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INVITED REVIEW

Silica-associated lung disease: An old-world exposure in modern industries

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ABSTRACT

Despite silica dust exposure being one of the earliest recognized causes of lung disease, Australia, USA, Israel, Turkey and other countries around the world have recently experienced significant outbreaks of silicosis. These outbreaks have occurred in modern industries such as denim jean production, domestic benchtop fabrication and jewellery polishing, where silica has been introduced without recognition and control of the hazard. Much of our understanding of silica-related lung disease is derived from traditional occupations such as mining, whereby workers may develop slowly progressive chronic silicosis. However, workers in modern industries are developing acute and accelerated silicosis over a short period of time, due to high-intensity silica concentrations, oxidative stress from freshly fractured silica and a rapid pro-inflammatory and pro-fibrotic response. Appropriate methods of screening and diagnosis remain unclear in these workers, and a significant proportion may go on to develop respiratory failure and death. There are no current effective treatments for silicosis. For those with near fatal respiratory failure, lung transplantation remains the only option. Strategies to reduce high-intensity silica dust exposure, enforced screening programmes and the identification of new treatments are urgently required.

Key words: interstitial lung diseases, occupational diseases, silicosis, silicon dioxide.

INTRODUCTION

Silicosis is not a new disease; the impact of silica dust on respiratory function was observed by Hippocrates in 430 B.C.[1] and in the 16th century by Agricol. In 1713, Rammazini described silicotic nodules in post-mortems of stone cutters presenting with respiratory symptoms.[2] In the mid-late 1800s, the introduction of mechanized tools in the mining sector rapidly increased levels of silica exposure, resulting in an increase in cases and our understanding of silicosis.[1]

Silica (silicon dioxide, SiO_2) is a naturally occurring mineral that accounts for 59% of the mass of the earth's crust and is the main constituent of more than 95% of rocks. Historically, most workers at risk of silicosis were those who encountered it in its natural environment, such as miners, tunnels and quarry workers. In developed countries, a greater understanding of the risk of silica exposure in these industries and advances in dust control measures has resulted in decline in silicosis-associated mortality.[3] Silica-related lung disease however remains a major health issue in the mining sector in low- and middle-income countries. In China, over half a million silicosis cases were reported between 1991 and 1995,[3] and in excess of 10 000 deaths over three decades from silicosis have been reported in South African miners.[4] Recent outbreaks of pneumoconiosis in the mining sector in the USA and Australia demonstrate that even in developed countries, vigilance needs to be constantly maintained regarding control of dust levels.[5,6]

Silicosis is a fibrotic respiratory disease caused by the inhalation and deposition of respirable crystalline silica (SiO_2) (particles <10 μm in diameter). Crystalline silica is the most well studied and thought to be the most toxic; however, amorphous silica may contribute to the development of pulmonary fibrosis, and nano-silica may cause inflammation and cytotoxicity.[7] The cumulative dose of silica exposure (respirable dust concentration multiplied by crystalline silica content and exposure duration) is the most important factor in the development of silicosis.[3] There are three described forms of silicosis primarily related to the characteristics of occupational exposure: (i) chronic silicosis, occurs after 10 or more years at low-moderate exposure dose, (ii) accelerated silicosis, develops within 10 years of moderate-high level exposure and (iii) acute silicosis, associated with very high-intensity exposure and may present within a range of weeks to 5 years from the time of initial exposure.[8]

Chronic silicosis has been well described in recently published reviews.[2,3] This review will focus on the accelerated and acute forms of silicosis and recent outbreaks of this disease outside the mining sector.

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CHRONIC SILICOSIS

Chronic silicosis typically develops following decades of exposure to silica dust and has two forms: simple or nodular silicosis and complicated silicosis or progressive massive fibrosis (PMF). Chronic silicosis has a long latency, usually over 20 years, therefore may only become apparent after workers leave employment.[8]

Simple silicosis is characterized by discrete, hard nodules (up to 1 cm in size), usually in an upper lobe predominant distribution on chest radiology. Patients may be asymptomatic, although up to 70% of patients in some case series report exertional dyspnoea, chronic cough and sputum production.[9] Silicotic nodules may coalesce to form conglomerate masses (>1 cm in size), which is characteristic of PMF. Central cavitation may occur, leading to increased risk of mycobacterial infections.[2] Enlarged hilar or mediastinal lymphadenopathy may be seen in up to 75% of silicosis patients.[10] Significant distortion of surrounding lung parenchyma and peribronchial vessels occurs in PMF and increases the risk of spontaneous pneumothoraces. Pleural thickening is often present[11] (Table 1).

