BONE AND ARTICULAR IMPAIRMENT IN TUBERCULOSIS. AN IMPORTANT EXTRAPULMONARY INVOLVEMENT: A REVIEW

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ABSTRACT

This is a literature review on the pathogenesis and epidemiology of bone tuberculosis (BTB). Full-text papers from 2001 to 2017 were included. After inclusion criteria were met, 23 papers were selected for analysis. Results show that in most cases of BTB, the spine is the main site involved, regardless of the geographical regions analyzed; hip and knee involvement are also frequent. These three sites are the most prevalent, totaling approximately 70 - 80% of infections. The major forms of involvement are tuberculous spondylitis, tuberculous osteomyelitis, primarily in areas of long-bone growth, as well as cases of chronic disease leading to tuberculous arthritis, mainly in endemic areas. The results also indicated that bone involvement is still prevalent, being the fifth cause of extrapulmonary disease involvement in Brazil. This review highlights the role of tuberculosis in public health, especially in economically active groups where BTB is most prevalent.

KEY WORDS: Tuberculosis; bone tuberculosis; epidemiology; Pott’s disease; spine.

INTRODUCTION

Tuberculosis (TB) is still an important public health issue. In 2016, 10.4 million people contracted the disease and, of these, about 1.3 million died. As stated by the World Health Organization (WHO), TB is the deadliest single-agent infectious disease, surpassing HIV (WHO, 2017). In Brazil, 69,569 new cases of TB were recorded in 2017, with 4,426 deaths in 2016 (Brasil, 2017).

The pulmonary site is notably the most frequently affected by TB. Extrapulmonary involvement is present in only about 10% of the cases, being classified according to location: laryngeal, peripheral ganglionic,
meningoencephalic, bone, genitourinary, miliary, cutaneous or ocular (Lopes et al., 2006). Bone TB (BTB) and articular TB most commonly affect the spine, the hip joint and the knee, although also occurring in several other sites (Garg et al., 2011; Kilborn et al., 2015). Spinal TB (STB), or Pott’s disease, accounts for 1 to 2% of all cases of extrapulmonary TB (ExTB) (Batirel et al., 2015; Ledbetter et al., 2016) and most commonly affects the lumbar and lower thoracic spine (Leonard et al., 2017).

In general, BTB manifests as arthritis and / or osteomyelitis, with inflammation and / or joint infection. Furthermore, it presents indolent progression when compared to non-specific osteomyelitis and septic arthritis, although with greater morbidity (Norbis et al., 2014; Pigrau-Serralach et al., 2013). Among the risk factors associated with the development of TB, geographic location, age, immunosuppressive treatment, diabetes mellitus, and HIV infection are of epidemiological importance (Garg et al., 2011).

The purpose of this paper is, therefore, to determine the profile of bone and joint impairment in TB through a review of the sites involved and the epidemiological profile that may help to establish clinical hypotheses in cases of ExTB, based on the high prevalence of TB in Brazil and the great importance of bone involvement in this disease.

METHODS

The articles selected for this review were published in national and international journals from 2001 to 2017. Systematic review studies and meta-analyses were also included. Since this review aims to delineate the characteristics of bone and joint involvement by *Mycobacterium tuberculosis* (MTB), only studies that focused directly on BTB and its relations were included. The following descriptors were used: “Tuberculosis”, “Epidemiology”, and “Bone tuberculosis” in articles made available by Scielo, BVS and Bireme System (MEDLINE, LILACS and BDENF). Their respective bibliography was also researched for articles to complement the review. Repeated articles, dissertations, theses, articles of validation and any that did not present the complete available text were excluded.

Considering this is a descriptive study and not directly involving human beings and their possible identification, the submission of the research project to the Ethics Committee was not necessary.

