# Evaluation of Osteoarticular Involvement Associated with Brucellosis in Children

Çocukluk Çağı Brusellozuna İlişkin Osteoartiküler Tutulumun Değerlendirilmesi

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## ABSTRACT

**Aim:** Brucellosis is a significant public health problem with high morbidity. Its most frequent complication is osteoarticular involvement. The study aimed to evaluate the relationship of osteoarticular involvement with clinical features and prognosis in children with brucellosis. **Material and Methods:** This retrospective study included pediatric patients between the ages

of 1 and 18 years who were hospitalized and diagnosed with brucellosis between 2015 and 2020, and were regularly followed up. and all their findings and osteoarticular involvement data within the last two years were recorded. Clinical features, laboratory findings, osteoarticular involvement, and relapse rates of the patients were evaluated.

**Results:** A total of 80 patients were included study. During the follow-up period, relapse developed in 14 (17.5%) patients. The most commonly affected joints were right (40%, n=32) and left (26.3%, n=21) hips, then right (27.5%, n=22) and left (23.8%, n=19) knees. Shoulder joint involvement rates and C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine transaminase (ALT), and aspartate aminotransferase (AST) levels were statistically significantly higher in the relapse group (p=0.016, p=0.003, p=0.001, p<0.001, p<0.001, respectively). There was no significant difference in demographic characteristics, clinical features, and treatment responses of the patients between age groups, except weakness and sweating complaints that were high among older children (p=0.036).

**Conclusion:** High admission ALT, AST, CRP, and ESR levels in brucellosis cases with osteoarticular involvement and the presence of shoulder joint involvement, albeit rarely, can be a warning sign in terms of relapse. Patients should be closely followed up in terms of brucellosis complications.

Keywords: Brucellosis; osteoarthritis; sacroiliac joint; shoulder joint; relapse.

#### ÖZ

**Amaç:** Bruselloz, yüksek morbiditeye sahip önemli bir halk sağlığı sorunudur. En sık görülen komplikasyonu osteoartiküler tutulumdur. Bu çalışmanın amacı, bruselloz tanılı çocuklarda osteoartiküler tutulumun klinik özellikler ve prognoz ile ilişkisini değerlendirmektir.

**Gereç ve Yöntemler:** Geriye dönük bu çalışmaya, 2015 ve 2020 yılları arasında bruselloz tanısıyla hastaneye yatırılan ve düzenli takipleri yapılan 1 ile 18 yaş aralığındaki pediatrik hastalar dahil edildi. Son iki yıldaki tüm bulguları ve osteoartiküler tutulum verileri kaydedildi. Hastaların klinik özellikleri, laboratuvar bulguları, osteoartiküler tutulum ve nüks oranları değerlendirildi.

**Bulgular:** Çalışmaya toplam 80 hasta dahil edildi. Takip süresinde hastaların 14 (%17,5) hastada relaps gelişti. En sık etkilenen eklemler sağ (%40, n=32) ve sol (%26,3, n=21) kalçalar, ardından sağ (%27,5, n=22) ve sol (%23,8, n=19) dizlerdi. Omuz eklem tutulum oranları ile C-reaktif protein (CRP), eritrosit sedimantasyon hızı (ESH), alanin transaminaz (ALT) ve aspartat aminotransferaz (AST) düzeyleri relaps grubunda istatistiksel olarak anlamlı şekilde daha yüksekti (sırasıyla p=0,016, p=0,003, p=0,001, p<0,001, p<0,001). Sadece yaşı büyük çocuklarda daha yüksek olan güçsüzlük ve terleme şikayetleri dışında (p=0,036), hastaların demografik özellikleri, klinik özellikleri ve tedavi yanıtları bakımından yaş grupları arasında anlamlı bir farklılık yoktu.

**Sonuç:** Osteoartiküler tutulumu olan bruselloz olgularında yüksek başvuru ALT, AST, CRP ve ESR düzeyleri ve nadir de olsa omuz eklem tutulumunun varlığı relaps açısından uyarıcı olabilir. Hastalar bruselloz komplikasyonları açısından yakından takip edilmelidir. **Anahtar kelimeler:** Bruselloz; osteoartrit; sakroiliak eklem; omuz eklemi; relaps.

