Diagnostic Performance of the Urinary Deoxypyridinoline in Spinal Tuberculosis

JIANDANG SHI, MD; ZILI WANG, MD; HAOMIN LI, MD; HAIFENG YUAN, MD

abstract

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This study investigated the diagnostic significance of urinary deoxypyridinoline measurement as a screening tool for spinal tuberculosis in patients with pulmonary tuberculosis.

Urinary deoxypyridinoline levels were measured by automated chemiluminescence immunoassay and automated chemistry methods in patients with spinal (n=33) and pulmonary tuberculosis (n=33) and in healthy controls (n=30). Urinary deoxypyridinoline was divided by urinary creatine to exclude the factors of body mass index and urine dilution. The results underwent validity analysis. The measurements of urinary deoxypyridinoline in the spinal tuberculosis, pulmonary tuberculosis, and control groups were 14.9±9.8, 6.4±2.6, and 6.3±2.0 µmol/molCr, respectively. Compared with the other 2 groups, the urinary deoxypyridinoline level in the spinal tuberculosis group was significantly increased (P<.001 and P<.000, respectively). However, urinary deoxypyridinoline levels were not significantly different between the pulmonary tuberculosis and control groups (P=.751). The receiver operating characteristic curve in the spinal tuberculosis group was 0.83. For deoxypyridinoline, the sensitivity (88%) and specificity (95%) were seen at the cutoff level of 8.0 µmol/molCr. The false positive and false negative were 12% and 5%, respectively. Diagnostic validity of the method was 93%.

Bone metabolism alteration occurs during the progression of spinal tuberculosis, which can be reflected by the sensitivity and specificity of urinary deoxypyridinoline. The detection of urinary deoxypyridinoline is a benefit of screening patients with pulmonary tuberculosis for spinal tuberculosis.

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Figure 1: Urinary deoxypyridinoline (DPD) values in the spinal tuberculosis (STB), pulmonary tuberculosis (PTB), and healthy control groups (concentration, mean value of measurements [horizontal solid line], upper limit of reference value [dashed line]).

Figure 2: Receiver operating characteristic curve of urinary deoxypyridinoline (DPD) for diagnosing spinal tuberculosis (deoxypyridinoline curve [thick dashed line], reference value with 0.5 areas under receiver operating characteristic [thin dashed line]). The receiver operating characteristic of deoxypyridinoline for diagnosing spinal tuberculosis was 0.83.
Spinal tuberculosis is a common form of extrapulmonary tuberculosis, although most primary tuberculosis lesions are pulmonary. If spinal tuberculosis can be detected and treated early in patients with pulmonary tuberculosis, the difficulty of surgery could be reduced and the cure rate could increase. Currently, clinical judgment based on radiologic imaging is the main method used to diagnose spinal tuberculosis. Danchaiwijitr et al and Dunn et al reported that magnetic resonance imaging (MRI) can detect spinal tuberculosis 3 months earlier than survey radiographs. However, it is too expensive to use as a practical screening test. Polymerase chain reaction is a highly sensitive test, but it requires extensive equipment. No suitable screening method has been found. Bone loss occurs during tuberculosis invasion, but it is poorly understood whether spinal tuberculosis can be detected early by measuring bone loss.

Urinary deoxypyridinoline has been accepted as a sensitive biochemical marker for bone resorption. The authors measured urinary deoxypyridinoline levels in a total of 96 subjects who had spinal tuberculosis, pulmonary tuberculosis, or were healthy controls.

**Materials and Methods**

**Patient Selection**

*Spinal Tuberculosis Group.* Thirty-three patients with confirmed spinal tuberculosis between May 2004 and May 2005 were randomly selected. The group included 16 men and 17 women aged 30 to 46 years (average age, 36.3 ± 8.5 years). All patients underwent chest radiographs or computed tomography (CT) scan to exclude active pulmonary tuberculosis. Spinal tuberculosis was confirmed by clinical examination, imaging, and histopathology.

*Pulmonary Tuberculosis Group.* Thirty-three patients with confirmed pulmonary tuberculosis were randomly selected between May 2004 and May 2005. The group included 17 men and 16 women, aged 28 to 43 years (average age, 34.4 ± 9.4 years). Radiographs, CT scans, or MRIs were obtained for all patients to rule out extrapulmonary tuberculosis.

