RELATIONSHIP BETWEEN TUBERCULOSIS AND FEMALE HORMONE LEVELS IN POST-MENOPAUSAL WOMEN

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Abstract. Tuberculosis (TB) is an intracellular infection controlled by T-lymphocyte. After menopause, T-lymphocyte cells counts increase suggesting a possible link between T-lymphocyte cell counts and estrogen and progesterone levels. In this study we compared post-menopausal women with and without TB to determine any differences in estrogen and progesterone levels between the two groups. The study group consisted of 38 post-menopausal women hospitalized for TB at Dr Suat Seren Chest Diseases and Surgery Training and Research Hospital for Tuberculosis, in Izmir, Turkey. The control group consisted of 30 post-menopausal women without TB. Both groups were selected from patients without immunosuppressive diseases or malignancies in whom PPD testing was not contraindicated. The mean progesterone level in the control group was 0.3896 ± 0.2014 ng/ml and in the study group was 0.3607 ± 0.3006 ng/ml (p=0.638). The mean estrogen level in the control group was 18.9873 ± 6.5332 pg/ml and in the study group was 26.2768 ± 14.3418 pg/ml; the difference was significant (p=0.007). The body mass index in the study group was significantly (p=0.034) lower than in the study group. In post-menopausal women, the mean estrogen level was significantly higher in participants with TB than those without TB.

Keywords: estrogens, menopause, progesterone, tuberculosis

INTRODUCTION

Tuberculosis (TB) is the world’s most common and sometimes fatal, infectious disease in adults (WHO, 2010). Approximately one-third of the world’s population is estimated to be infected with *Mycobacterium tuberculosis* (Kilicaslan, 2002). TB is an intracellular infection controlled by the cellular immune response (Daniel, 1980). The host’s ability to control TB depends on an effective cellular immune response (Daniel, 1980). T-lymphocytes play an important role in control of TB (Fauci et al, 1997).

CD4 lymphocytes with major histocompatibility complex (MHC) class 2 play a central role in TB immunity (Fauci et al, 1997). Th1 cells in the CD4 class increase immune activity by producing promoting cytokines, such as interleukin-2, interleukin-12 and interpheron-gamma (Mosmann et al, 2005). Stimulation of macrophages by interpheron-gamma results
in an increase in the expression of MHC class 2 surface molecules (Townsend et al, 1989), resulting in an increased ability to present antigen. CD4 T helper cells have a unique response to this antigen presentation method (Townsend et al, 1989). Th2 cells secrete a different set of cytokines, primarily interleukin-4, interleukin-10, and interleukin-13, which promote humoral immunity and depress cell mediated immunity (Elenkov, 2002). These Th2 cytokines inhibit macrophage activation, T cell proliferation, and the production of proinflammatory cytokines (Fauci et al, 1997).

Women spend approximately one-third their life post-menopause (Sternberg, 2001). Post-menopausal women (PMW) may experience physiological and psychological symptoms from diminished hormone production. Waning estradiol (E2) in the body is a major factor associates with these symptoms. Changes occur in the immune system and other organ systems during menopause. (Bates, 1990; Godsland et al, 1993). Estrogens and progesterone have an effect on the immune system. They can inhibit pro-inflammatory cytokine expression in immune cells expressing the respective receptor (McKay and Cidlowski, 1999). Estrogen receptors are expressed on a variety of immunocompetent cells, CD4+ and CD8+ T cells and macrophages (Salem, 2004). Estrogens have modulator effects on Th1 and Th2 cells (Salem, 2004). Salem (2004) reported estrogen inhibits Th1 proinflammatory cytokine (IL-2, IFN-gamma, and TNF-alfa) production and stimulates Th2 anti-inflammatory cytokine production. Thus, estrogen may suppress Th-dependent diseases while potentiating Th2-dependent diseases. One study suggests that estrogen may enhance the accumulation of Th1 T cells in response to antigens (Maret et al, 2003).