The relationship between the dose of silica exposure and morbidity/mortality has been reported in a number of studies.[12,13] The current National Institute for Occupational Health and Safety (NIOSH) USA exposure limit is 0.05 mg/m^3, but even at these levels, the risk of developing simple silicosis over a life time of work in the environment is 20–40%.[13]

Large retrospective cohort studies demonstrate that the progression from simple silicosis to PMF occurs in 18–37% of workers over an average of 5 years.[14,15] Ongoing silica exposure and smoking are significant factors that increase the risk of radiological progression from simple to complicated silicosis, as well as progressive loss of lung function.[16] Mortality is increased for those diagnosed at a younger age, the presence of conglomerate disease, history of smoking and coexistent tuberculosis.[17] Genetic variants, such as single nucleotide polymorphisms of tumour necrosis factor (TNF)-alpha[2] or rs2076304 in the DSP gene (a novel variant of desmoplakin),[18] have also been associated with an increased risk of mortality.

ACUTE AND ACCELERATED SILICOSIS

Reports of acute and accelerated silicosis are limited to small series and case reports. Both forms are associated with high-intensity silica exposure, over a much shorter period of time than chronic silicosis.

Acute silicosis (also known as silicoproteinosis) may develop within a few weeks to less than 5 years of high-intensity silica exposure and presents with dyspnoea that may progress rapidly to respiratory failure and death. The dose of exposure required to develop acute silicosis is poorly studied but thought to be in the order of 1–10 mg/m^3/year.[19]

Accelerated silicosis is a more rapidly progressive disease compared to chronic silicosis, and the presenting features depend on the stage at which disease is identified. Initially, there may be a similar pattern to simple silicosis, followed by more rapid development of coalescent masses, parenchymal distortion and fibrosis.[3] Silica exposure is usually of high intensity, over 2–10 years. Currently, there is a marked gap in knowledge regarding the dose of exposure associated with accelerated silicosis. There may

Table 1 Forms of silicosis

Form	Duration of exposure	Radiological findings	Clinical findings
Simple chronic	>10 years	Round or irregular nodules <1 cm ± calcification of nodules Upper lobe predominant	Asymptomatic Chronic cough Exertional dyspnoea Obstructive, restrictive or mixed defects
Complicated chronic/conglomerate/PMF	>10 years	Conglomerate masses >1 cm migrating to the hilum ± calcification of nodules: uniform (53%) or speckled (26%) pattern; rarely with an eggshell pattern (5%) ± central cavitation Diffuse reticulonodular fibrosis Surrounding emphysema Pleural thickening	Asymptomatic Chronic cough Exertional dyspnoea Weight loss Respiratory failure
Acute silicoproteinosis	<5 years	Bilateral perihilar consolidation Centrilobular nodules Ground-glass changes Crazy paving	Dyspnoea Cough Weight loss Respiratory failure
Accelerated	2–10 years	Rapidly progressive nodules and masses Features of PMF	Dyspnoea Cough Respiratory failure

PMF, progressive massive fibrosis.

be an overlap with acute and accelerated silicosis, and both are at higher risk of developing PMF,[2] despite the lack of ongoing exposure.[20] In addition, very little is known about the risk factors that are associated with the development of either acute or accelerated silicosis.

PATHOGENESIS OF ACUTE AND ACCELERATED SILICOSIS

Silicosis has a strict exposure–response relationship; however, most of our understanding comes from low-moderate exposure over many years and the development of chronic silicosis. Understanding of high-intensity short exposure is much less, although there appears to be a plume effect whereby short-term high concentration exposure (>2 mg/m^3) has an effect three times as great as a cumulative equivalent longer term exposure at lower levels.[21]

