

# The Epidemiology of Skeletal Tuberculosis in Northeast of Iran: A Review of 229 Cases

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## What's Known

- Tuberculosis (TB) is the leading cause of death from infectious disease in the world.
- Skeletal tuberculosis is uncommon and an important component of extra-pulmonary tuberculosis. Spinal TB is the most dangerous of any bone and joint tuberculosis.

## What's New

- Demographic data, diagnostic methods, and clinical features of 229 skeletal TB patients, over a period of 10 years, were evaluated in Golestan province, Iran.
- The spinal column was the most commonly involved skeletal site affecting 81.2% of all cases. The majority of patients presented with pain and swelling.

## Abstract

**Background:** The incidence of tuberculosis (TB) has increased in recent years in both developed and developing countries. Skeletal tuberculosis occurs in approximately 1% of patients with tuberculosis. The present study aimed to evaluate the epidemiology of skeletal tuberculosis in Golestan province in northeastern Iran during 2005-2014.

**Methods:** In the present retrospective study, the epidemiology of skeletal tuberculosis was studied in 229 skeletal tuberculosis patients who were diagnosed during 2005-2014. The prevalence rate of skeletal TB has been reported according to demographic and clinical features.

**Results:** Over the 10-year period of this study, 229 known skeletal TB cases were identified in which 56.3% were male. The mean age of the patients was  $44.0 \pm 17.7$  (range 7-87). All of the patients were new cases. Most of the patients (56.8%) were from the rural areas and most were diagnosed by the private healthcare system (63.8%). The highest rate of skeletal TB was seen in 2013 (15.3%). Spinal TB (81.2%) scored the highest rate and pain (96.9%) was the most prevalent symptom of skeletal TB.

**Conclusion:** The findings suggest that skeletal tuberculosis in northeastern Iran should always be considered as a differential diagnosis for fever and pain on the spinal column. Due to the high level of tuberculosis in the Golestan province (Iran), further research on continued awareness of skeletal TB is stressed.

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**Keywords** • Tuberculosis • Skeletal tuberculosis • Spinal tuberculosis • Bone tuberculosis • Epidemiology • Review • Iran

## Introduction

Tuberculosis (TB) is the leading cause of death from infectious disease in the world. The World Health Organization (WHO) estimated that there were 9.6 million cases of tuberculosis (TB) in the world in 2014 and 1.5 million died from the disease.<sup>1</sup> The incidence of tuberculosis (TB) has increased in recent years in both developed and developing countries.<sup>2</sup> According to the reports of the Iranian Ministry of Health and Medical Education in 2014, Golestan province was ranked second with an incidence rate of 38.26 per 100,000.

Pulmonary tuberculosis is the most frequent kind of TB in Golestan province in which 19.8% were sputum smear positive.<sup>3</sup> Extra-pulmonary TB consists 28% of the TB patients. Sistan-Balouchestan and Golestan provinces have the highest incidence

and prevalence of TB among all provinces in Iran.<sup>4</sup>

Skeletal TB is uncommon and an important component of extra-pulmonary tuberculosis.<sup>5</sup> It represents 10-20% of all extra-pulmonary TB and 1-2% of all TB cases.<sup>6</sup> It is generally accepted that spinal TB is the most dangerous of all bone and joint TB because of its ability to cause bone destruction, deformity, and paraplegia.<sup>7</sup> Tuberculosis involving the synovial joints is the second commonest site of involvement in skeletal TB. Tuberculosis osteomyelitis is less common than spinal or articular TB.<sup>8</sup>

Bacille Calmette-Guerin (BCG) osteomyelitis is radiographically indistinguishable from TB osteomyelitis.<sup>9</sup> It is recognized that early diagnosis is important since early treatment results in cure and avoids the high morbidity that occurred before antituberculous therapy was introduced.<sup>10</sup> Skeletal TB is usually presented in a slowly indolent manner with nonspecific clinical presentations such that the diagnosis of tuberculous arthritis is often difficult and delayed. It remains a great challenge for clinicians.<sup>11</sup>

There is a few published literature on the epidemiology and clinical features of skeletal TB in Iran and Golestan province. One study was conducted to assess the frequency and clinical findings in osteoarticular TB in two referral hospitals in Tehran, during 2003-2005. Weight loss, fever, and night sweats were the most common constitutional symptoms. The knee, ankle, hip, and shoulder joints were the most frequent sites for TB arthritis. Osteomyelitis equally affects the proximal long and short bones. The lumbar (22.7%) and thoracic (50%) vertebrae were the most prevalent involved sites in isolated TB spondylitis.<sup>12</sup>

The present study aimed to evaluate demographic data, diagnostic methods, and clinical features of 229 skeletal TB patients treated at the Tuberculosis Control Health Center in Golestan province (Iran) over a period of 10 years (2005-2014).

