

## Osteoarticular manifestations of human brucellosis: A review

Seyed Mokhtar Esmailnejad-Ganji, Seyed Mohammad Reza Esmailnejad-Ganji

**ORCID number:** Seyed Mokhtar Esmailnejad-Ganji (0000-0001-7562-0835); Seyed Mohammad Reza Esmailnejad-Ganji (0000-0003-4152-5324).

### Author contributions:

Esmailnejad-Ganji SM contributed to study design; Esmailnejad-Ganji SM and Esmailnejad-Ganji SMR contributed to data collection and writing the draft; Esmailnejad-Ganji SM contributed to manuscript revision; all authors approved the final version of the manuscript.

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**Seyed Mokhtar Esmailnejad-Ganji**, Clinical Research Development Center, Shahid Beheshti Hospital, Babol University of Medical Sciences, Babol 47176-47745, Iran

**Seyed Mokhtar Esmailnejad-Ganji**, Department of Orthopedics, Babol University of Medical Sciences, Babol 47176-47745, Iran

**Seyed Mokhtar Esmailnejad-Ganji**, Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol 47176-47745, Iran

**Seyed Mohammad Reza Esmailnejad-Ganji**, Boston University School of Medicine, Boston, MA 02118, United States

**Corresponding author:** Seyed Mokhtar Esmailnejad-Ganji, MD, Associate Professor, Department of Orthopedics, Babol University of Medical Sciences, Ganjafrooz Street, Babol 47176-47745, Mazandaran, Iran. [smsganji@yahoo.com](mailto:smsganji@yahoo.com)

**Telephone:** +98-11-32199936

**Fax:** +98-11-32190181

### Abstract

Brucellosis is a common global zoonotic disease, which is responsible for a range of clinical manifestations. Fever, sweating and musculoskeletal pains are observed in most patients. The most frequent complication of brucellosis is osteoarticular involvement, with 10% to 85% of patients affected. The sacroiliac (up to 80%) and spinal joints (up to 54%) are the most common affected sites. Spondylitis and spondylodiscitis are the most frequent complications of brucellar spinal involvement. Peripheral arthritis, osteomyelitis, discitis, bursitis and tenosynovitis are other osteoarticular manifestations, but with a lower prevalence. Spinal brucellosis has two forms: focal and diffuse. Epidural abscess is a rare complication of spinal brucellosis but can lead to permanent neurological deficits or even death if not treated promptly. Spondylodiscitis is the most severe form of osteoarticular involvement by brucellosis, and can have single- or multi-focal involvement. Early and appropriate diagnosis and treatment of the disease is important in order to have a successful management of the patients with osteoarticular brucellosis. Brucellosis should be considered as a differential diagnosis for sciatic and back pain, especially in endemic regions. Patients with septic arthritis living in endemic areas also need to be evaluated in terms of brucellosis. Physical examination, laboratory tests and imaging techniques are needed to diagnose the disease. Radiography, computed tomography, magnetic resonance imaging (MRI) and bone scintigraphy are imaging techniques for the diagnosis of osteoarticular brucellosis. MRI is helpful to differentiate between pyogenic spondylitis and brucellar spondylitis. Drug medications (antibiotics) and surgery are the only two options for the treatment and cure of osteoarticular

brucellosis.

**Key words:** Brucellosis; Brucella; Osteoarticular manifestations; Musculoskeletal pain; Bone; Joint

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**Core tip:** The most frequent complication of brucellosis is osteoarticular involvement, with a rate of 10%-85%. Sacroiliac and spinal joints are the most common affected sites. Spondylitis and spondylodiscitis are the most frequent complications of brucellar spinal involvement. Peripheral arthritis, osteomyelitis, discitis, bursitis and tenosynovitis are other osteoarticular manifestations. Epidural abscess is a rare complication of spinal brucellosis but can lead to permanent neurological deficits or even death if not treated promptly. Spondylodiscitis is the most severe form of osteoarticular involvement by brucellosis. Brucellosis should be considered as a differential diagnosis for sciatica, back pain and septic arthritis in endemic regions.

