

## Management of Respirable Silica-Associated Tuberculosis

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Silicosis, a fibrosing lung disease caused by inhalation and deposition of crystalline silica particles, resulting in pulmonary response that is the most prevalent of the pneumoconiosis. The association between silicosis and tuberculosis (TB) has been investigated since the beginning of the 20th century. Comparing to health populations, the risk of developing pulmonary TB is approximately 2.8 to 39 times, whereas the risk of a patient with silicosis developing extrapulmonary TB is around 3.7 times. The pleural form is the most common, accounting around 61% of the cases, followed by the pericardial form and the lymph node form. Occupations and environments contributing to the greatest risk of silicosis include the following: ceramic and glass production, mining of gold and precious stones, mining and processing of stone, sandblasting, iron smelting, and well drilling. Silicosis clinically can present in three different forms: acute, accelerated, and chronic forms. The acute form is caused by substantial exposure to silica and usually presents within two years after initial silica exposure. In accelerated form, clinical symptoms appear after 2 to 10 years. Chronic form is characteristically oligosymptomatic and develops more than 10 years after silica exposure, but it can be rapid evolved to progressive dyspnea on exertion and death within a few months or years. Additionally, the importance of silicosis as an occupational lung disease, silicosis-or even exposure to silica developed disease-is associated with increased risk of developing several pulmonary and systemic comorbidities. In patients with silicosis, there are higher prevalence of TB, non-tuberculous mycobacterial diseases, chronic obstructive pulmonary disease (COPD), lung cancer, glomerulonephritis, rheumatoid arthritis, scleroderma, and other autoimmune diseases.

A previous study in more than 2,000 gold miners with 27 years of monitoring revealed that the risk of developing pulmonary TB is proportional to the severity of silicosis and the intensity of the exposure and demonstrated a mean interval of 6.8 years between the diagnosis of silicosis and the onset of TB. A previous study in 2,255 gold miners for 27 years demonstrated that 115 cases of pulmonary TB were diagnosed by sputum smear microscopy or autopsy (histological finding) and the TB risk was 4.01 in those with the greatest exposure. The diagnosis of TB was made, on average, 7.6 years after the end of silica exposure. A previous prospective study in 1,153 gold miners demonstrated that the annual incidence of TB was 2.7 % in those with silicosis, compared to 0.98 % in those without silicosis. The TB incidence was proportional to the severity of silicosis, increasing to 6.3 % in patients whose chest roentgenograms demonstrated intense nodule profusion. A previous study in efficacy in TB chemoprophylaxis in patients with silicosis revealed that the annual incidence of TB was 7 % in the group of patients receiving placebo. The previous largest study reviewing more than 4 million death certificates issued between 1982 and 1995 in the United States showed that 22 % of 6,570 cases of pulmonary TB presented silica exposure. The mean odds ratio (OR) identified was 1.47 and was proportional to the degree of exposure.

Among the workers classified as having been exposed to very high levels of silica, they were miners and foundry workers. A previous cross-sectional study revealed that the risk for developing active TB was directly related to the cumulative degree of silica exposure, similar to a dose-response effect. In those with the least exposure and in those with the greatest exposure, the TB prevalence ranged from 20 % to 35 %, respectively. In isolation, the length of time working in mining was dependently related to the TB prevalence. A previous study

in 381 gold miners with positive sputum culture for *Mycobacterium tuberculosis* revealed that the TB risk was increased for those who had worked in mining for more than 10 years (OR = 1.9). In consideration of miners with nontuberculous mycobacteria-related diseases, the following risk factors were associated with the development of mycobacteria-related diseases : having a history of TB (OR = 9.6), having worked in mining for more than 20 years (OR = 7.1), having silicosis (OR = 5.0), being HIV-infected (OR = 3.6), and having worked in mining for more than 10 years (OR = 2.6). Another previous study showed that the risk factors for the development of nontuberculous mycobacteria-related diseases were silicosis (OR = 12.6) and previous treatment of TB (OR = 3.61). In those with periods of exposure longer than 15 years, the TB risk was about 4 times higher than that identified for control subjects. Consideration of occupations involving higher silica exposure (for example, surface work versus underground work) at the diagnosis, a non-significant tendency towards TB risk was identified (OR = 1.3, confidential interval = 0.82-1.94).

The diagnosis of silicosis is made by chest imaging following the International Labour Organization (ILO) Classification, characterized by symmetrically distributed, small (usually 1 - 3 mm.) rounded opacities, initially in the upper lung zones. These opacities may occasionally not be visible on a chest roentgenogram, although in advanced silicosis determined by histology. In chronic silicosis, pulmonary function in spirometric tests are often normal in early disease. Occasionally, there may be airflow limitation, even in the absence of roentgenographic silicosis. This airflow limitation is likely due to associated pulmonary TB or pulmonary emphysema. In patients with suspected silicosis-associated pulmonary TB, sputum microscopic examinations and cultures and interferon-gamma-release assay (IGRA) including molecular testing are additionally recommended in addition to evaluation of the clinical features.

In the aspects of primary prevention and control of respirable silica-dust exposure, the American Conference of Government Industrial Hygienists (ACGIH) has recommended a threshold limit value (TLV) of 0.025 mg/m<sup>3</sup>, whereas widely used current standards of 0.05 - 0.1 mg/m<sup>3</sup> of the respirable silica-dust exposure. Currently, the World Health Organization (WHO) recommends both testing and chemoprophylaxis for latent TB infection for silicosis patients in high- or middle-income countries with a low TB incidence rate (< 100 per 100,000 population). Chemoprophylaxis can reduce the TB incidence rate in patients with silicosis by 12 % to 17 %. The five recommended regimens are 6INH, 9INH, 3-4RIF, 3-4 (RIF + INH), and 3 (RPT + INH)-none of which has demonstrated superiority over the conventional 6INH or 9INH chemoprophylaxis (INH = isoniazid, RIF = rifampicin, RPT = rifapentine). For countries with limited resources, whether to treat latent TB infection in patients with silicosis remain to be discussed.

In conclusion, the prevention of silicosis requires the monitoring and reduction of silica dust levels which is primarily a technical problem but again it is important that the control of the disease is addressed jointly by the mine management, the mine medical services, and the trade unions. Good primary health care interventions are needed that focus on prevention and early detection of problems. This will not only be more cost-effective but will also create associations between the medical aspects of disease and the social context of disease transmission on the mines. Silicosis contribute to a significantly increased TB reactivation rate, and for countries with a low TB prevalence, patients with highly respirable-silica dust exposure or silicosis should undergo screening and treatment for latent TB infection. The management goals of incurable silicosis are to detect early case of silicosis and TB via monitoring of both currently and formerly silica exposed workers, to slow disease progression, to prevent TB, to reduce disability, and to establish surveillance programs. Workers with silicosis or silicosis-associated TB may be excluded from many jobs because of abnormal chest roentgenogram, so compensation benefits are provided generally for families and medical costs although in the absence of respiratory symptoms or impairment.

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