*Healthy Control Group.* Thirty healthy adults with no history of pulmonary or extrapulmonary tuberculosis were selected and matched to the disease groups regarding age and sex. The group included 15 men and 15 women, aged 25 to 39 years (average age, 26 ± 8.4 years). To avoid factors that may affect deoxypyridinoline levels, patient requirements were: (1) no immunosuppressant medication, calcium supplement, Vitamin D supplement, or other drugs that affect bone metabolism could be administered 1 month prior to or during the study; (2) no chronic diseases, including severe liver or renal inadequacy, digestive system diseases, endocrine system disorders, hypertension, metabolic bone disease, malignant tumor, or bone fracture, could be diagnosed within the previous 6 months; (3) no human immunodeficiency virus infection or pregnancy could be present.

**Collection and Treatment of Specimens**

According to the method used by Zaninotto et al, all patients fasted for 10 hours overnight, prior to the collection of 10 mL of urina sanguinis the next morning. Specimens were numbered and refrigerated at −2°C. Deoxypyridinoline levels were measured after the specimens were thawed and centrifuged at 1000 r/min for 15 minutes. Three mL of the supernatant was extracted for further examination.

**Main Instrument and Reagent**

An ACS:180 SE automated chemiluminescence immuno analyzer (Bayer, Tarrytown, New York) and automatic biochemistry analyzer (Beckman Coulter, Inc, Brea, California) were used. The urinary deoxypyridinoline kit and deoxypyridinoline ELISA assay kit were purchased from Bayer. The reagent for creatinine detection was purchased from Beckman Coulter, Inc.

**Experimental Methods**

ACS:180 SE automated chemiluminescence immune analyzer deoxypyridinoline assay was performed according to the operating manual with a double-blind method. Urinary deoxypyridinoline was divided by urinary creatinine to exclude the factors of body mass index (BMI) and urine dilution. The detection of urine creatinine was measured by an automatic biochemistry analyzer (Beckman Coulter, Inc) with Jaffe’s kinetic and Picric acid methods. The measurement results were expressed as urinary deoxypyridinoline concentration (nmol/L): urine creatinine (mmol/L).

**Statistical Analysis**

Data were expressed as mean ± SD. Testing showed that heterogeneity of variance existed. Rank sum test was performed for group comparison, and linear correlation was used for the correlation between 2 factors. The relative efficiency was evaluated by a ratio of receiver operating characteristic curve sensitivity to 1-specificity. A value of *P* < .05 was considered statistically significant.

**Results**

The urinary deoxypyridinoline data for the 3 groups are shown in Table 1. Urinary deoxypyridinoline levels in the spinal tuberculosis, pulmonary tuberculosis, and control groups were 14.9 ± 9.8, 6.4 ± 2.6, and 6.3 ± 2.0 µmol/moLCr, respectively. Compared with the other 2 groups, the urinary deoxypyridinoline level in the spinal tuberculosis group was dramatically increased (*P* = .001 vs *P* = .000, respectively). However, the urinary deoxypyridinoline levels were not significantly different between the pulmonary tuberculosis and control groups (*P* = .751). The reference range for urinary deoxypyridinoline in healthy controls was 5.6 to 7.11.

All measured deoxypyridinoline values are labeled in Figure 1. The urinary deoxypyridinoline value in the spinal tuberculosis group was greater than those in the pulmonary tuberculosis and control.
groups. Eight µmol/molCr served as the critical value. For deoxypyridinoline, the sensitivity of the assay in the spinal tuberculosis group was 88% (29/33) and specificity was 95% (60/63). The false positive and false negative were 12% (4/33) and 5% (3/63), respectively (Table 2). The diagnostic validity of the method was 93% (89/96).

The receiver operating characteristic of deoxypyridinoline for diagnosing the spinal tuberculosis receiver operating characteristic was used to evaluate the performance of the diagnostic test. The cutoff value was altered to obtain multiple values of sensitivity and 1-specificity, which served as the Y and X axes, respectively, to draw the receiver operating characteristic figures. The features of the diagnostic method were evaluated by calculating the area under the receiver operating characteristic, which was 0.832, with a standard error of 0.054 (P = .000; 95% confidence interval [CI], 0.727-0.937). The theoretical value was between 0.5 and 1. If the value is equal to 0.5, the diagnostic method was meaningless; if it is equal to 1, the diagnostic method was perfect. The receiver operating characteristic of deoxypyridinoline for diagnosing spinal tuberculosis was 0.83 (Figure 2). For deoxypyridinoline, the sensitivity (88%) and specificity (95%) were seen at the cutoff level of 8.0 µmol/mol creatinine.

**Discussion**

Currently, although focal debridement and spinal reconstruction surgery have improved, the postoperative disunion and recurrence rates reach 13% to 26%. Most cases of spinal tuberculosis can be cured by standard treatments, such as medication, if they can be detected at an early stage. Early diagnosis also reduces surgical difficulty, minimizes the size of the surgical wound and any complications due to it, and increases the cure rate.

