

ORIGINAL COMMUNICATION

A Hypothesis for Reactivation of Pulmonary Tuberculosis: How Thoracic Wall Shape Affects the Epidemiology of Tuberculosis

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This study was aimed at determining the cause for the high incidence of tuberculosis (TB) reactivation occurring in males with a low body mass index (BMI). Current thinking about pulmonary TB describes infection in the lung apex resulting in cavitation after reactivation. A different hypothesis is put forward for TB infection, suggesting that this occurs in subclinical apical cavities caused by increased pleural stress due to a low BMI body habitus. A finite element analysis (FEA) model of a lung was constructed including indentations for the first rib guided by paramedian sagittal CT reconstructions, and simulations were conducted with varying antero-posterior (AP) diameters to mimic chests with a different thoracic index (ratio of AP to the transverse chest diameters). A Pubmed search was conducted about gender and thoracic index, and the effects of BMI on TB. FEA modeling revealed a tenfold increase in stress levels at the lung apex in low BMI chests, and a four-fold increase with a low thoracic index, $r^2 = 0.9748$ $P < 0.001$. Low thoracic index was related to BMI, $P = 0.001$. The mean thoracic index was statistically significantly lower in males, $P = 0.001$, and increased with age in both genders. This article is the first to suggest a possible mechanism linking pulmonary TB reactivation to low BMI due to the flattened thoracic wall shape of young male adults. The low thoracic index in young males may promote TB reactivation due to tissue destruction in the lung apex from high pleural stress levels. Clin. Anat. 00:000–000, 2015. © 2015 Wiley Periodicals, Inc.

Key words: tuberculosis; body mass index; reactivation; epidemiology

INTRODUCTION

Tuberculosis (TB) remains a major infectious and costly disease even in this century (Man and Nicolau, 2012), but continues to evolve, with its presentation changing over time. Up to the 1950s, it was a disease of females and was linked to malnutrition, poor hygiene, and overcrowding (Ottmani and Uplekar, 2008) but then the incidence of TB in males increased:

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"in industrialized countries at present Men's disease rates exceeding women's after the age of 15 years" (Comstock et al., 1974). Since then, in both industrialized and poor African and Asian countries, it has become a disease of predominantly males (Holmes et al., 1998).

TB infection occurs in two stages: initial primary infection with Mycobacterium TB and progression to active secondary disease (Cegielski and McMurray, 2004). There is no independent association between primary TB and malnutrition and the incidence of tuberculin positive tests in the USA, where BCG immunization is not offered, is not affected by body weight, height or body mass index (BMI) (Cegielski and McMurray, 2004). Reactivation occurs in about 5% of patients and active pulmonary TB usually develops in the apex of the upper lobe, or rarely in the apex of the lower lobe (Jeong and Lee, 2008), often in low BMI males (Tverdal, 1986; Leung et al., 2007; Hanrahan et al., 2010; Lonroth et al., 2010; Cegielski et al., 2012).

Secondary pulmonary TB is unusual in that an association with low BMI occurs across various levels of TB burden without an obvious biological mechanism (Cegielski and McMurray, 2004). Active or secondary TB infection is not related to body mass or BMI at the time of primary infection, although high body mass may be protective (Hanrahan et al., 2010). Active TB infection is not related to general population height. However, there is a strong relationship between active TB and BMI occurring in different countries (Cegielski et al., 2012).

The reason as to why TB selects the apex of low BMI males for reactivation has remained elusive (Lonroth et al., 2010). Any work that may elucidate the biological mechanism for reactivation and development of secondary active pulmonary TB with lung cavitation in this group of healthy low BMI males may help limit the spread of a major infectious disease, since dissemination of disease through lung cavitation is the major pathway for TB transmission (Donald et al., 2010).