## **INTRODUCTION**

Brucellosis is a zoonotic disease caused by gram-negative Brucella species bacteria (1). Its incidence rate varies between 0.3-100/100.000 and from region to region, and the incidence rate of osteoarticular involvement varies between 10-85% all around the world (2). This disease is more frequently seen in developing countries, infects humans through direct contact with infected animals, inhalation, and consumption of non-pasteurized milk or dairy products, and leads to severe problems, especially in children (1-3). It is endemic in certain regions of Türkiye (3). The disease affects mostly hematological, gastrointestinal, cardiorespiratory, and musculoskeletal systems (1,4). It has a low mortality, but delayed or inappropriate/inadequate treatment increases its morbidity risk (4,5). This disease puts patients at risk in terms of severe complications and relapse (5).

The most frequent complication seen in brucellosis is osteoarticular involvement, which can cause severe morbidity (6,7). Osteoarticular brucellosis covers arthritis, tenosynovitis, bursitis, sacroiliitis, spondylitis, and osteomyelitis. Detailed physical examination and history are necessary for correct diagnosis and treatment management in order not to overlook cases of brucellosis with osteoarticular involvement. Data on the effect of joint involvement sites on the rate of relapse are limited.

The study aimed to evaluate osteoarticular involvement in cases with brucellosis, along with patient characteristics and in line with the literature, and to reveal its relationship with the clinical features and the prognosis in terms of demonstrating their quality of life.

### MATERIAL AND METHODS

Eighty cases between the ages of 1 and 18 years who were hospitalized and diagnosed with brucellosis in the pediatric clinic of our hospital between 2015 and 2020 were regularly followed up, and all their findings and osteoarticular involvement data within the last two years were recorded. Those having joint dysplasia, arthritis, chronic arthritis, and trauma before the diagnosis were excluded from the study.

A form was developed to record the patients' age, gender, admission duration, complaints, intra-family infection, physical examination findings, and detailed joint findings, as well as admission whole blood count, acute phase reactants (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) value), liver function tests, serum creatinine values, *Brucella* standard tube agglutination test, Coombs test, blood culture results, if any, radiological examination results, if any, and all information covering treatment approaches, duration, and results. An increase in the *Brucella* tube agglutination test values of the patients within six months of the follow-up and/or the development of clinical findings (any of them: fever, hepatomegaly, splenomegaly, weakness, and/or arthralgia or arthritis) was defined as relapse.

In addition to clinical symptoms and findings, brucellosis was diagnosed when the *Brucella* standard tube agglutination test was positive (1/160 titer), or there was at least a four-fold increase in the titer in serum samples collected with an interval of 2-3 weeks, and/or *Brucella* spp. bacteria developed in the blood or sterile body fluid culture. If the patient's complaints lasted less than 2 months, it was

considered acute, if between 2 months and 1 year, it was considered subacute, and if it continued for more than 1 year, it was considered chronic brucellosis (5,6). All cases were examined with abdominal ultrasonography (USG). Osteoarticular involvement means arthralgia and arthritis. For determining arthritis, in addition to arthralgia, movement limitation, increased interarticular fluid, and edema were evaluated. Only leg pain or joint pain was not evaluated as joint involvement. Joint USG was performed on patients for whom clinical osteoarticular involvement was detected. Abdominal USG was performed on every patient with brucellosis diagnosis admitted to the service in order to screen for the presence of hepatosplenomegaly that could not be detected during examination. Joint USG was performed on all patients. Magnetic resonance imaging (MRI) was performed on only 3 patients. The standard treatment approach in children older than 8 years is a combination of doxycycline with rifampin and/or gentamicin. Doxycycline is not used in children younger than 8 years because it causes discoloration of the teeth. In this age group, gentamicin, streptomycin, or rifampicin treatments are added to trimethoprim-sulfamethoxazole treatment (5,6).

Patients were divided into three groups according to their ages as 1-5 years, 6-11 years, and  $\geq$ 12 years. Patients who did not show complete clinical recovery within 4 weeks, and especially those with slow regression of joint findings, were considered to have a partial response. All results were recorded from patient files.

The study was approved by the local ethics committee of the Kafkas University (26.02.2020, 06/22).