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## INTRODUCTION

Brucellosis is the most common microbial zoonotic disease in the world and found endemically in most developed and developing countries. *Brucella*, an intracellular bacterium, causes brucellosis and *Brucella melitensis* spp. is the most common of the *Brucella* species<sup>[1-3]</sup>. This disease was first diagnosed in the Mediterranean area, where it received its initial name “Malta fever”<sup>[4]</sup>. Thousands of new cases of brucellosis are reported annually worldwide: its annual incidence per million population was reported to be 238.6 in Iran, 262.2 in Turkey, 214.4 in Saudi Arabia and 278.4 in Iraq<sup>[5]</sup>. Humans can acquire the infection mainly through occupational contact (*e.g.*, veterinary, butcher, animal husbandry) or consumption of contaminated dairy products, especially milk, butter and cheese<sup>[6-8]</sup>.

Brucellosis can involve the human body systemically. The most common clinical presentations of human brucellosis are fever, sweating, musculoskeletal pains, lymphadenopathy or hepatosplenomegaly<sup>[9,10]</sup>. The musculoskeletal system is particularly involved. Presentations of brucellosis are variable, deceptive and often non-specific, and they can mimic other infectious and non-infectious diseases<sup>[11-13]</sup>.

For the diagnosis of brucellosis, after primary physical examination, serological tests [the Wright and 2-Mercaptoethanol (2-ME) tests], cultural and imaging methods (radiography, computed tomography, magnetic resonance imaging (MRI) and bone scintigraphy) should be helpful<sup>[14,15]</sup>. To definitely diagnose brucellosis, the organism needs to be isolated from blood, bone marrow, wounds, purulent discharge or other body tissues and fluids, with culture or molecular/histological assessment<sup>[16-18]</sup>. In the present review, we have examined the literature concerning the osteoarticular manifestations of brucellosis, aiming to help physicians and orthopedic surgeons to provide better clinical management for these patients.

## OSTEOARTICULAR MANIFESTATIONS

Osteoarticular involvement is the most frequent complication of brucellosis and can occur in 10% to 85% of the patients infected with the disease<sup>[19]</sup>. It is usually seen as sacroiliitis, spondylitis, osteomyelitis, peripheral arthritis, bursitis and tenosynovitis<sup>[15,20]</sup>. The type of skeletal involvement mainly depends on a patient’s age. This range of manifestations can lead patients to initially visit general practitioners, and ultimately orthopedic and rheumatology specialists. Variable clinical features and lack of specific symptoms often cause a delay in diagnosis of osteoarticular brucellosis.

### Spinal brucellosis

The spine is one of the most common organs involved in brucellosis infection with a rate of 2%-54%, and the lumbar vertebrae are the most frequently affected<sup>[21,22]</sup>. It mainly manifests as spondylitis, spondylodiscitis and/or discitis. Back pain is the most common complaint in spinal brucellosis and reported by about half of the patients. Some patients with spinal brucellosis, who have back pain and sciatic radiculopathy, are misdiagnosed as having disease of an intervertebral disc and undergo surgery<sup>[23,24]</sup>. Given the high prevalence of backache, brucellosis should be considered as a differential diagnosis for sciatic and back pain, especially in the patients who are at occupational risk of brucellosis in endemic areas. Serological screening tests need to be conducted in all such patients<sup>[13,22,25,26]</sup>, although serology may not be positive in all cases. A radionuclide scan can be a useful tool to determine the affected site<sup>[27,28]</sup>. MRI may be the best method to diagnosis and localize the cause of spondylodiscitis, epidural abscess, or compression on the spine and spinal nerves related to brucellosis. Epidural abscess is a rare complication of spinal brucellosis but can lead to severe outcomes, such as permanent neurological deficits, or even death if not treated timely.