METHODS

A finite element model of a lung as a pressure vessel was constructed to investigate the location of stress in the pleura. The apex of the lung was constructed with a groove representing a first rib furrow that was present in all cases of a series of 30 consecutive thoracic CT scans of adult Caucasians see Figure 1. The height of the lung model was 25 cm, the transverse radius of the lung 10 cm and the antero-posterior radius of the lung was variably modeled to obtain a range of ratios in antero-posterior (AP) to transverse lung diameters from 5:8 to 1:1 to assess how the variation in AP diameter would influence stress distribution patterns in the apex. The model was built and analyzed in Ansys v11 (ANSYS, PA), finite element simulation package using linear modelling and meshed using the element SOLID 187, assuming that the composing material was elastic with a Poisson's ratio of 0.3. The base of the model was constrained vertically but allowed to inflate freely in the transverse plane whilst the other parts of the model could inflate



Fig. 1. Coronal and parasagittal CT reconstructions showing indentations on the lung produced by the upper ribs, especially the first ribs. The arrows show the grooving caused by the first rib. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

freely. All models were subjected to a cough pressure of 40 kPa (Casha et al., 2014).

Thirty consecutive adult thoracic CT scans were collected and weight, height, BMI measurements and AP and lateral thoracic wall diameters were measured at the seventh rib in the midaxillary line.

A Pubmed search was undertaken on the epidemiology of TB and to investigate changes in thoracic index in the general population. The keywords used were TB and nutrition, malnutrition, epidemiology, BMI, weight, or wasting. In addition, WHO reports about TB were identified and Web of Knowledge was used to deepen the searches by looking through citations. Local ethics committee approval was obtained for this study.

STATISTICS

The BMI and CT measurements were analyzed using Pearson correlation and two-way ANOVA with

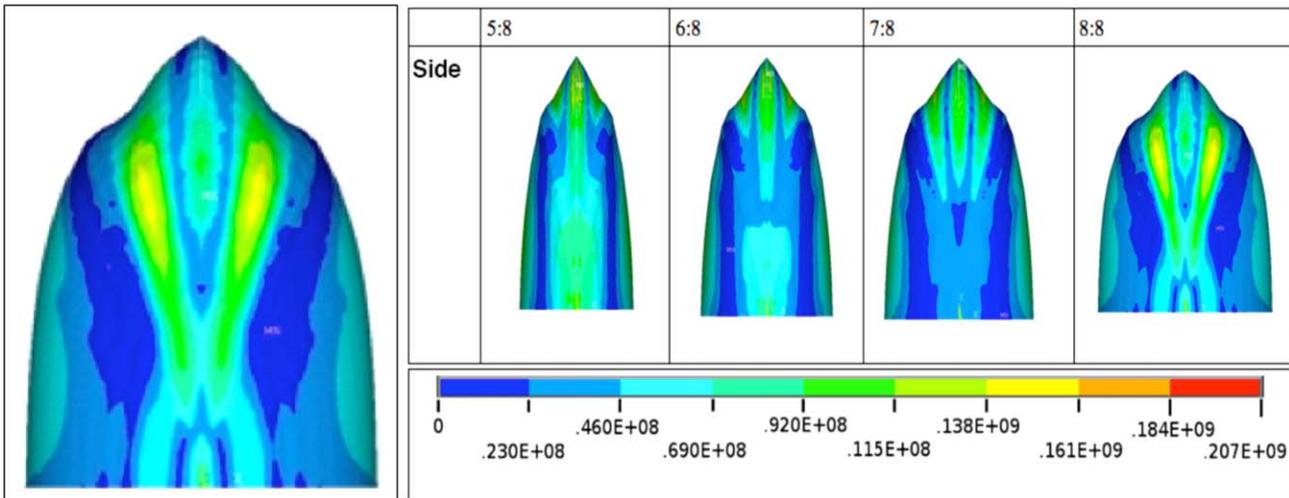


Fig. 2. A: FEA model of the lung showing increased a 10-fold increase in pleural stress at apex and within the furrows produced by the first rib on coughing. B: FEA model with the antero-posterior radius of the lung variably modelled to obtain a range of thoracic index. There is

an almost four-fold increase in pleural stress in individuals with a thoracic index of 0.63, compared with a thoracic index of 1.0. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

interaction using SPSS (IBM, Armonk). A one-factor regression model was used to relate AP diameter against BMI. An independent samples *t* test was used to compare mean thoracic indices using data reported by Takahashi and Atsumi (1955).

RESULTS

FEA simulation showed the presence of three areas of high stress activity in the apical region present near the apex and within two grooves on either side of the apex caused by the first rib furrows, with pleural stress of a 10-fold magnitude compared to the base, see Figure 2A. The series of four FEA simulations (Fig.