Laboratory diagnosis by smear, bacteriological culture, and immunological detection is used for determining tuberculosis. Bacterial detection is considered the gold standard for diagnosing tuberculosis, but it has the disadvantages of low sensitivity, complexity, and a long completion time. Clinical symptoms and imaging data are currently the basis of most spinal tuberculosis diagnoses. However, the clinical symptoms cannot be found on radiographs until the bone destruction is in the mid or advanced stage, with 60% bone mineral density loss. Use of MRI- or CT-guided percutaneous biopsy is limited for initial screening due to its invasive nature and high price. Therefore, it is necessary to find a method for the early detection of spinal tuberculosis with an ease of operation and low cost.

Inflammatory mediators, such as interleukin-1, interleukin-6, and tumor necrosis factor α, are produced during bone infection. These cytokines affect osteoclasts via immune pathways directly or through mediators, which can result in bone resorption. These cytokines also precipitate dramatic increases of interleukin-8 and aseptic inflammation, which may induce tuberculous infiltration. Mineral matter occupies 65% of the extracellular matrix in bone tissues; therefore, examining the biochemical markers of bone metabolism in body fluids can indirectly reflect the bone’s physical status. The authors determined if bone resorption markers can identify bone destruction at an early stage to find bone tuberculosis in patients with pulmonary tuberculosis. Over the past few years, many new biochemical markers have been found relating to bone metabolism, including deoxypyridinoline. Several methods exist for detecting deoxypyridinoline, but the ACS:180 SE automated chemiluminescence immune analyzer is commonly used because of its

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>µmol/molCr</th>
<th>P</th>
</tr>
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<tr>
<td>Spinal tuberculosis</td>
<td>33</td>
<td>14.9±9.8</td>
<td>.001a</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>33</td>
<td>6.4±2.6</td>
<td>.751b</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>6.3±2.0</td>
<td>.006c</td>
</tr>
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*Spinal tuberculosis group vs pulmonary tuberculosis group.
  *Pulmonary tuberculosis group vs control group.
  *Sporal tuberculosis group vs control group.

**Figure 1:** Urinary deoxypyridinoline (DPD) values in the spinal tuberculosis, pulmonary tuberculosis, and control groups (concentration, mean value of measurements [horizontal solid line], upper limit of reference value [dashed line]).
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### Table 2
**Validity of Spinal Tuberculosis Diagnoses**

<table>
<thead>
<tr>
<th>Histopathologic Result</th>
<th>DPD, µmol/mol Cr</th>
<th>Total</th>
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<tbody>
<tr>
<td>Positive</td>
<td>&gt;8</td>
<td>29</td>
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<tr>
<td>Negative</td>
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<tr>
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<td></td>
<td></td>
<td>63</td>
</tr>
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<td></td>
<td></td>
<td>96</td>
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</tbody>
</table>

**Abbreviation:** DPD, deoxypyridinoline.

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The authors used the ACS:180 SE chemiluminescence immunoassay system to measure urinary deoxypyridinoline/Cr in patients with spinal tuberculosis, and the result was compared with that of patients with pulmonary tuberculosis and with healthy controls. The results demonstrated that deoxypyridinoline was greatest in the spinal tuberculosis group, followed by the pulmonary tuberculosis group, and finally the control group. An increase in the urinary deoxypyridinoline level in the spinal tuberculosis group implies that spinal tuberculosis stimulates osteoclasts and enhances bone destruction, where type I collagen, the main composition of bone tissues, is broken down to deoxypyridinoline and excreted with prototypeto the urine rather than through liver metabolism. Unlike in the spinal tuberculosis group, no bone lesions were found in the pulmonary tuberculosis or control groups; therefore, the urinary deoxypyridinoline levels were normal. Urinary deoxypyridinoline level is a reliable biochemical marker for bone destruction in patients with spinal tuberculosis. The authors also used the receiver operating characteristic curve to evaluate the efficiency of the diagnostic test. The area under the receiver operating characteristic curve in the spinal tuberculosis group was 0.83. The correctness of urinary deoxypyridinoline is moderate.

**CONCLUSION**

Bone metabolism alteration occurs during the progression of spinal tuberculosis, which can be reflected by the sensitivity and specificity of urinary deoxypyridinoline. The detection of urinary deoxypyridinoline is a benefit of screening patients with pulmonary tuberculosis for spinal tuberculosis. Characterized by small interference, a non-invasive examination, and rapid results, the determination of urinary deoxypyridinoline may provide an important reference value for the assessment of spinal tuberculosis secondary to pulmonary tuberculosis.

**REFERENCES**