During the post-menopausal period, estrogen is synthesized by extraglandular tissue and androgens by aromatization (Wich and Carnes, 1995). Aromatase is expressed in adipose tissue and skin after menopause; these tissues are an important source for estrogen production during the post-menopausal period (Kiliçturgay, 2003). Therefore, body mass index (BMI) may be an important parameter for estimating endogenous estrogen production (Wich and Carnes, 1995).

In this study we investigated the relationship between estrogen and progesterone levels in patients with and without TB.

MATERIALS AND METHODS

Setting

Thirty-eight consecutive PMW hospitalized at the Izmir Dr Suat Seren Chest Diseases and Surgery Training and Research Hospital during 2004 and 2008 with tuberculosis were included in the study. Exclusion criteria were: having a malignancy, having immune suppression, taking hormone replacement therapy, corticosteroids, beta agonists or antagonist, or taking other immunosuppressive drugs.

Control subjects were 30 consecutive PMW hospitalized at the same institution. Exclusion criteria were: having TB, having a malignancy, being immunosuppressed, and taking hormone replacement therapy, corticosteroids, beta agonists or antagonist or immunosuppressive drugs. None of the patients, control or study groups refused participation in the study.

Definition of menopausal state

Being post-menopausal was defined as not having a menstrual period for 12 months. A BMI was calculated for each subject as weight in kilograms divided by
height in meters squared (kg/m²). A morning venous blood sample was collected from each patient for estradiol and progesterone levels, which were determined using an electrochemiluminescence technique in an autoanalyzer (Cobas e601, Roche Diagnostics, Istanbul, Turkey).

**Diagnosis of TB**

TB was diagnosed using any of the following criteria (WHO, 2007): isolation of *M. tuberculosis* from a culture of the sputum or other body samples, a biopsy specimen showing caseation in a granuloma with or without acid-fast bacilli, a biopsy specimen showing non-caseation in a granuloma in cases responding to treatment, a patient with a positive PPD test having signs and symptoms consistent with active TB, such as having an abnormal chest radiograph or clinical evidence of active TB disease (e.g., fever, night sweats, cough, weight loss, hemoptysis).

**Microbiological diagnosis**

Microscopic examination of sputum by Kinyoun staining and culture for *M. tuberculosis* in both Lowenstein-Jensen medium and liquid medium (BACTEC 960 system; Becton Dickinson, Sparks, MD) were used to identify cases of TB.

**Treatment of TB**

All patients with TB received treatment following WHO criteria (WHO, 2007). Treatment was extended or modified, based on response to treatment and occurrence of drug resistance.

Patients were transferred to respective regional TB treatment offices after hospitalization to continue treatment following national TB treatment policies. Treatment outcomes were not recorded as part of this study.

A PPD test (BBMCIPD, Sofia, Bulgaria; 5 TU/0.1 ml) was performed intradermally (0.1 ml, or 5 TU) on all subjects. The test was read at 72 hours and induration >10 mm was considered positive.

The data were evaluated using SPSS, version 10.0 (SPSS, Chicago, IL). We compared group averages and parameters using a *t*-test and Pearson’s correlation. A *p*-value < 0.05 was considered statistically significant. This study was approved by the Dr Suat Seren Chest Diseases and Surgery Research and Training Hospital Ethics Committee. All participants gave written informed consent prior to participation.

**RESULTS**

The mean age of the TB subjects was 61 (range: 48-83) years and of the controls was 61 (range, 49-76) years (*p*=0.920) (Table 1). Of the 38 TB cases studied, 32 had pulmonary TB and 6 had extrapulmonary TB (TB lymphadenitis in 5 patients and TB pleuritis in one patient). The mean ages of menarche, menopause, the social status, education level, economic level and residence location (urban vs rural) were not significantly different between subjects with and without TB (*p*>0.05) (Table 1).

The mean progesterone level among TB cases was 0.4 (± 0.2) ng/ml and among controls was 0.4 (± 0.3) ng/ml (*p*=0.638) (Table 1).

The mean estrogen level among TB subjects was 26.3 (± 14.3) pg/ml and among controls was 19 (± 6.5) pg/ml. This difference was significant (*p*=0.007). The mean BMI among TB cases (25 ± 4) was significantly higher than controls (23 ± 4) (*p*=0.034) (Table 1).