### **Statistical Analysis**

The data was evaluated using the IBM SPSS v.26.0 software. The Shapiro-Wilk and Kolmogorov-Smirnov normality tests were used to determine the distribution patterns of the variables. Continuous data are presented as mean and standard deviation, or median, accompanied by the interquartile range, minimum-maximum values. The Mann-Whitney U test and Student's t-test were used for comparisons between two groups of continuous variables, and the Kruskal-Wallis test and One-Way ANOVA tests were used for comparisons between more than two groups, respectively. The chi-squared test, Fisher's exact test, and Fisher-Freeman-Halton test were used to analyze categorical variables. Statistical significance will be accepted at the level of p<0.05.

## RESULTS

Of the 80 patients with osteoarticular involvement included in the study, 54 (67.5%) were male and 26 (32.5%) were female. The median age was 12 (range, 1-17) years. 52.5% (n=42) of the cases were admitted in the summer, and 95% (n=76) of the patients had a history of livestock/domestic transmission, while 70% (n=56) had a history of raw milk/dairy products consumption.

All patients had arthralgia. While 57.5% (n=46) of the patients were admitted with monoarthritis/arthralgia, 42.5% (n=34) presented with at least 2 joint involvements. Weakness and sweating complaints were significantly higher in older children (p=0.036). Among the most frequently involved joints, the right hip was involved by 40% (n=32), the left hip by 26.3% (n=21), the right knee

by 27.5% (n=22), and the left knee by 23.8% (n=19). 93.7% (n=75) of the patients presented with an acute clinic, while 6.3% (n=5) had a subacute clinic. Rose Bengal and agglutination test positivity was 93.8% (n=75) and 96.3% (n=77), respectively, and the growth rate in blood/joint aspirate culture was 6.3% (n=5). Demographic and clinical characteristics of the patients were presented in Table 1.

Blood cultures were taken from 42 patients, but positivity was detected in 3 patients. Joint fluid cultures were taken from 2 patients, and positivity was detected. Kx result information could not be accessed from the file or the system. The file contained information that a growth signal was received.

Relapse developed in 14 (17.5%) patients within six months. Septic arthritis developed only in two patients, a 13-year-old female and a 14-year-old male. Response to non-complication treatment was taken, and they recovered. No headache was seen in patients with relapse, while there were 19 (28.8%) patients with headache in those without (p=0.003). ESR (p=0.001), CRP (p=0.003),

ALT (p<0.001), and AST (p<0.001) values at admission were found statistically significantly higher in the relapse group. There was no other significant difference between the patients with and without relapse (Table 2).

The rate of sacroiliac joint was higher in the relapse group, but the difference was not at the level of statistical significance (p=0.068). On the other hand, shoulder joint involvement both for left and right shoulders was found significantly higher in the patients with relapse (p=0.016). No other significant difference was found in joint involvement sites between the patients with and without relapse (Table 3).

### DISCUSSION

In the present study, relapse developed in 14 out of the 80 children diagnosed with brucellosis, accompanied by active osteoarticular involvement. The most frequent involvement was the hip, and the upper extremity joints were rarely involved. Admission ALT, AST, CRP, and ESR values were higher, and shoulder joint involvement was more frequent in the patients with relapse.