RESULTS AND DISCUSSION

73 relevant papers were found, 23 of which were selected after reading their abstracts and applying the inclusion criteria. Subsequently, complete versions of the papers were obtained for analysis (Table).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Clinical Presentation</th>
<th>Bone or Joint Affected</th>
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<tbody>
<tr>
<td>Davidson P.T., Horowitz I.</td>
<td>1970</td>
<td>USA</td>
<td>Arthritis, Osteomyelitis and Spondylitis</td>
<td>Hip, Knee and Spine</td>
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<td>Naim-ur-Rahman</td>
<td>1980</td>
<td>Saudi Arabia</td>
<td>Osteomyelitis and Spondylitis</td>
<td>Spine</td>
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<td>Colmenero J.D. et al</td>
<td>2004</td>
<td>Spain</td>
<td>Osteomyelitis</td>
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<tr>
<td>Franco-Paredes C. et al</td>
<td>2006</td>
<td>USA</td>
<td>Arthritis</td>
<td>Femur, Knee, Psoas muscle and Spine</td>
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<td>Hong L. et al</td>
<td>2010</td>
<td>China</td>
<td>Arthritis, Osteomyelitis and Spondylitis</td>
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<td>Shikhare S. et al</td>
<td>2011</td>
<td>Singapore</td>
<td>Osteomyelitis and Spondylitis</td>
<td>Calcaneus, Hand, Knee, Spine, Scapula and Ulna</td>
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<tr>
<td>Pattamaspongsong N., Mutterak M., Sivasomboon C.</td>
<td>2011</td>
<td>Thailand</td>
<td>Arthritis and Tenosynovitis</td>
<td>Flexor tendon sheaths, Knee, Hip Shoulder and Wrist</td>
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<tr>
<td>Al-Qattan M.M. et al</td>
<td>2011</td>
<td>Canada</td>
<td>Monoarthritis and Tenosynovitis</td>
<td>Hand</td>
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<tr>
<td>Garg R.K., Somvanshi D.S.</td>
<td>2011</td>
<td>India</td>
<td>Osteomyelitis and Spondylitis</td>
<td>Spine</td>
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<td>Tahasildar N. et al</td>
<td>2012</td>
<td>India</td>
<td>Arthritis</td>
<td>Hip</td>
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<tr>
<td>Pigrau-Serralach C., Rodriguez-Pardo D.</td>
<td>2013</td>
<td>Spain</td>
<td>Bursitis, Sacroiliitis and Spondylitis</td>
<td>Spine, Sacroiliac joint and Trochanteric Bursa</td>
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<td>Kim S-J., Kim J.H.</td>
<td>2013</td>
<td>USA</td>
<td>Osteomyelitis</td>
<td>Knee</td>
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<tr>
<td>Norbis L. et al</td>
<td>2014</td>
<td>Italy</td>
<td>Spondylitis</td>
<td>Spine</td>
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<td>Murray M.R., Schroeder G.D., Hsu W.K.</td>
<td>2015</td>
<td>USA</td>
<td>Osteomyelitis and Spondylitis</td>
<td>Spine</td>
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<td>Kilborn T., van Rensburg P.J., Candy S.</td>
<td>2015</td>
<td>South Africa</td>
<td>Osteomyelitis and Spondylitis</td>
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<td>Turkey</td>
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<td>2016</td>
<td>USA</td>
<td>Neuroarthropathy</td>
<td>Spine</td>
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<td>Kumar K.</td>
<td>2016</td>
<td>USA</td>
<td>Osteomyelitis and Spondylitis</td>
<td>Spine</td>
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<td>Sahli H. et al</td>
<td>2017</td>
<td>Tunisia</td>
<td>Arthritis</td>
<td>Hand</td>
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<td>Leonard M.K., Blumberg H.M.</td>
<td>2017</td>
<td>USA</td>
<td>Arthritis, Osteomyelitis and Spondylitis</td>
<td>Knee, Hip, Rib and Spine</td>
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<tr>
<td>Huaman M.A., Brawley R., Ashkin D.</td>
<td>2017</td>
<td>USA</td>
<td>Osteomyelitis and Spondylitis</td>
<td>Spine</td>
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<tr>
<td>Hogan J.J., Nelson S.B.</td>
<td>2017</td>
<td>USA</td>
<td>Arthritis, Osteomyelitis, Spondylitis and Tenosynovitis</td>
<td>Knee, Hip and Spine</td>
</tr>
<tr>
<td>Narayan V. et al</td>
<td>2018</td>
<td>USA</td>
<td>Spondylolisthesis</td>
<td>Spine</td>
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</table>
BTB cases account for about 2 to 3% of all TB cases notified in the United States and in some reported series in the United Kingdom, for more than 6% of the cases. In these countries, there are reports of an increasing racial disparity in the latest years, with most cases reported amongst minorities and individuals born overseas (CDC, 2015; Hodson & Ormerod, 1990). These immigrants were responsible for increasing the incidence of the disease in those countries. Due to the indolent course of the disease and its low clinical suspicion in areas with low TB incidence, diagnostic delay is frequent in developed countries (Talbot., 2007; Colmenero et al., 2004).