2B) showed a fourfold increase in pleural stress levels in the apical area from the narrowest model (5:8) to the round (8:8) model. The maximum stress reached for all models in shown in Figure 3. There was a twentyfold increase in pleural stress between the apical area and the base in the flat chest (narrow) 5:8 ratio model. All the thoracic CT scans examined showed furrows on the lung caused by the ribs, more markedly in the upper ribs and especially by the first rib, see Figure 1, ranging from slight to very marked. There was no obvious correlation between the size of the rib grooving and body habitus. The CT data showed that the apex was not a simple ellipsoid as is commonly illustrated, but had a flattened teat appearance to the apex with shouldering caused by the grooves, see Figure 2.

A two-way ANOVA with interaction was used to relate AP diameter to both gender and BMI collectively. The test revealed that BMI was the sole significant predictor of AP diameter, $F(1,25)=13.197$, $P=0.001$, and that neither gender ($P=0.796$), nor the interaction effect between gender and BMI ($P=0.528$) were significant. The Pearson product-moment correlation coefficient, r , showed a statistically significant correlation between AP diameter and BMI, $r=0.780$, $P<0.001$ in males; and in females $r=0.101$; $P=0.05$.

A one-factor regression model for AP diameter against BMI in males showed that:

$$\text{AP diameter} = 0.195 \text{ BMI} + 11.344$$

with statistical significance of $P<0.0001$ for both terms in the equation, the regression coefficient or gradient, and the constant. The rate of change in AP diameter against BMI in males varied within the range of 0.105 to 0.285 with 95% degrees of confidence. This regression coefficient was significantly greater than zero, with $P<0.0001$; moreover, the 95% confidence intervals

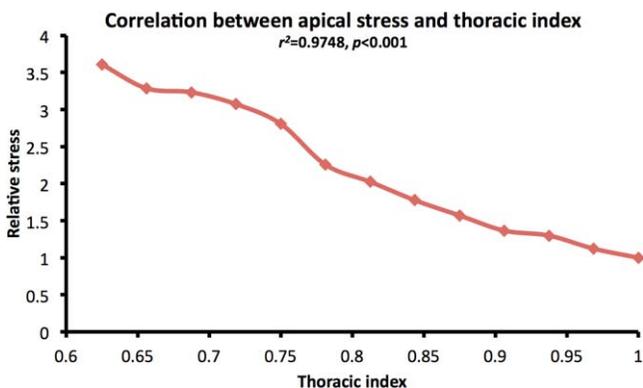


Fig. 3. Correlation between apical stress and thoracic index (or low AP diameter), $r^2=0.9748$ $P<0.001$; where low thoracic index or low AP diameter is a marker for low BMI, with AP diameter related to BMI, two way ANOVA $P=0.001$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

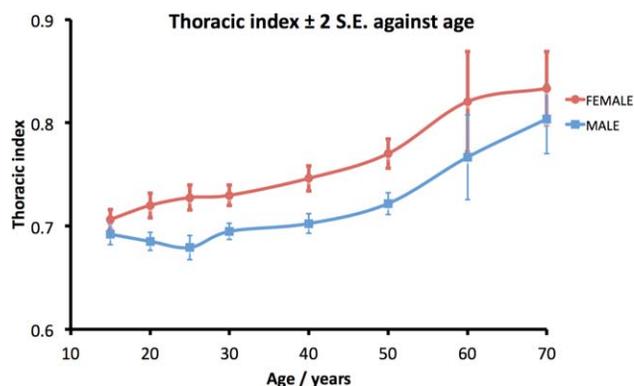


Fig. 4. In the general population, males have a flatter chest, as compared with females, with higher pleural stress levels, $P=0.001$. Changes in thoracic index ± 2 standard error (SE*) for the sample mean, with age according to gender. *2 SE are the 0.975 quantile of the normal distribution, equal to the upper and lower 95% confidence limits. Redrawn after Takahashi [14]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

excluded zero. This predictor model for BMI explained 60.9% of the total variation in AP diameter.

The mean thoracic index from Takahashi's data was statistically significantly lower in males, t test $P=0.001$, see Figure 4. Seven cohort studies on TB were identified linking BMI and incidence of TB across several countries and shown in Table 1.