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	1-5 years	6-11 years 12-18 years		n	Total
	( <b>n=9</b> )	(n=23)	( <b>n=48</b> )	þ	( <b>n=80</b> )
Gender, n (%)					
Male	5 (55.6)	14 (60.9)	35 (72.9)	0.430	54 (67.5)
Female	4 (44.4)	9 (39.1)	13 (27.1)	0.450	26 (32.5)
Follow-up period (months)	28.33±12.91	$21.98 \pm 2.49$	$22.55 \pm 1.81$	0.941	22.28±1.37
Admission Season, n (%)					
Spring	3 (33.3)	2 (8.7)	6 (12.5)		11 (13.8)
Summer	4 (44.4)	10 (43.5)	28 (58.3)		42 (52.5)
Autumn	1 (11.1)	4 (17.4)	7 (14.6)	0.427	12 (15.0)
Winter	1 (11.1)	7 (30.4)	7 (14.6)		15 (18.8)
Livestock/Domestic Transmission, n (%)	8 (88.9)	21 (91.3)	47 (97.9)	0.199	76 (95.0)
<b>Raw Milk/Dairy Product Consumption</b> , n (%)	4 (44.4)	15 (65.2)	37 (77.1)	0.123	56 (70.0)
<b>Fever</b> , n (%)	8 (88.9)	17 (73.9)	38 (79.2)	0.723	63 (78.8)
Weakness/Sweating, n (%)	0 (0.0)	7 (30.4)	21 (43.8)	0.036	28 (35.0)
Stomachache, n (%)	3 (33.3)	4 (17.4)	7 (14.6)	0.360	14 (17.5)
Headache, n (%)	5 (55.6)	4 (17.4)	10 (20.8)	0.056	19 (23.8)
Joint Involvement, n (%)					
Monoarthritis/arthralgia	8 (89.9)	12 (52.2)	26 (54.2)	0.129	46 (57.5)
Polyarthritis/arthralgia	1 (11.1)	11 (47.8)	22 (45.8)	0.128	34 (42.5)
Joint Involvement, n (%)					
Monoarthritis/arthralgia	8 (88.9)	12 (52.2)	26 (54.2)		46 (57.5)
2	1 (11.1)	7(30.4)	14 (29.2)	0 791	22 (27.5)
3	0 (0.0)	2 (8.7)	4 (8.3)	0.771	6 (7.5)
>4	0 (0.0)	2 (8.7)	4 (8.3)		6 (7.5)
Hepatosplenomegaly, n (%)	1 (11.1)	4 (17.4)	10 (20.8)	0.919	15 (18.9)
Neurological Involvement, n (%)	0 (0.0)	0 (0.0)	2 (4.2)	>0.999	2 (2.5)
Rose Bengal (+), n (%)	8 (88.9)	22 (95.6)	45(93.7)	0.632	75 (93.8)
Agglutination test (+), n (%)	9 (100)	22 (95.6)	46 (95.8)	>0.999	77 (96.3)
Blood/Joint Aspirate Culture (+), n (%)	1 (11.1)	1 (4.3)	3 (6.3)	0.632	5 (6.3)
Treatment, n (%)					
TMP-STX + Genta	9 (100)	10 (43.5)	-		19 (23.8)
Dox + RIF + Genta	-	13 (56.5)	48 (100)	-	61 (76.2)
Treatment Response, n (%)					
Full Response	7 (10.6)	20 (30.3)	39 (59.1)	0.756	66 (82.5)
Partial Response	2 (14.3)	3 (21.4)	9 (64.3)	0.750	14 (17.5)

IMP-STX: trimethoprim suffamethoxazole, Genta: gentamicin, Dox: doxycycline, RIF: rifampicin, patients who did not show complete clinical recovery within 4 weeks, and especially those with slow regression of joint findings, were considered to have a partial response

	<b>Relapse</b> (+) (n=14)	<b>Relapse</b> (-) (n=66)	р	
Age Group, n (%)				
1-5 years	2 (14.3)	7 (10.6)		
6-11 years	3 (21.4)	20 (30.3)	0.756	
12-18 years	9 (64.3)	39 (59.1)		
Gender, n (%)				
Male	9 (64.3)	45 (68.2)	0.763	
Female	5 (35.7)	21 (31.8)		
Admission Season, n (%)	2 (21.4)	9 (12 1)		
Summer	5 (21.4) 9 (64.3)	8 (12.1) 33 (50 0)		
Autumn	$\frac{1}{7}$	11 (16 7)	0.435	
Winter	1(7.1) 1(7.1)	14(212)		
Fever, n (%)	12 (85.7)	51 (77.3)	0.722	
Weakness/Sweating, n (%)	7 (50.0)	21 (31.8)	0.226	
Stomachache, n (%)	0 (0.0)	14 (21.2)	0.114	
Headache, n (%)	0 (0.0)	19 (28.8)	0.033	
Joint Involvement, n (%)				
Monoarthritis/arthralgia	9 (64.3)	37 (56.1)	0.572	
Polyarthritis/arthralgia	5 (35.7)	29 (43.9)		
Joint Involvement, n (%)				
Monoarthritis/arthralgia	9 (64.3)	37 (56.1)		
2	3 (21.4)	19 (28.8)	0.954	
3	1(7.1)	5 (7.6)		
>4	1 (7.1)	5 (7.6)		
Hepatosplenomegaly, n (%)	3 (21.4)	12 (18.2)	0.720	
Neurological Involvement, n (%)	1 (7.1)	1 (1.7)	0.321	
<b>WBC</b> (/mm3)	6.1 (5.5-6.8) [3.3-8.2]	6.5 (5.1-7.9) [3.2-13.5]	0.449	
Hb (g/dL)	13.2 (12-14) [10-15.6]	13.3 (12-14) [8.3-16.7]	0.819	
<b>PLT</b> (/mm3)	263.5 (242-324) [192-414]	282.5 (230-358) [170-473]	0.767	
ESR (mm/hour)	25 (14-39) [4-67]	8 (5-20) [2-37]	0.001	
<b>CRP</b> (mg/dL)	1.3 (0.1-3.7) [0.04-8.9]	0.3 (0.1-0.9) [0.01-4.85]	0.003	
ALT (U/L)	131 (60-226) [29-388]	30 (22-56) [11-141]	<0.001	
AST (U/L)	96 (78-119) [21-382]	25 (15-51) [10-211]	< 0.001	
Urea (mg/dL)	22.92±6.56	24.04±6.75	0.574	
<b>Creatinine</b> (mg/dL)	0 54+0 19	0 57+0 16	0 563	