In countries where TB is endemic, older children and young adults are more commonly affected by BTB, whereas in developed countries the disease is more frequently observed in the elderly (Ludwig & Lazarus, 2007). Historically, BTB affected the infant age group and young adults shortly after the development of primary infection. In areas with limited resources, it is still frequent, whereas in developed countries BTB results more commonly from relapses (Davidson et al., 1970).

Regarding risk factors, ExTB is more common amongst HIV infected patients, however BTB did not present the same proportion ratio when compared to seronegative patients (Kim & Kim, 2013; Leibert et al., 1996). The advent of anti-tumor necrosis factor α (TNF-α) therapy is a risk factor associated with disseminated TB amongst patients with TB latent infection, and studies have noted that it includes the development of serious musculoskeletal lesions (Franco-Paredes et al., 2006).

Data from DATASUS (Department of Informatics in the Unified Health System in Brazil), which utilizes SINAN (Notification of Injury Information System) as a source of recorded confirmed TB cases in Brazil, showed that, in 2017, of the 89,487 TB cases, 13,357 were classified as ExTB, and, of these, 639 as BTB, corresponding to 4.8% of the ExTB cases – which places it in the 5th position regarding ExTB forms. The Northern Region presented the highest percentage increase in the total amount of TB and BTB cases from 2001 to 2017: in 2001, 7,582 TB cases were diagnosed, of which 37 were classified as BTB. In 2017, the total amount of cases in this region increased by 33%, to 10,109 cases, and BTB cases increased by 59.6%, to 59 cases – which corresponded to 9.2% of the total BTB cases in Brazil for that year.

In 2017 45 BTB cases were diagnosed in patients 19 or less years of age in the entire country, which corresponded to 7.0% of the total. 429 recorded BTB cases were diagnosed in patients 20 to 59 years old, corresponding to 67.1% of the total. 164 cases were recorded in patients 60 or more years of age, corresponding to 25.7% of the total.
It must be noted that the notification system still fails to report the sites and degree of involvement of the cases, which limits comparison with international literature and worldwide BTB epidemiology. This limitation, as well as the many variants in underreporting, impair the analysis of the BTB scenario in the country in previous periods.

PATHOGENESIS

MTB is an aerobic bacterium, but it also behaves as a facultative anaerobic bacterium, thus being able to remain in its host for a long time. Tuberculosis arthritis and osteomyelitis derive from reactivation foci of stored bacilli originated from the hematogenous spread of the primary infection. The musculoskeletal system receives hematogenic strains originating from primary sites, mainly the lungs and the genitourinary tract, and shows less replication than in this primary site (Leonard et al., 2017; Norbis et al., 2014).

The broad vascularization of vertebrae and long bones is the major determinant in the preferential affection of these by the bacillus, especially the metaphyseal region (Pigrau-Serrallach et al., 2013). Infrequently, MTB are carried from the lungs to distant sites such as the spine; in this case, the route may be the paravertebral venous plexus or the paraaortic lymph nodes’ draining lymphatics. The osteoarticular infections caused by nontuberculous mycobacteria (NTM) usually arise secondarily to inoculation, after a trauma or surgical procedures (Hogan et al., 2017).