DISCUSSION

Until recently, spontaneous pneumothorax patients were thought to have a 'heritable defect' (Voge and

Anthracite, 1986) with a flattened thoracic wall shape with low anteroposterior diameter and thoracic index (Peters et al., 1978). The associated morphological defects were subpleural blebs and bullae seen on computerized tomography (CT) scanning (Lesur et al., 1990). Pleural stress has long been postulated to be the cause of apical bullae in pneumothorax (West, 1971). This article investigates a possible correlation between thoracic wall shape, pleural stress, and TB by means of computer simulation modelling of pleural stresses in a lung model.

The hypothesis considered here is that pre-existing high apical pleural stress levels predispose to TB reactivation. It is theorized that high apical pleural stress levels result in apical lung tissue destruction similar to that in spontaneous pneumothorax (Casha et al., 2014). For this hypothesis to be considered as potentially valid, the incidence of TB reactivation would be expected to increase in the four states where apical pleural mechanical stress is high, namely low AP chest diameter or low thoracic index, young age, male gender, and apical location, states that are all present in spontaneous pneumothorax (Casha et al., 2014). If these characteristics are fulfilled, then the hypothesis that high apical pleural mechanical stress levels predisposes to TB reactivation, may be held to be valid.

Low BMI

The association between pulmonary TB and low BMI is well documented (Tverdal, 1986; Leung et al., 2007; Hanrahan et al., 2010; Lonroth et al., 2010; Cegielski et al., 2012). The correlation between low BMI and TB was first recognized by Hippocrates. Palmer's group investigated about 68,754 US Navy recruits. Edwards extended Palmer's study to [mt]823,000 Navy recruits and found that TB developed "three times more often in

TABLE 1. The Relationship Between BMI and TB

| | Date | Subjects | Follow-up (years) | BMI | % Sample | Incidence/10 ⁵ |
|-----------|---------|---------------|-------------------|-----------|----------|---------------------------|
| Palmer | 1949–55 | 68,754 | 4 | <19.2 | 11 | 75.1 |
| USA | | Navy recruits | | 19.3–23.7 | 69 | 40.1 |
| USA | | 17–21 y | | >23.7 | 21 | 18.9 |
| Edwards | 1958–67 | 823,199 | 4 | <19.6 | 18 | 79.1 |
| USA | | Navy recruits | | 19.7–23.9 | 59 | 46.5 |
| USA | | 17–21 y | | >23.9 | 24 | 22.5 |
| Hemila | 1985–93 | 26,975 | 7 | <23 | 19 | 116 |
| Finland | | Male smokers | | 23–27 | 42 | 55.2 |
| Finland | | | | <27 | 39 | 32.7 |
| Tverdal | 1963–82 | 1,717,655 | 12 | <21 | 17 | 16.7 |
| Norway | | >14 y | | 21–30.9 | 77 | 7.6 |
| Norway | | | | >31 | 6 | 3.1 |
| Leung | 2000–05 | 42,116 | 5 | <18.5 | 5 | 599 |
| USA | | >65 y | | 18.5–29.9 | 89 | 221 |
| Hong Kong | | | | >30 | 6 | 102 |
| Cegielski | 1971–92 | 13,211 | 11 | <18.5 | 5 | 173.9 |
| USA | | 25–74 y | | 18.5–30 | 75 | 22.9 |
| USA | | | | >30 | 20 | 8.5 |
| Hanrahan | 2003–08 | 3,456 | 3.2 | <18.5 | 10 | 7.3 |
| USA | | >18 y | | 18.5–25 | 49 | 6.0 |
| S. Africa | | | | >25 | 41 | 2.6 |

There is a spectrum of TB incidence ranging from Hong Kong (high), USA (intermediate), and Norway (low). In spite of this, there is a clear relationship between TB incidence and BMI. Based on Lonroth [8].