## Patients and Methods

Over the 10-year period from 2005 through 2014, 229 patients were diagnosed with skeletal TB. The patients in the present study referred to health centers in Gorgan (Iran) for the "directly observed treatment, short-course (DOTS)." Gorgan is in the center of Golestan province in northern Iran, just southeast of the Caspian Sea.<sup>13</sup>

In order to complete the questionnaire, initially all TB patients that suffered from skeletal TB were identified by the TB register software

(electronic files for patients) and their primary data were recorded. For completeness of the clinical data, the operators also visited patients' residence for further information. Demographic data, such as age, gender, weight at the time of diagnosis, ethnicity, location, patient's TB history, complaints, and physical examination findings were extracted from the clinical records. The diagnosis of skeletal TB was confirmed by a combination of clinical suspicion and biopsy findings. After the primary diagnosis of patients by doctors, they were referred to a health center in Gorgan and continued treatment as planned. All data on skeletal TB cases reported in 2005 and 2014 were collected from district databases (disease prevention and control units) in the Vice-Chancellery for Health, Golestan University of Medical Sciences, Golestan, Iran, and then categorized for data analysis.

The diagnosis of skeletal TB was established following full clinical, laboratory, and radiological investigation based on the 2015 infectious diseases society of America (IDSA) guideline.<sup>14</sup> Suggestive diagnostic criteria for TB included a positive smear report in the presence/absence of positive culture or pathology in one or more samples (bone biopsy or synovial biopsy) and compatible imaging reports (simple X-ray, computed tomography scan, or magnetic resonance imaging). The definitive diagnosis of spinal TB is usually established by CT-guided needle aspiration cytology biopsy and culture on Löwenstein medium, or by histological examination, which is highly suggestive of spinal TB (when caseating granulomas are observed) and diagnostic (when acid-fast bacilli are found). Culture and histological study of a bone specimen obtained by surgery have a slightly higher diagnostic yield.<sup>15</sup>

In 1978, according to the guideline by the World Health Organization (WHO),<sup>16</sup> the Ministry of Health and Medical Education of Iran effectively implemented the DOTS strategy to fight tuberculosis. Based on the national strategy of DOTS, new patients were treated with a short-term diet for the period of 6 months, followed by re-treatment with a regimen of 9 months. Both regimens consisted of two phases, namely attack and maintenance.<sup>17</sup> The DOTS regimen was put into practice in Gorgan in June 1998. The records of the skeletal TB cases that were treated between January 2005 and June 2014 were reviewed. The skeletal TB regimens used in the health centers in Gorgan are presented in table 1. In the present study, the standard 6-month anti-TB therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol) was commenced with good clinical response. The continuation

phase lasted 4 months with isoniazid and rifampin on a daily basis and the regime's maintenance phase continued for another 3 months. Ethics approval was obtained and approved by the Ethical Committee of Golestan University of Medical Science (Iran).

Data relating to the duration of therapy and administration of DOTS were recorded with the SPSS software (version 21.0). Descriptive analyses were performed to detect differences between subgroups.

## Results

In total, 229 cases of skeletal tuberculosis during 2005-2014 in Golestan province were reviewed by the authors. The mean age of the patients was 44.0±17.7 (range 7-87) and 130 (56.8%) patients were male. All of the patients were new cases. Most of the patients (56.8%) were from the rural areas and diagnosed by the private healthcare system (63.8%). The characteristics of the patients are presented in table 2. The spinal column was the most commonly involved skeletal site affecting 81.2% of all cases, as summarized in table 3. The highest prevalence rate of skeletal TB was seen in 2013 (15.3%), as summarized in table 4. The time series plot of the prevalence of skeletal tuberculosis is graphically shown in figure 1.

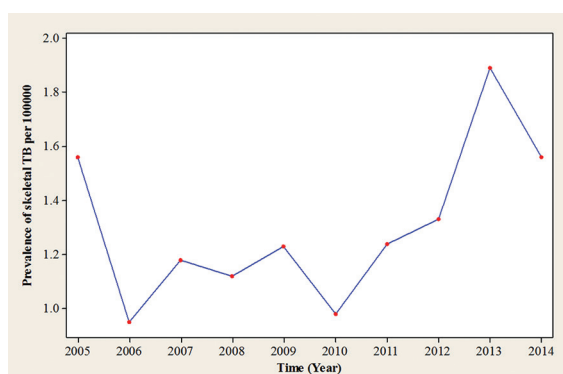


Figure 1: Time series plot of the prevalence of skeletal tuberculosis in northeastern Iran (2005-2014).