Table 2. Evaluation of patients with and without relapse in terms of demographic characteristics and laboratory results at admission

 Creatinine (mg/dL)
 0.54±0.19
 0.57±0.16
 0.563

 WBC: white blood cell, Hb: hemoglobin, PLT: platelet, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: alanine transaminase, AST: aspartate aminotransferase, descriptive statistics for numerical variables were presented as median (25<sup>th</sup>-75<sup>th</sup> percentile) [minimum-maximum] or mean±standard deviation

Table 3. Evaluating the relationship	p between the osteoarticular involvement site and relapse
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	<b>Relapse</b> (+) (n=14)	<b>Relapse</b> (-) (n=66)	р	Total (n=80)
Right Hip, n (%)	7 (50.0)	25 (37.9)	0.400	32 (40.0)
Left Hip, n (%)	3 (21.4)	18 (27.3)	0.751	21 (26.3)
Right Knee, n (%)	2 (14.3)	20 (30.3)	0.328	22 (27.5)
Left Knee, n (%)	3 (21.4)	16 (24.2)	>0.999	19 (23.8)
Right Ankle, n (%)	0 (0.0)	9 (13.6)	0.348	9 (11.3)
Left Ankle, n (%)	0 (0.0)	7 (10.6)	0.344	7 (8.8)
Sacroiliac Joint, n (%)	4 (28.6)	6 (9.1)	0.068	10 (12.5)
Right Shoulder, n (%)	3 (21.4)	1 (1.5)	0.016	4 (5.0)
Left Shoulder, n (%)	3 (21.4)	1 (1.5)	0.016	4 (5.0)
Right Elbow, n (%)	1 (7.1)	1 (1.5)	0.321	2 (2.5)
Left Elbow, n (%)	0 (0.0)	6 (9.1)	0.584	6 (7.5)
Right Wrist, n (%)	1 (7.1)	5 (7.6)	>0.999	6 (7.5)
Left Wrist, n (%)	2 (14.3)	3 (4.5)	0.209	5 (6.3)

Various studies conducted on Brucella reported that the highest risk factor for the disease was non-pasteurized dairy products, especially cheese (2,8-10). Likewise, in the present study, the patients had a history of direct raw milk/dairy products consumption by 70% (n=56) and livestock/domestic transmission by 95% (n=76).

The clinical course can be acute, subacute, and chronic. The disease can sometimes display subclinical and localized infection symptoms (9). 93.8% of the complaints of patients in the present study developed acutely. The main clinical symptoms seen in children with brucellosis are fever, loss of appetite, weight loss, diffuse muscle, joint pain, headache, stomachache, and night sweats (3,9,10). The main complaints of the patients in this study were fever, arthralgia, weakness and sweating, headache, and stomachache, which were compatible with the literature.

In the laboratory, the gold standard for diagnosis is culture positivity, but it is highly difficult to detect. The culture positivity rate in studies is around 3-36% (5,11,12). Therefore, when serological tests are not helpful for diagnosis, producing microorganisms in blood, bone marrow, or other infected tissue cultures and joint aspiration material can help with diagnosis (11). In the present study, blood/joint fluid culture positivity was determined in 6.3% (n=5) of the patients. In the whole blood count, we can find some clues. Mild leukocytosis is expected in the whole blood count in the presence of brucellosis with osteoarticular involvement (5). The related studies revealed a distinct increase in acute-phase reactants, especially in the inflammation period (13,14). In the present study, acute phase reactants as well as ALT and AST values were distinctively higher than the admission laboratory values of the patients with relapse. In their study, Bozukluhan et al. (15) found that serum ALT and AST values were significantly higher in brucellosis cases compared to healthy controls. It is known that ALT and AST values increase in case of inflammation in the liver (15,16). Higher values in patients with relapse can indicate that subclinical inflammation will continue.