From the dissemination, a granuloma is formed in the site of the injury, with prostaglandin E 2 (PGE-2) being released to increase the inflammatory recruitment, and a necrosis focus is formed as result of the response to the infectious cells, in which are involved both bacterial enzymes, that digest and destroy the surrounding tissue, and the host’s exacerbated protective response (Norbis et al., 2014). The resulting inflammatory focus leads to caseous necrosis and to the typical TB granulomas, which then lead to an increase of compression in these foci and to the collapse of the joint or the vertebral bone. In addition, there may be nerve root compression or secondary neurologic disorders (Hong et al., 2010).

In general, immunocompromised conditions, whether acquired or drug-induced, are important risk factors for the contraction of TB infection. In this context, the relation of STB with HIV should be highlighted, since TB is the main opportunistic infection in such patients. This is justified because patients with the acquired immune deficiency syndrome (AIDS) present heavily compromised cellular immunity, due to the progressive depletion of TCD4+ lymphocytes, resulting in increased risk for TB infection, relapse and extrapulmonary spread, in comparison to healthy individuals (Batirel et al., 2015; Naim-ur-Rahman, 1980).
Tuberculous Spondylitis

Tuberculous spondylitis, known as Pott’s disease, initially results from involvement of the subchondral region of the terminal endplate by MTB. In the beginning, it does not affect the disc, due to poor vascularization, despite the rich blood supply to the vertebrae, which in turn suffers lytic destruction without the formation of new bone tissue (sclerosis). The anterior region of the vertebra is the most damaged part whereas its posterior components are only slightly affected. Tuberculous discitis in children may occur as a primary disease, as a result of the remaining blood supply to the intervertebral disk. However, after childhood, in view of the disc’s avascular structure, its involvement may only happen due to continuity of foci originating from the vertebral body (Calderone et al., 1996).

The destruction of the anterior region of the vertebral body results in kyphosis (Figure 1). The severity of kyphosis is related to the amount of damage to the anterior regions of the vertebrae. There may be compression of neurologic structures due to angular deformity or due to direct compression by the caseous tissue. Furthermore, paraspinal abscesses may be present. (Figure 2) (Kumar et al., 2016; Narayan et al., 2018).

Figure 1. Computer tomography (CT) of the thoracic spine showing destruction of vertebral bodies and kyphosis of the segment at T10-T12.
Tuberculous Osteomyelitis

Tuberculous osteomyelitis may affect bones and joints. In this disorder, there is a significant difference in clinical manifestations according to the affected age group. In children there is the characteristic involvement of several bones with multiple lesions, especially in the feet and hands (Figure 3). However, after childhood, patients present single lesions that may involve any bone.

Tuberculous osteomyelitis occurs mainly in the metaphyseal region of long bones such as the femur and tibia. In children, intra-articular involvement is common due to contiguous dissemination (Shikhare et al., 2011). When growth plates are involved, there may be shortening and deformation of the affected limb (Huaman et al., 2017; Murray et al., 2015).

Figure 2. Patient with acquired immunodeficiency syndrome under treatment for pulmonary TB that evolved with decreased muscle strength in the lower limbs. The images show the destruction of the vertebral body and a paraspinal abscess. The left lateral radiography shows collapse of the intervertebral disc and vertebral bodies at T10-T12 that are sclerotic. The right T2 image by Magnetic Resonance Imaging (MRI) presents a paravertebral abscess and destruction of the thoracic vertebra and the intervertebral discs, associated with an exuberant paravertebral soft tissue component and dorsal kyphosis.
Tuberculous Arthritis

Although tuberculous arthritis can affect any joint, it tends to appear in joints that are subjected to greater weight loads such as the knee and hip. The impairment of the intra-articular region may occur due to hematogenic or contiguous spread, the latter occurring through the erosion of the epiphyseal (in adults) or metaphyseal (in children) bone (Al-Qattan et al., 2011). Involvement due to contiguous spread may also occur from other organs (Tahasildar et al., 2012). Once the joint space and the synovial fluid have been affected, the result is erosive arthritis with the formation of pannus that manifests clinically with joint deformities, commonly seen in other types of advanced arthritis such as rheumatoid arthritis. Tuberculous arthritis is monoarticular in about 90% of the cases (Pattamapaspong et al., 2011; Sahli et al., 2017).