### Spondylitis

Spondylitis or vertebral osteomyelitis is inflammation and infection of vertebrae which has a prevalence rate of 2%-60% and mostly observed in men aged > 40 years old<sup>[22,29]</sup>. Lumbar (60%), sacral (19%) and cervical (12%) vertebrae were the most common affected sites, respectively, in a survey by Bozgeyik *et al*<sup>[30]</sup>. There are two types of spinal brucellosis, focal and diffuse. In focal involvement, osteomyelitis is localized in the anterior aspect of an endplate at the discovertebral junction, but in the diffuse type, osteomyelitis affects the entire vertebral endplate or the whole vertebral body<sup>[30,31]</sup>. Spondylitis is the dangerous complication of brucellosis due to its association with epidural, paravertebral and psoas abscess and potential resultant nerve compression. In one report, rapidly progressive spinal epidural abscess was observed following brucellar spondylitis, which was primarily misdiagnosed as a lumbar disc herniation<sup>[32]</sup>; delay in diagnosis and treatment were responsible for rapid progression of the disease. Another study reported a seronegative patient who developed a psoas abscess following brucellar spondylitis<sup>[33]</sup>. The basis of spondylitis diagnosis is microbiological or histopathological assessment of the tissue obtained by biopsy using a needle with computed tomography guidance. Epidural abscess is a rare complication of spondylitis and its diagnosis is difficult due to non-specific symptoms. Among the serological tests and radiological techniques, MRI is the most valuable method to diagnose spinal brucellosis or spinal epidural abscess<sup>[34,35]</sup>. MRI is also helpful to differentiate between pyogenic spondylitis and brucellar spondylitis<sup>[36]</sup>.

### Spondylodiscitis

This is simultaneous inflammation of vertebrae and disc, and usually occurs via hematogenous spread. It is the most severe form of osteoarticular involvement of brucellosis, because it makes a high rate of skeletal and neurological sequels despite therapy<sup>[32,37,38]</sup>. It is stated that 6%-85% of brucellosis osteoarticular involvements are related to brucellar spondylodiscitis. Lumbar (60%-69%), thoracic (19%) and cervical segments (6%-12%) are reported to be more involved in the spinal area<sup>[39-41]</sup>. Spondylodiscitis can be seen as single-focal and/or contiguous or non-contiguous multi-focal involvements. Multi-focal skeletal involvement in the spinal system was seen in 3%-14% of patients<sup>[41,42]</sup>. Radionuclide bone scintigraphy is an important technique in determination of musculoskeletal region of brucellosis. Increased uptake of the involved region on bone scintigraphy is more in favor of brucellar spondylodiscitis than tuberculous spondylodiscitis<sup>[43,44]</sup>. MRI is the choice for diagnosis of spondylodiscitis, epidural abscess and cord or root compression relevant to brucellosis<sup>[30,45,46]</sup>. In MRI, the lesion is found as destructive appearance (Pedro Pons' sign) at antero-superior corner of vertebrae accompanied by prominent osteosclerosis, which is a pathognomonic finding<sup>[47,48]</sup>. Back pain is the main symptom of spondylodiscitis, however, it is not a specific symptom and usually leads to a delay in diagnosis and late treatment. Therefore, in the endemic regions, it is necessary to consider spondylodiscitis as a differential diagnosis for long-term cervical, lumbar and sacral pain (especially among elderly patients) and perform screening serological tests to achieve early diagnosis and prevent its late complications<sup>[49,50]</sup>.

### Discitis

The intervertebral disc can be infected without spondylitis, which is named discitis. In addition to back pain, disc herniation and sciatica can be described by the patient with discitis<sup>[51,52]</sup>, therefore, this disease should be considered in the differential diagnosis of those symptoms. It was observed that the simultaneous existence of spondylolysis

and spondylolisthesis with brucellar discitis caused misdiagnosis<sup>[53]</sup>.