Table 1: Skeletal TB treatment regimens<sup>15</sup>

Treatment time	Initial phase regimens	Continuation phase regimens
6 months	2 months of isoniazid, rifampycine, pyrazinamide, ethambutol, or streptomycin	4 months of isoniazid and rifampycine
9 months	2 months of isoniazid, rifampycine, pyrazinamide, ethambutol, or streptomycin	7 months of isoniazid and rifampycine

The patients mainly presented with pain (96.9%), swelling (21%) as local symptoms, fever (51.1%), and weight loss (40.6%) as the systematic symptoms, as shown in table 5. Biopsy and radiography were conducted for 117 (51.1%) patients. Clinical responses and standard radiography were performed on 98 (42.8%) patients. The skeletal TB diagnostic criteria were based on biopsy and clinical response with standard radiography. Of the

Table 2: Patient characteristics of the skeletal tuberculosis (n=229) in northeastern Iran (2005-2014)

Characteristics	N (%)
Sex	
Male	130 (56.8)
Female	99 (43.2)
Ethnicity	
Persian	84 (36.7)
Sistani	82 (35.8)
Turkmen	58 (25.3)
Others	5 (2.2)
Location	
Urban	98 (42.8)
Rural	131 (57.2)
Health system	
Governmental	83 (36.2)
Private	146 (63.8)
History of contact with tuberculosis	
Yes	36 (15.7)
No	193 (84.3)
Vaccination	
Yes	78 (34.1)
No	151 (65.9)
Smoking	
Yes	44 (19.2)
No	185 (80.8)
Drug addiction	
Yes	47 (20.5)
No	182 (79.5)
Method of diagnosis	
Pathology and radiography	117 (51.1)
Responding to medication and standard radiography	98 (42.8)
Culture	4 (1.7)
Smear	8 (3.5)
PCR	2 (0.9)
Treatment	
Anti-TB drugs	180 (78.6)
Surgery and anti-TB drugs	49 (21.4)
Outcome of treatment	
Full recovery	197 (86)
Death	14 (6.1)
Fail in medication	10 (4.4)
Discontinued the treatment	5 (2.2)
Migration	3 (1.3)

**Table 3:** Sites involved with skeletal tuberculosis in northeastern Iran (2005-2014)

Confliction location	Frequency (%)
Spinal column	186 (81.2)
Lower limb	13 (5.7)
Upper limb	7 (3.1)
lower joint	6 (2.6)
Upper joint	6 (2.6)
Sternum and chest	6 (2.6)
Pelvic bone	5 (2.2)

**Table 4:** The absolute frequency of distribution, frequency percentage for outbreak range and outbreak range per 100,000 TB patients based on annual division in northeastern Iran (2005-2014)

Year	Frequency (%)	Total population in a year	TB patients per 100,000
2005	26 (11.4)	1,662,720	1.56
2006	16 (7)	1,672,756	0.95
2007	20 (8.7)	1,682,853	1.18
2008	19 (8.3)	1,693,011	1.12
2009	21 (9.2)	1,703,024	1.23
2010	17 (7.4)	1,723,237	0.98
2011	22 (9.6)	1,767,345	1.24
2012	24 (10.5)	1,798,325	1.33
2013	35 (15.3)	1,842,330	1.89
2014	29 (12.7)	1,853,384	1.56

**Table 5:** Frequency distribution of different clinical symptoms in skeletal tuberculosis in northeastern Iran (2005-2014)

Clinical symptoms	Frequency (%)
Spinal column	
Pain	222 (96.9)
Swelling	48 (21)
Side effect	
Abscess	10 (4.4)
Fracture	4 (1.7)
Systematic symptoms	
Fever	117 (51.1)
Losing weight	93 (40.6)
Sweating	51 (22.3)
Coughing	35 (15.3)
Bloody sputum (hemoptysis)	3 (1.3)

229 patients, 49 (21.4%) underwent surgery and anti-tuberculosis drug therapy. Moreover, 180 (78.6%) patients just underwent anti-tuberculosis drug therapy. As an outcome of the treatment, 197 (86%) patients completed therapy with full recovery, 14 (6.1%) died during medication, 10 (4.4%) with failed treatment, 5 (2.2%) with interrupted treatment, and 3 (1.3%) were transferred out. The treatment success rate was 86%. A 6-9 month treatment regimen was administered to 77.3 % of the patients in which

21.8% were cured in less than 6 months, and the rest were treated for more than 9 months.

