p = 0.004$) were significantly lower in high activity group ($N = 25$) and ESR ($p < 0.001$) was significantly higher.

Conclusion: The direct Bb in patients with AS were found significantly low and negatively correlated with disease activity, this supports the role of oxidative stress in AS disease pathogenesis. Bb can be used as a biomarker in diagnosis and follow up in AS disease.

Keywords: Ankylosing spondylitis, Bilirubin, Inflammation, Oxidative stress

Öz

Amaç: Ankilozan spondilit (AS) aksiyal değişiklikler, periferik artrit ve sistemik tutulum içeren kronik bir hastalıktır. AS herhangi bir komplike romatizmal hastalık gibi sadece en güçlü genetik katkı ile karakterize edilmez, aynı zamanda çevresel ve immünolojik faktörlerden de etkilenir. Tümör nekroz faktörü (TNF), interlökin- (IL-) 1, IL-6, IL17 / 28 gibi çeşitli proinflamatuar sitokinler muhtemelen AS patogenezinde rol oynar. Son yıllarda hastalık patogenezinde IL-23 / IL-17 yolu gösterilmiştir. Bilirubin (Bb) hem katabolik yolun son ürünüdür hem de son on yılda antioksidan, antienflamatuar ve immünmodülatör özellikleri olan çeşitli çalışmaların konusu olmuştur. Burada AS hastalarında serum Bb parametrelerinin klinik önemi analiz edilmiştir.

Yöntemler: Çalışma vaka-kontrol olarak planlandı. Uluslar arası Ankilozan Spondilit Topluluğu 2010 Sınıflandırma Kriterleri'ne göre (ASAS) aksiyal AS tanısı almış 100 hasta (N = 100) çalışmaya dahil edildi. Kontrol grubu benzer yaş, cinsiyet ve VKİ olan 75 kişiden oluşmaktaydı. Katılımcıların yaş, cinsiyet, vücut kitle indeksi (BMI), hastalık skoru puanları ve laboratuvar verileri hastane verilerinden kaydedildi. Hastalık aktivitesi Bath Ankilozan Spondilit Hastalığı Aktivite İndeksi (BASDAI), Bath Ankilozan Spondilit Fonksiyonel İndeks (BASFI) ve Ankilozan Spondilit Hastalığı Aktivite skoru-C-reaktif protein (ASDAS_CRP) ile değerlendirildi. Bu üç puan için, internette otomatik hesaplama formülleri kullanıldı. ASDAS_CRP> 3,5 yüksek hastalık aktivitesi için eşik değer olarak kabul edildi. Serum direkt Bb, indirekt Bb, total Bb, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), alkalen fosfataz (ALP), laktat dehidrojenaz (LDH), gama glutamil transferaz (GGT), amilaz, lipaz, eritrosit sedimentasyon hızı (ESR) ve C-reaktif protein (CRP) değerleri hastane kayıtlarından kaydedildi.

Bulgular: Çalışmaya yaş ortalaması 37,9 ± 12 yıl olan 100 AS hastası, yaş ortalaması 39,2 ± 5,2 yıl olan 75 kontrol alındı. İki grup arasında yaş ($p = 0.12$), cinsiyet ($p = 0.32$) ve VKİ ($p = 0.067$) açısından anlamlı fark yoktu. AS grubunda ESR ($p < 0.001$), CRP ($p< 0.001$), Bb ($p = 0.016$) anlamlı düşük; ürik asit ($p< 0.001$) kontrollerden anlamlı olarak yüksek bulundu.

Korelasyon analizinde, Bb parametreleri ve hastalık aktivite parametreleri birbirleriyle negatif korelasyon göstermiştir. ASDAS_CRP> 3,5'e göre gruplandırıldığında, direkt Bb ($p = 0,020$), total Bb ($p = 0,029$) ve AST ($p = 0,004$) yüksek aktivite grubunda ($N = 25$) anlamlı düşük; ESR ($p <0,001$) anlamlı olarak daha yüksekti.

Sonuç: AS'li hastalarda direk Bb, hastalık aktivitesi ile negatif ilişkili ve düşük idi, bu sonuç AS hastalık patogenezinde oksidatif stresin rolünü desteklemektedir. Direk Bb, AS hastalığında tanı ve izlemede biyobelirteç olarak kullanılabilir.