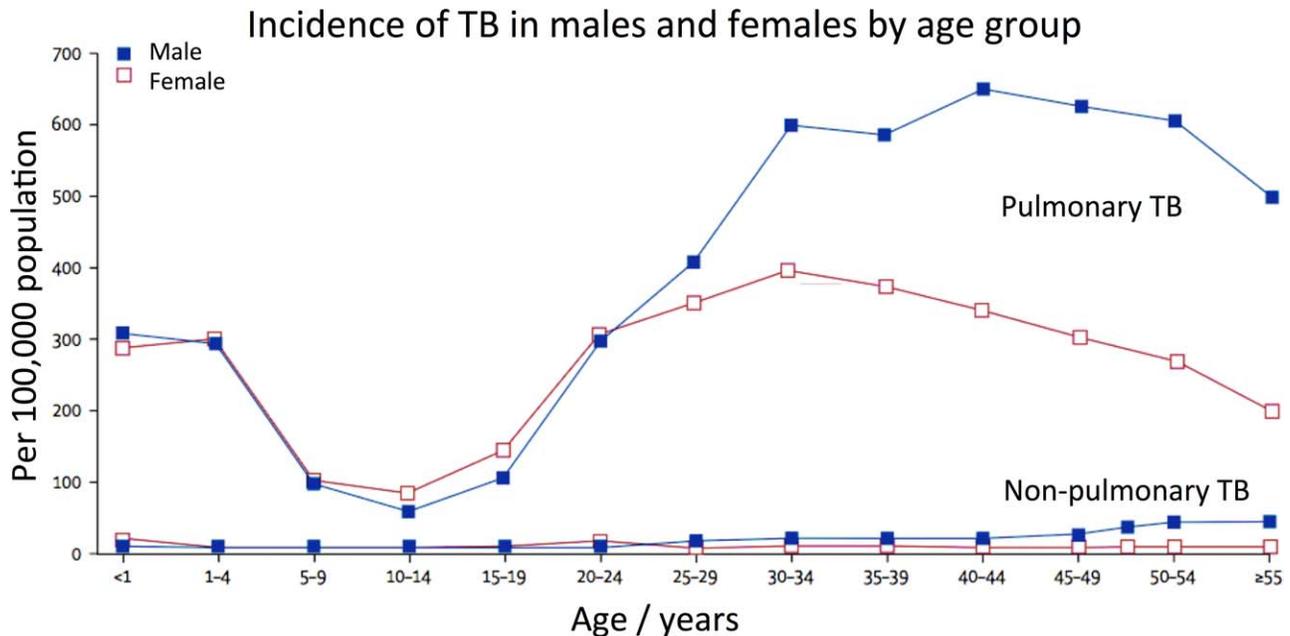


Fig. 5. Incidence of TB in males and females by age group. Note the sudden increase in male disease in adolescence, marking a sudden increase in pulmonary TB, but not in non-pulmonary TB. Redrawn after Donald [12]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

young men 10% or more below their ideal body weight than in those 10% or more above it" (Edwards et al., 1971). Tverdal from Norway gathered data from 1.7 million Norwegians with 12.1 years follow up. "The age-adjusted incidence of new pulmonary TB was five times higher in the lowest BMI category than in the highest." Tverdal argued that this relationship was a "function of body build." He suggested that "body build may influence susceptibility to TB because of differences in pulmonary mechanics" (Tverdal, 1986). There was an increase in the incidence of pulmonary TB with decreasing BMI in both sexes in all age groups with a five-fold range between the lowest and highest BMIs (Edwards et al., 1971).

Low BMI was associated with low AP diameter in males, Pearson $r=0.780$; $P<0.001$; and females, $r=0.101$; $P=0.05$. The AP diameter of the chest increased at a faster rate against BMI (1.883 mm, $P=0.0001$) than lateral chest diameter (0.883 mm, $P=0.0009$) in a linear regression model reported by Bellemare, especially in the lower chest and in males (Bellemare et al., 2001), indicating that thoracic index would increase with increasing BMI. The FEA model showed that low AP chest diameter and low thoracic index was associated with an almost fourfold increase in apical pleural stress.

Apex of the Lung

Reactivation of pulmonary TB usually occurs in the apical and posterior segments of the upper lobes or in the superior segments of the lower lobes in younger people (Jeong and Lee, 2008), sites related to high

pleural stress due to their bullet shape. In contrast pulmonary TB in the elderly results in lower lobe pneumonia, similar to other bacterial infections (Fitzgerald et al., 2014). The conventional theory is that these are sites of impaired lymphatic drainage (MacGregor, 1993), and high pO_2 levels (Fitzgerald et al., 2014). As pulmonary TB also has a predilection to the apical region of the lower lobe (Jeong and Lee, 2008), this suggests that oxygen levels and gravity may not be such important factors; however our FEA model showed that the lung apex was an area of high pleural stress levels, ten-fold that of surrounding areas. Geometrically the apex of the lung has an elongated spheroidal shape where the height to base ratio exceeds 1.42 resulting in buckling and tearing of the lung, as in the circumferential stress component becomes negative (Fryer and Harvey, 1997). The "bullet" shape of the lobe apex would result in increased pleural stress, partly limited in the case of the apex of the lower lobe by the support provided by the adjacent upper lobe. Another important factor was the negative curvature of the first ribs furrows that also resulted in a large increase in pleural stress due to a reversal of the normal surface circumferential stress (Fryer and Harvey, 1997).