### Sacroiliitis

Large joints, like sacroiliac, are the most common regions of musculoskeletal involvement of brucellosis<sup>[31]</sup>. Sacroiliitis, or inflammation of sacroiliac joint, has been observed in nearly 80% of patients with focal complications and more frequently in adults<sup>[51,46]</sup>. Its clinical symptoms (septic or reactive forms) mimic acute low back pain or lumbar disc herniation and the back pain may radiate into the thigh, however, chronic sacroiliitis is associated with chronic back pain<sup>[54,55]</sup>. Although low back pain is the important symptom, 24% of the patients were asymptomatic in a study<sup>[56]</sup>. It is reported that the rate of sacroiliitis is high in those patients who are infected with *B. melitensis* spp.<sup>[15,57]</sup>. Both of unilateral and bilateral forms of brucellar sacroiliitis have been reported<sup>[56,58]</sup>. Sacroiliitis was also simultaneously seen with dactylitis, olecranon bursitis, humerus osteomyelitis and iliac muscle abscess, and with other systemic diseases, like endocarditis, pyelonephritis and thyroiditis<sup>[59-62]</sup>. A study showed that high-resolution MRI has a higher sensitivity than scintigraphy in the diagnosis of brucellar sacroiliitis<sup>[63]</sup>.

### Limbs

Brucellosis with peripheral skeleton involvement is less prevalent compared with vertebral features. It can manifest as arthralgia, enthesopathy, osteomyelitis, arthritis, bursitis, tendonitis and tenosynovitis<sup>[64-67]</sup>. Arthritis occurs in 14%-26% of the patients suffering from acute, sub-acute or chronic brucellosis<sup>[68,69]</sup>. Knee, hip and ankle joints are among the most common peripheral regions affected by brucellosis and these patients present with arthritis<sup>[15,70]</sup>. Shoulders, wrists, elbows, interphalangeal and sternoclavicular joints may also be involved<sup>[28,69,71]</sup>. Chronic knee arthritis along with osteomyelitis have also been reported<sup>[72,73]</sup>. Multiple joint arthritis caused by brucellosis was reported in 17% of patients in a study<sup>[74]</sup>. In children, monoarthritis is the most common type of musculoskeletal brucellosis that mostly involves hip and knee joints, but adjacent bone osteomyelitis may also exist simultaneously<sup>[15,75,76]</sup>. Brucellosis can involve the peripheral joints through septic (with presence of pathogen) and reactive (lack of the pathogen) mechanisms<sup>[64,77]</sup>.

Septic arthritis caused by brucellosis has been reported in the literature and it has been recommended that patients with septic arthritis living in the endemic areas, be examined in terms of brucellosis<sup>[68,74,78]</sup>. Septic arthritis in brucellosis progresses slowly and starts with small pericapsular erosions. Blood culture is positive in 20%-70% of such patients. Although synovial fluid assessment is the most useful diagnostic method, the isolation of the pathogen from synovial fluid is not easy<sup>[79]</sup>. In relation to the diagnosis of purulent arthritis, it may be necessary to rely on bone marrow culture in those patients with negative serology<sup>[80-82]</sup>.

Knee arthritis has obvious symptoms and is less difficult to diagnose and treat due to easy access. However, the diagnosis and treatment of hip arthritis is more difficult and delay in diagnosis and treatment may lead to serious and irreparable complications, such as dislocation and necrosis of the femoral head<sup>[73,83]</sup>. Brucellosis should be considered in the differential diagnosis for a patient presenting with knee or hip arthritis symptoms in endemic regions to prevent misdiagnosis and serious complications. For example, misdiagnosis due to serological false negative test and improper interference in surgery was reported about brucellar arthritis of hip<sup>[84]</sup>. Almajid reported a rare case of brucellar olecranon bursitis whose serology was negative, but the blood and aspirate cultures were positive<sup>[85]</sup>. Brucellar arthritis following implantation of artificial knee and hip joints has been reported, which the medications may not be enough and removing the prosthesis might be needed<sup>[86-88]</sup>. Due to the synovial involvement of the disease, pathological evidence may not be found on radiograph in the early phase of infection.