Anahtar kelimeler: Ankilozan spondilit, Bilirubin, İnflamasyon, Oksidatif stres

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that causes insidious, progressive, axial and peripheral joint involvement lead to physical disability. The presence of genetic predisposition and autoantibodies leads to autoimmune and autoinflammatory etiology. Microbiota and biomechanical stress focus on the initiation and maintenance of inflammation for environmental factors that trigger genetic [1]. Although the underlying mechanism of AS pathogenesis is not yet elucidated, it is known that human leucocyte antigen (HLA)-B27 is responsible for a significant increase in the risk of disease development. Current treatment includes non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatismal drugs (DMARD). In recent years, the prominent effect of interleukin (IL) -23 / IL-17 on the pathogenesis of disease and the use of targeted therapies have been demonstrated [2].

Bilirubin (Bb) is a tetrapyrrole which is the product of hem destruction. Majority of the Bb is obtained from hemoprotein breakdown and a smaller part from the hemoglobin breakdown. In serum, Bb is measured as both direct and total Bb. Excessive production or a defect in the intake or conjugation can lead to a sudden hyperbilirubinemia. In its indirect form, Bb dissolves in water and sticks to the brain, sclera and mucous membranes. Attempts are made to reduce this effect by ensuring the albumin attaches to the plasma. Bb has been shown to be an essential antioxidant both in vitro and in vivo. Bb reacts with reactive oxygen species to form hydrophilic products and they are excreted by the urine. Oxidative metabolites of Bb, biopyrrins are sensitive urinary markers of oxidative stress [3].

The aim of the present study was to examine the clinic importance of Bb parameters and its association with disease activity in AS.

Materials and methods

The study designed as case-control. One hundred (N=100) patients with axial AS diagnosed by 2010 Assessment in Ankylosing Spondylitis International Society (ASAS) Classification Criteria were included to the study. Control group was consisted of 75 patients of similar age, gender and BMI. Participants' age, gender, body mass index (BMI), disease activity scores and laboratory data were recorded from the hospital data.

Disease activity evaluated by Bath Ankylosing spondylitis disease activity (BASDAI), Bath Ankylosing spondylitis functional index (BASFI) and Ankylosing spondylitis disease activity score-C-reactive protein (ASDAS_CRP). For these three scores, automatic calculation formulas were used on Internet. ASDAS_CRP>3.5 were accepted as cut-off value for high disease activity.

Serum direct Bb, indirect Bb, total Bb, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), amylase, lipase, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were recorded from the hospital records. The acute phase reactants (ESR and CRP) were used for disease activity. Patients with other inflammatory rheumatological disease, malignancy, infection, primary liver disease and a history of hepatobiliary surgery were not included in the study.

Statistical analysis

Analyses were performed using Statistical Package for the Social Sciences 22 (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, USA). Continuous data were presented as mean±SD and categorical variables were summarized as percentages. Kolmogorov Smirnov test was used for the evaluation of normal distribution. Comparisons between groups were made using Chi-square tests for categorical variables, independent samples Student's t tests for normally distributed continuous variables and Mann-Whitney U tests when the distribution was skewed. Spearman test is used for correlation analysis. A p value <0.05 was considered statistically significant. As a result of the power analysis performed, the minimum number of subjects required in each group was determined as 65 so that the difference of 0.05 units between the two group averages could be meaningful. Type 1 error = 0.01, power of test: 0.08.

Results

The study included 100 AS patients at mean age of 37.9 ± 12 years, 75 controls at mean age of 39.2 ± 5.2 years. There was no significant difference between the two groups in terms of age (p = 0.12), gender (p = 0.32), and BMI (p = 0.067). The descriptive and analytical data for the study are summarized in Table 1. In the AS group, ESR (p <0.001), CRP (p < 0.001), and uric acid (p < 0.001) were significantly higher whereas direct Bb (p = 0.016) was lower than control (Figure 1).

Table 1: Descriptive and analytic data of the groups

	AS (N=100) mean±std	Control (N=75) mean±std	P
Age (year)	37.9±12	39.2±5.2	0.12
Gender (female/male)	29/69	12/63	0.078
BMI (kg/m^2)	27.0±4.5	26.7±6.9	0.08
ESR (mm/h)*	29.5±18.3	12.3±10	<0.001
CRP (mg/dL)*	8.2±9.6	1.1±1.6	<0.001
Direct Bb* (0.1-0.4 mg/dL)	0.166±0.077	0.197±0.061	0.016
İndirect Bb (0.2-0.7 mg/dL)	0.426±0.332	0.339±0.174	0.068
TotalBb (0.2-1.2 mg/dL)	0.594±0.360	0.537±0.226	0.302
Uric acid* (mg/dL)	5.5±1.3	4.2±1.3	<0.001
AST (0-40 UI/L)	25±7.6	23.5±5.3	0.64
ALT (0-56 UI/L)	25.2±17.1	24.4±10.1	0.63
GGT (0-65 UI/L)	28±15.1	27.4±12.3	0.83
ALP (25-100 IU/L)	79.1±20.6	79.2±24.1	0.25
LDH (U/L)	184.1±32.3	167.4±28.1	0.08
Amylase (U/L)	61.8±24.2	60±17.6	0.34
Lipase (U/L)	32.9±12.6	27±15.4	0.06
BASDAI (0-10 cm)	4.1±2.0	-	
BASFI (0-10 cm)	3.5±2.3	-	
ASDAS_CRP	2.7±1	-	