There were no significant differences in mean hormone levels between pulmonary TB cases and extrapulmonary TB cases studied (Table 2).
Tuberculosis and Female Hormones

Table 1
Progesterone, estrogen and BMI levels among study and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 38)</td>
<td>(n = 30)</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61 ± 11</td>
<td>61 ± 10</td>
<td>0.920</td>
</tr>
<tr>
<td>Menarche age (years)</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
<td>0.940</td>
</tr>
<tr>
<td>Menopause age (years)</td>
<td>46 ± 5.7</td>
<td>46 ± 4.9</td>
<td>0.816</td>
</tr>
<tr>
<td>Mean progesterone level (ng/ml)</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.3</td>
<td>0.638</td>
</tr>
<tr>
<td>Mean estrogen level (pg/ml)</td>
<td>26.3 ± 14.3</td>
<td>19 ± 6.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>25 ± 4</td>
<td>23 ± 4</td>
<td>0.034</td>
</tr>
</tbody>
</table>

BMI, body mass index.

Table 2
Mean progesterone and estrogen levels in pulmonary and extrapulmonary TB patients.

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary TB</th>
<th>Extrapulmonary</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 32)</td>
<td>(n = 6)</td>
<td></td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.2</td>
<td>0.341</td>
</tr>
<tr>
<td>Estrogen (pg/ml)</td>
<td>26 ± 12.1</td>
<td>28.1 ± 24.6</td>
<td>0.739</td>
</tr>
</tbody>
</table>

DISCUSSION

One-third of the world’s population is estimated to be infected with M. tuberculosis (WHO, 2010). About half of these are women (Kilicaslan, 2002). About 700,000 women die annually from TB and three million contract the disease (WHO, 2013).

The incidence of TB is greater among adolescent men than women (Atre et al., 2004). Some studies have speculated this is due to differences in exposure, infection risk and progression from inactive infection to active disease (Holmes et al., 1998; Sony et al., 2003; WHO, 2013). Progression to active TB disease occurs in about 10% of inactive infections (Andrews et al., 2012). Studies conducted in countries with a high TB prevalence show the disease progression rate is higher in reproductive females than the males of the same age period (Holmes et al., 1998; Zeana and El-Sadr, 2004). Some studies have found women with TB have a higher case fatality rate when the subject is in her early reproductive years (Holmes et al., 1998; WHO, 2013). The Ministry of Health China reported the mortality rate for TB among reproductive age women is higher than among males the same age in China (Ministry of Health, 2001).

By the third year post-menopause, ovaries stop producing estrogen and progesterone (Wich and Carnes, 1995), and the adipose tissue becomes a more important source of estrogen (Kiliçturgay, 2003). Studies have found serum estrogen concentrations are directly associated with BMI in PMW (Lamar et al., 2003; Karim et al., 2009). Women with a BMI > 25 kg/m² were found to have significantly higher estrogen levels than women with a BMI < 25 kg/m² (Karim et al., 2009). In our study PMW with TB had signifi-
Significantly higher BMI than those without TB. This may explain why the estrogen levels were significantly higher in TB patients than patients without TB in our study.

There is very limited numbers of literature regarding sex hormones and TB disease in humans. Neyrolles and Quntana-Murci (2009) reported both innate immune cells (monocytes, macrophages, and dendritic cells) and T cells expressed specific receptors for steroid hormones. They suggested that variation in the X chromosome may be involved in the genetic predisposition to TB and sex-specific genetic effects lead to differences in the prevalence of TB between men and women. Nhamoyebo and Leslie (2014) indicated that low levels of estrogens promoted Th1 differentiation and production of cytokines such as TNF-α, while high levels promoted Th2 polarization, with a consequent effect on cytokines. That might explain our results.

Our study has some limitations. The major limitation is low number of subjects, the other is the absence of immunological marker measurements.

In conclusion, in our study, estrogen levels in PMW with TB were significantly higher than those without TB, but progesterone levels were not different.

REFERENCES


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