### Other manifestations

Spondyloarthritis following brucellosis was reported<sup>[77]</sup>. Sternal osteomyelitis caused by *B. melitensis* was observed following median sternotomy<sup>[89]</sup>. In a study by Ebrahimpour *et al*<sup>[69]</sup>, brucellosis was attributed to sternoclavicular (4.5%), wrist (2.4%), elbow (1.07%) and shoulder (0.6%) arthritis. Delay in the diagnosis of brucellosis results in prolong disease duration which can lead to osteomyelitis or osteolytic lesions. Brucellar osteomyelitis has been observed in closed femur fracture and a pathologic humerus fracture<sup>[90,91]</sup>. It was also seen in association with prosthetic extra-articular hardware<sup>[92]</sup>. We reported the first case of brucellar osteomyelitis of pubic symphysis, who was symptom free within two-year follow-up despite inappropriate initial antibiotherapy<sup>[93]</sup>.

## LABORATORY INVESTIGATIONS

Laboratory tests following physical examinations are essential in order to diagnose brucellosis. Serology is often positive in the patients. In the acute infection, immunoglobulin M (IgM) antibody firstly appears, followed by immunoglobulin G (IgG) and immunoglobulin A (IgA)<sup>[14,94,95]</sup>. The Wright test, which is a standard agglutination test (SAT), measures the total amount of IgM and IgG antibodies, and the 2-ME test measures IgG antibody. In the endemic regions, a SAT titer  $\geq 1:160$  and 2-ME titer  $\geq 1:80$  is in favor of brucellosis diagnosis<sup>[94,96,97]</sup>. Enzyme-Linked Immunosorbent Assay (ELISA) is another type of serological test, but has less sensitivity and specificity<sup>[98]</sup>. Polymerase chain reaction (PCR) is a molecular method which can be very useful due to its quick procedure and high sensitivity and specificity, if it is available<sup>[99]</sup>.

## TREATMENT

The main purpose of antimicrobial medications in brucellosis is to treat the disease and its symptoms and signs, and to prevent the relapse. Combinations of doxycycline, streptomycin, gentamicin, ciprofloxacin, ofloxacin, co-trimoxazole (trimethoprim plus sulfamethoxazole) and rifampicin are used for antibiotherapy<sup>[100-102]</sup>. No standard therapy exists for osteoarticular brucellosis and physicians prescribe drugs based on their experiences and conditions of the disease (the involved site, and being complicated/uncomplicated). Triple regimen containing streptomycin (1 g daily) plus doxycycline (100 mg twice daily) plus rifampin (15 mg/kg daily) over 6 months had 100% efficacy on brucellar spondylitis<sup>[21]</sup>. Similar results were found using this regimen<sup>[103,104]</sup>. In contrast, double therapy with doxycycline and rifampin was associated with relapses<sup>[19,104]</sup>. With respect to brucellar spondylitis, patients need a long-term anti-bacterial medication (usually at least three months), mainly aiming to prevent relapses. Those patients who failed antibiotic therapy or presented with progressive neurological deficit, need surgical intervention<sup>[34,105,106]</sup>. The rate of surgical drainage in spinal brucellosis was reported in the range of 7.6%-33%<sup>[107]</sup>. In case of abscess in those patients with spondylodiscitis, treatment duration will be prolonged and surgery may be needed<sup>[47]</sup>.

## CONCLUSION

Brucellosis has variable clinical features and osteoarticular manifestations are the most common. Sacroiliac and spinal joints are the most frequently involved regions. Monoarthritis (knee/hip), sacroiliitis and spondylitis predominate in children, adults and the elderly, respectively. In order to diagnose the disease, physical examinations, laboratory tests and imaging techniques are needed. Brucellosis should be considered as a differential diagnosis for sciatic and back pain, especially in the endemic regions. Radiological assessments would be very helpful in such cases. Patients whose big joints, bone and artificial joints are involved, may be referred to a rheumatology center. Considering that these patients usually need orthopedic evaluation and treatment, it is recommended to refer them to an orthopedic center in order to prevent adverse effects caused by delay in the treatment. Early and appropriate diagnosis and treatment of the disease is the key of success in management of the patients with the osteoarticular manifestation of brucellosis. This is feasible by an early collaboration of orthopedic surgeon with a specialist in infectious diseases.

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