Figure 3. X-ray of a 2-year-old child with tuberculous dactylitis showing the diaphyseal enlargement and osteolytic lesion with blurred limits of the first metatarsal bone, demonstrating a decrease in bone density that is characteristic in this type of condition.
DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of BTB is reasoned on clinical and imaging findings. Radiological study is of great relevance for the diagnosis; lytic patterns (osteolytic, subperiosteal with sclerotic margins and fragmentation) indicating bone destruction are highly suggestive for BTB if there is clinical and epidemiological reason for suspicion (Pigrau-Serralach et al., 2013). Hematological data is of little contribution for laboratory research, and the number of leukocytes is not very sensitive to change. The tuberculosis skin test (also known as the tuberculin or PPD test) is positive in most cases, even though it cannot be considered when dealing with endemic areas and immunocompromised populations. The gold standard for diagnosis is the isolation of MTB from samples by aspiration cytology-biopsy and culture, or by histological bone specimen, which will also be useful in determining resistance to medication (Norbis et al., 2014; Pigrau-Serralach et al., 2013). Multiplex real-time PCR may be useful for diagnosis and can distinguish typical from atypical mycobacteria in synovial biopsy, but as this method does not identify if the microorganism is alive or dead, it is not indicated to establish the activity of the disease.

BTB, especially tuberculous spondylitis, must initially be differentiated from metastatic neoplasms that affect the vertebrae, such as myeloma, and some solid tumors (Ledbetter et al., 2016). It should also be differentiated from pyogenic diseases in cases of abscesses and inflammatory arthritis. The focus for the differential diagnosis always depends on well-established clinical and epidemiological suspicions with suggestive image findings (Kumar et al., 2016; Narayan et al., 2018).

TREATMENT

Preference should be given to clinical treatment in cases without significant motor and neurological damage; in cases with neurological deficits, surgical treatment may be indicated, varying according to the particularity of each case. In tuberculous osteomyelitis combined anti-tuberculosis drugs produce similar long-term results when compared to the surgical approach by debridement and fusion or anterior debridement alone (Pigrau-Serralach et al., 2013). The combined use of rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months followed by the association of rifampicin and isoniazid for a total period of 6-18 months is the most frequent protocol used for BTB treatment which should start as soon as possible.

WHO recommends 9 month treatment for BTB (WHO, 2010). The Brazilian Ministry of Health recommends a two phase treatment for meningoencephalic and osteoarticular TB totaling 12 months: an intensive (or attack) phase in the first 2 months with a complete regimen, to rapidly
reduce the bacilli population and eliminate bacilli naturally resistant to any drugs. Subsequently a maintenance phase over the remaining 10 months with a double regimen of rifampicin and isoniazid for both adults and adolescents, with varied doses of medication according to age group and weight, with a view to eliminating latent or persistent bacilli and reducing the possibility of disease recurrence (Brazil, 2018).

In cases of vertebral involvement, the surgical approach is indicated when there is neurologic damage, large abscesses and instability or deformity (kyphotic angles of 30 degrees or more), and non-response to clinical treatment with antibiotics due to resistance (Colmenero et al., 2004).

CONCLUDING REMARKS

BTB is still one of the main sites of extrapulmonary involvement. Even though any joint or bone may be damaged by TB, there is greater involvement of the spine and large joints, such as the hip and knee, which are responsible for the majority of cases. In countries where TB is endemic, older children and young adults are most commonly affected by BTB, while in developed countries the disease is often reported in the elderly. The population most affected by this disease in Brazil, in the analyzed period, consisted of young people in the workforce. The main forms of clinical presentation are tuberculous spondylitis, tuberculous osteomyelitis and tuberculous arthritis. The diagnosis is mostly based on clinical and radiological studies with laboratory support for differential cases. The mainstay of treatment is a multidrug anti-tuberculosis chemotherapy combination (rifampicin, isoniazid, ethambutol, and pyrazinamide); surgery is recommended in special cases, mainly when there is neuroarticular damage.

REFERENCES