## Discussion

In Golestan province, compared with other provinces in Iran, the incidence of TB remains high despite advances in anti-mycobacterial therapy and the implementation of the well-known TB control measures.<sup>3</sup> Skeletal TB is uncommon and represents 10-20% of all extra-pulmonary TB and 1-2% of all TB cases.<sup>18</sup> Our survey revealed that skeletal tuberculosis occurs in approximately 1.11% of patients with tuberculosis over a period of 10 years and the highest rate of skeletal TB was seen in 2013 (1.89%).

Skeletal TB can occur at any age and almost any site of the body. The spine is involved in up to 50% of skeletal TB cases and the thoracolumbar region of the spine is the most commonly affected site.<sup>19</sup> The mean age of the patients was 44 years and 56.8% were male. Lafond et al. found that a majority of the patients were young men and the disease was located in weight-bearing joints, especially in the axial skeleton.<sup>20</sup> In the present study, the spinal column was the most commonly involved skeletal site affecting 81.2% of all cases.

Biopsy and radiography were conducted for almost half of the patients and clinical response and standard radiography were performed on the remaining patients. The skeletal TB diagnostic criteria were based on biopsy and clinical response. Clinical response was defined as improvement of signs and symptoms associated with tuberculosis as judged by the treating physician.<sup>21</sup> Hosalkar et al. performed a retrospective review of all pediatric biopsy-proven skeletal (extra-spinal) cases of tuberculosis over a five-year period; biopsy and culture are the gold standards in diagnosis.<sup>22</sup>

In the present study, the reported prevalent symptoms were bone pain and swelling as local symptoms. The most common systematic symptoms were fever and weight loss. In a study by Hadadi et al., the frequency of osteoarticular TB in two referral hospitals in Tehran (Iran) was reported. They showed that the most frequent general manifestations were pain, weight loss, night sweats, and fever. In TB spondylitis, the lumbar and thoracic vertebrae have been the most frequently involved sites.<sup>12</sup> A similar study in the United States of America demonstrated that the presenting symptoms in all of the patients were persistent pain, swelling, and stiffness or lack of full motion across the involved joint/location.<sup>22</sup>

Approximately 50% of patients with bone and joint tuberculosis have negative findings on chest X-ray. The difficulty in diagnosing multifocal skeletal tuberculosis is due to both the generalized somatic symptoms at presentation and the non-specific physical findings and radiologic results, all of which give rise to a large differential diagnosis.<sup>23</sup> Therefore, physicians should maintain a high degree of suspicion for tuberculosis if a patient presents with multiple somatic symptoms, particularly if the patient is from an area where tuberculosis is endemic. In the present study, we found that the skeletal TB diagnostic criteria were based on biopsy and clinical response.

The mainstay of treatment for spinal tuberculosis is to eradicate the infection, prevent or treat neurological deficits, correct kyphosis deformities, and finally to achieve normal sagittal contours of the spinal column, unrestricted motility, and full activities of daily living as soon as possible.<sup>24</sup> The main treatment of skeletal tuberculosis is conservative management with bracing and anti-tuberculosis drugs. Surgery is needed only if there is a neurologic deficit or spinal instability. These lesions respond rapidly to anti-tuberculosis drugs. In the present study, of the 229 patients, 49 (21.4%) underwent surgery and anti-tuberculosis drug therapy, and 180 (78.6%) underwent just anti-tuberculosis drug therapy. Our treatment success rate was 86%.

While the current study has provided much useful information about the prevalence rate of skeletal tuberculosis and clinical features in northeastern Iran, it has several limitations that must be acknowledged. This study provided information about 229 skeletal tuberculosis cases and did not include a control group to compare demographic and clinical symptoms. The study was limited exclusively to patients from the health centers of Golestan province and not the whole community of Iran. Another limitation is that biopsy was not conducted on 112 patients. More research is required to investigate the prevalence of skeletal tuberculosis in other studied populations.

## Conclusion

The result showed that contact with infected TB people and a case history of TB can be seen as the main elements in suffering from skeletal TB. The spinal column is the most common zone of conflict among patients. On the other hand, pain and fever are the most common signs among cases. According to the results, it can be stated that skeletal TB should be considered

as a differential diagnosis in which patients suffer from fever and pain in the spinal column, particularly in areas with high prevalence of TB (e.g. Golestan province). Radiography could aid to confirm or reject the diagnosis of skeletal TB, but the final diagnosis should be done by pathology or cultivation. It is recommended to conduct supplementary research to evaluate effective elements and probabilistic factors on skeletal TB.

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**Conflict of Interest:** None declared.

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