The involvement mostly manifests itself in the joints as arthritis. The incidence rate of this involvement varies between 10-85% all around the world. In another study, Brucella arthritis incidence was reported to vary between 10% and 56% (8,17). It was compatible with the literature. The most frequently involved joints are large joints such as the knee, hip, ankle, and sacroiliac joints. It is rarely seen in the upper extremities (4,6,7,18). Joint involvements determined in the present study are compatible with the literature. Arthritis is generally in the form of monoarthritis or asymmetrical peripheral oligoarthritis (6,7). Likewise, monoarthritis/arthralgia percentage (57.5%) was higher than in polyarthritis patients in the present study. 42.5% of the cases had involvement in more than one joint. Brucella arthritis generally does not cause destruction or permanent functional disorder. Response to treatment is good, and relapse is rarely seen. Joint symptoms did not repeat in patients with relapse in the present study (2,17,19).

In brucellosis cases who did not develop complications, relapse rates ranged between 3.6-4.5%, while high relapse rates were reported (10.6-21%) in cases with focal and osteoarticular involvements (20,21). In the present study,

the relapse rate of the patients with osteoarticular involvement was 17.5% (n=14), which was slightly higher compared to the literature. This situation can be explained by the fact that 95% of the patients in the present study were engaged in livestock, as well as high risks of interfamily and recurrent infections.

Among joint involvements in adult brucellosis cases, sacroiliitis is the most frequently seen clinical form, and its incidence rate has been reported to vary between 8-20% by numerous studies. Sacroiliac involvement has been reported in 10-60% of the cases with arthritis (2,22,23). Sacroiliitis is mostly unilateral and seen in young patients in an acute disease course. Sacroiliac involvement is more rarely seen in young children. Some studies have reported mostly knee and hip localization (8,24). In the present study, the sacroiliac involvement rate was 12.5%. This high rate might have been because the majority of the patients were 12-18 years old. In line with the literature, the highest involvements were observed in the hip and knee joints.

A previous study reported that peripheral involvement rates were detected in the sternoclavicular joint (4.5%), wrist (2.4%), elbow (1.07%), and shoulder (0.6%) (25). Shoulder involvement, right and left elbow involvement, and right and left wrist involvement were slightly higher in the present study compared to other studies. In addition, relapse rates of shoulder joint involvement were higher. There are studies in the literature reporting that the presence of osteoarticular involvement is associated with relapse (26); however, data on which joint involvement is limited.

Nervous system involvement is a serious complication that is seen at rates of 2.6-14.4% in adults and 1-2.2% in children (25,26). Neurological complications include such as meningitis, meningoencephalitis, cranial nerve involvement, and radiculitis (27). Mortality of these complications is low, but the probability of sequela is high. In the present study, 2.5% of the patients were diagnosed with meningoencephalitis, and they recovered without sequela.

The limitation of the study was that the first relapse group was small. Second, joint MRI could not be performed on every patient. The patients were followed up for approximately 22 months, but long-term results of 5-10 years could not be evaluated. The strength of the study was that it was conducted in childhood and produced hypotheses about the relationship between the location of joint involvement and relapse.

## CONCLUSION

High admission ALT, AST, CRP, and ESR levels in brucellosis cases with osteoarticular involvement and the presence of shoulder joint involvement, albeit rarely, can be a warning sign in terms of relapse. Therefore, these patients should be followed more carefully, maybe they should receive the treatment at the maximum dose and frequency, and if possible, they should be treated as hospitalized, which may be a suggestion to reduce relapse rates. However, for all these, new studies need to be planned regarding the duration and type of treatment. There is a need for further studies with larger populations. Patients should be closely monitored in terms of complications. **Ethics Committee Approval:** The study was approved by the Ethics Committee of Kafkas University Faculty of Medicine (26.02.2020, 22).

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