BMI: body mass Index, Bb: bilirubin, ESR: Erythrocytes sedimentation rate, CRP: C-reactive protein, BASDAI: Bath Ankylosing spondylitis disease activity Index, ASDAS_CRP: Ankylosing spondylitis disease activity score-C-reactive protein, BASFI: Bath Ankylosing spondylitis functional index, * statistically significance, p<0.05

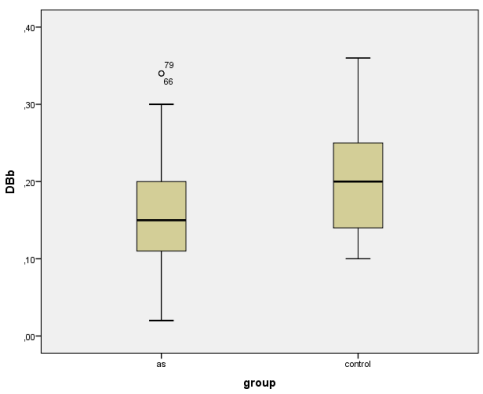

Figure 1: Boxplot of direct Bb (DBb) according to the groups

In correlation analysis, Bb parameters and disease activity parameters were negatively correlated with each other (Table 2). When we divided the group according to ASDAS_CRP> 3.5, direct Bb (p = 0.020) (Figure 2), total Bb (p = 0.029) and AST (p = 0.004) were significantly lower in the high activity group (N = 25); whereas ESR (p < 0.001) was significantly higher than inactive group (N=75).

Table 2: Correlation analysis of bilirubin parameters with disease activity scores

	rho	P
Direct Bb-CRP	-0.299	0.013
Direct Bb-ASDAS_CRP	-0.357	0.020
Direct Bb-BASFI	-0.702	<0.001
Indirect Bb-ESR	-0.315	0.001
Indirect Bb-ASDAS_CRP	-0.312	0.045
Indirect Bb-BASFI	-0.615	<0.001
Total Bb-ESR	-0.214	0.021
Total Bb-ASDAS_CRP	-0.357	0.020
Total Bb-BASFI	-0.684	<0.001

Bb: bilirubin, ESR: Erythrocytes sedimentation rate, CRP: C-reactive protein, BASDAI: Bath Ankylosing spondylitis disease activity index, ASDAS_CRP: Ankylosing spondylitis disease activity score-C-reactive protein, BASFI: Bath Ankylosing spondylitis functional index, * statistically significance, p<0.05.

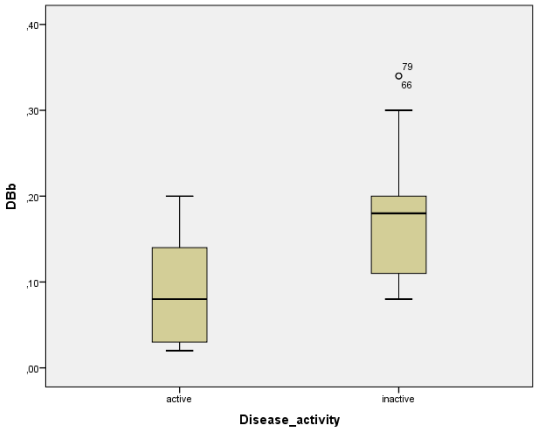

Figure 2: Boxplot of Direct Bb (DBb) according to the disease activity in AS group

Discussion

Spondyloarthropathies (SpA) describe a group of inflammatory diseases characterized by inflammation involving axial joints and / or peripheral arthritis, enthesitis, and dactilitis. Disease development is determined by the presence of genes, especially HLA-B27. In animal models, the direct effect of HLAB27 on disease development has been demonstrated. The propensity of HLAB27 to be expressed in the natural immune system and to form different structural forms that can lead to activation has been discovered [4]. Genetic studies have specifically identified the immunological function associated with gene polymorphism that controls interleukin (IL) -23 / IL-17 pathway. The efficacy of IL-17 inhibitors in SpA patients supports the importance of this pathway [5]. The demonstration of microscopic gout inflammation in the vast majority of SpA patients supports the pathogenic effect of commensal microbiota [6,7].