Gender

The reason why males have a higher incidence of TB remained elusive (Diwan and Thorson, 1999). Worldwide, the prevalence of TB is identically low in both sexes until adolescence, after which it is higher in males (Holmes et al., 1998). The increase in incidence occurs

in puberty and is rapid, see Figure 5. The increase in male infection rate in adolescence is marked by the “sudden emergence” of cavitating lung disease typical of adults (Donald et al., 2010). Males have a statistically significant lower thoracic index than females from adolescence (Takahashi and Atsumi, 1955), *t* test $P = 0.001$, see Figure 4, indicating higher pleural stress predisposing to apical lung bullae.

Young Age

Reactivation of pulmonary TB increases in adolescence and young adults, males more than females, however, reactivation of nonpulmonary TB remains constant (Donald et al., 2010), see Figure 5. The rib cage shape changes with increased age such that there is mostly an increase in AP chest diameter (Gayzik et al., 2008) leading to a reduction in apical pleural stress. The slender thoracic wall shape is lost with aging as the BMI increases, with the lowest thoracic index in humans occurring after adolescence (Openshaw et al., 1984).

NUTRITION AND TB

Traditionally, it has been assumed that both poor nutrition and low BMI are different manifestations or markers of the same causative factor. However, one may instead look at nutrition and BMI as independent factors, with BMI acting as a marker of low AP thoracic diameter. This would explain why the incidence of new pulmonary TB was five times higher in the lowest BMI group ($BMI < 21$) as compared with the highest group ($BMI > 31$) in prospective studies that remove the confounding effect of weight loss of TB (Lonroth et al., 2010). This remarkable association was not observed for extrapulmonary TB (Tverdal, 1986), suggesting that low BMI predisposes to an increased risk for pulmonary TB only, but not for nonpulmonary TB. As BMI increases with age, this means that in adulthood, BMI rises and new reactivation of pulmonary TB decreases due to the effect of the change in thoracic wall shape resulting in lower pleural stress decreasing the risk of cavitation.

It can be predicted that pathologies with the same pathophysiology should occur concurrently more frequently than by simple chance. With the hypothesis that TB and spontaneous pneumothorax may both be caused by high pleural stress levels, it would be expected that these pathologies occur concurrently fairly frequently even though both diseases are rare. Incidence of TB is typically about 7:100,000 (World Bank website accessed 2015) and that of spontaneous pneumothorax 18:100,000 (Noppen, 2010) in Swedish males. However, 5.4% of spontaneous pneumothorax patients had TB and 2.1% of patients with TB had spontaneous pneumothorax (Freixinet et al., 2011).

Furthermore, lung bullae occur in about 15% of “normal” subjects, with this cohort having a significantly lower BMI than controls (Amjadi et al., 2007). In patients with low BMI and a flat thoracic wall

shape, the increased pleural stress leads to progression of apical bullae to clinical disease.

Although a mechanism for TB progression based on pleural stress has been identified, it is clear that additional work is required for a better understanding of this mechanism. It is hoped that this study will stimulate further investigations in this field, in particular to assess the effectiveness of population screening for TB using chest AP diameter or thoracic index as markers for future disease. This may deliver important public health consequences in terms of screening, especially as a tool in conjunction with contact investigation, to aid the World Health Organization’s STOP TB strategy (Raviglione, 2007), as cavitating pulmonary TB is the major pathway for TB transmission.

CONCLUSION

This article is the first to suggest a possible biomechanical mechanism for the predominant presentation of pulmonary TB in young males with low BMI. It is suggested that subclinical apical pleural destruction caused by stress concentrations at the apex leads to tissue destruction and cavity or bulla formation and predisposes to TB reactivation. Mild changes in thoracic index occurring in females or with aging result in lower stress levels that may explain the predilection for reactivation of pulmonary TB in the apex of the upper or lower lobes of young, low BMI males.

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