AS is the prototype of SpA and is characterized by spinal inflammation that starts with sacroiliac joints and results in joint ankylosis. The genetic relationship between HLA-B27 and inflammatory cytokine pathways has been shown in a number of studies. Inflammatory cytokines, tumor necrosis factor (TNF), interleukin- (IL-) 1, IL-6, and IL-23 / IL-17 are prominent. In particular, IL-17 plays a dominant role in the inflammatory and proliferative pathway [8-10]. Early diagnosis of the disease is important in terms of treatment effectiveness. Since 1984 modified New York criteria used in the diagnosis of the disease was unsuccessful in early period of the disease, ASAS developed new criteria: (1) A predominantly axial disease, AS and non-radiographic axial SpA including termed axial SpA; (2) New criteria for peripheral SpA have been developed in 2010. Criteria developed by ASAS for axial SpA are an important step in early diagnosis and disease control, while the non-radiographic axial SpA clinical process is still unclear [11].

Serum total Bb is routinely used in the identification of hepatobiliary and hemolytic diseases. Especially hepatocyte damage including acute hepatitis, cholestatic problems, genetic diseases related to Bb uptake or secretion, hemolytic diseases lead to increase in blood total Bb in adults. In the last decade, Bb, a product of hem degradation, has begun to attract attention. The benefits of increased Bb are supported by antioxidant, anti-inflammatory and immunosuppressive properties in both animal and in vitro experiments. The most well-known immunomodulatory effect that suppresses inflammation is its redox (antioxidative) capacity [12-16]. Clinical trials have been associated high Bb with low risk of myocardial infarction, coronary artery disease, stroke, lung cancer, diabetes, schizophrenia, and chronic obstructive lung disease [17-19]. For the patients with psoriasis, a negative relation was found between total Bb values and inflammatory parameters [20]. Peng et al. [21] detected lower direct Bb values and higher CRP values when assessing neurogenic inflammation in patients with migraine similary with our study. Up to date there is no study examining the Bb parameters in AS in the literature.

Endoplasmic retinaculum (ER) stress, oxidative stress, and inflammatory responses contain common major defense networks for the rescue and adaptation of cells from stressful situations caused by biochemical, physiological and pathological stimuli. In many current publications we see that oxidative stress and inflammation are related to the onset and progression of a wide variety of diseases [22]. In chronic inflammatory rheumatological diseases various biomarkers have been the subjects of clinical trials [23]. New cheap and practical biomarkers which correctly show chronic inflammation are needed in the clinical follow up of the diseases [24]. Liver functional tests in AS have been the subject of some studies. Robinson et al. [25] observed abnormal high GGT and ALP levels as secondary to inflammation in AS patients. İn the study by Seehan et al. [26] they similarly found abnormal high levels of ALP unrelated with drug therapy or disease activity in AS patients. They suggest that bone is the source of the increased ALP. İn our study serum GGT, ALP levels was found similar with control group.

Additionally, we found that direct Bb was significantly lower in AS group. All Bb parameters were negatively correlated with disease activity scores. We can say that the chronic inflammation and oxidative stress involved in the pathogenesis of AS increasing with the severity of the disease. This is supported by the low Bb parameters that are indicative of oxidative stress. Often, even if the disease is active in AS patients, the elevation of acute phase reactants does not correlate with clinical relevance. Measurement of serum Bb parameters can be useful in this case as practical and easy biomarkers. Additionally the serum uric acid level was found significantly

higher in AS as expected. İn most of chronic inflammatory rheumatological diseases we find high uric acid results depending on the high inflammation. Hyperuricemia is not only a risk factor for gout but also an independent determinant of hypertension, diabetes, and chronic kidney diseases. Also low-grade inflammation is found positively associated with hyperuricemia [27].

Limitation of the study

In chronic inflammatory rheumatological diseases the disease itself and the use of NSAIDs, biological and non-biological DMARDs may effect liver enzymes included serum Bb parameters. It is the limit of study not considering the medication used by patients. Smoking, anemia may also affect the Bb values. Additionally we see that the patients in the study group mostly were in inactive period according to ASDAS_CRP results.

Conclusion

The direct Bb in patients with AS were found significantly low and negatively correlated with disease activity, this supports the role of oxidative stress in AS disease pathogenesis. Direct Bb can be used as a biomarker in diagnosis and follow up in AS disease.

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