Inhalation of respirable silica particles leads to deposition in the distal airways. Silica particles are engulfed by alveolar macrophages, which in turn upregulate several pro-inflammatory and pro-fibrotic pathways. The interleukin (IL)-1 signalling pathway is stimulated directly by the macrophage and indirectly via toll-like receptors, and in turn produce IL-1 and TNF, and capase-1, which stimulate fibroblast growth factor. In addition, inflammation and fibrosis can occur independent of lymphocyte interaction by modulation of the NALP3 (NACHT, LLR and PYD domains containing protein 3) inflammasome, which increases regulatory T cells to express cytotoxic T-lymphocyte antigen 4, IL-10 and transforming growth factor beta (TGF-β) (Fig. 1).[3]

Subsequent ingestion of silica by alveolar macrophages leads to cell death, autophagy and release of intracellular silica, which attracts further macrophages, releases cytotoxic oxidants and proteases, inflammatory cytokines and arachidonic acid metabolites. This perpetual cycle leads to further alveolitis and fibrosis.[22] Acute, high-intensity silica exposure leads to hypertrophic type II pneumocytes that produce excessive amounts of proteinaceous material and surfactant protein, filling the alveoli.[2] Macroscopic pathological findings include the presence of eosinophilic-rich proteinaceous material in alveolar spaces, which leads to pulmonary oedema and interstitial inflammation.[11]

Through numerous pathways, a constant production of fibrotic factors leads to ongoing recruitment of type II pneumocytes and fibroblasts, producing excess collagen and fibronectin.[23] In addition to silicotic nodules, it also results in scar tissue of the surrounding lung parenchyma, leading to permanent distortion and fibrosis and a reduction in gas exchange surfaces.

Crystalline silica is piezoelectric, that is, it produces opposite electric charges on opposite sides of the physical structure when force is applied. This piezoelectricity contributes to the formation of oxygen-free radicals produced on the cleaved surfaces of silica molecules. Freshly fractured silica, such as that generated in abrasive blasting, has an increased redox potential on the fresh surface, which is highly reactive with hydrogen, oxygen, carbon and nitric oxide, and is more likely to produce ongoing free radicals.[24,25] Silica-induced oxidative stress stimulates specific transcription factors through interaction with toll-like receptors on alveolar macrophages, mediated through nuclear factor kappa-B (NF-κB) and activator protein (AP)-1, which further increases cytokine expression, perpetuating inflammation and fibrosis.[24]

RECENT SILICOSIS OUTBREAKS IN MODERN INDUSTRIES

There have been a number of recent case series reporting outbreaks of acute and accelerated silicosis in modern occupations (Table 2).

Artificial stone benchtop fabricators

The increased use of artificial stone (also known as engineered, reconstituted, manufactured stone and agglomerated quartz) for the fabrication of benchtops has led to workers being exposed to exceptionally high levels of crystalline silica.[58] In comparison to traditionally used natural stones, artificial stone is cheaper than marble, is non-porous, scratch and stain resistant, has four times the flexural strength and double the impact resistance of granite.[59] Artificial stone is formed from finely crushed rocks (predominantly quartz, with the addition of coloured glass, shells and metals) that are bound by a polymer resin, moulded into shape and heat-cured.[59] Artificial stone contains 85–93% crystalline silica, far higher than any other material commonly used for benchtop fabrication.[58,60] Workers use high-powered hand tools such as grinders to cut these slabs to shape and create cut-outs for sinks and taps, followed by polishing the final product. These processes generate extremely high levels of exposure to respirable crystalline silica dust.

The current respirable crystalline silica exposure limit in the USA and many other countries is 0.05 mg/m^3 over an 8-h work period (8-h time-weighted average (TWA)).[12] Although short-term exposure limits are generally not regulated, it is recommended that a worker should not be exposed to a level three times the 8-h TWA for more than a total of 30 min during a work day and never be exposed to a level five times the 8-h TWA.[61] Dry cutting artificial stone has been noted to generate silica levels of 44 mg/m^3 over 30 min, almost 300 times the recommended limit.[62] Cutting artificial stone with water dust suppression still noted levels that are 30 times above the limit, reflecting the extremely high silica content of the material.[62]

In Spain, there has been an increase in silicosis cases from 95 in 2003 to 295 in 2011, all of which were associated with exposure to artificial stone in the manufacturing of countertops. Only 32% of workplaces had wet cutting available and only 11% had adequate ventilation. At least 82% of workers had respiratory symptoms and one worker had died of silicosis.[41]

In Israel, at least 82 patients with artificial stone-associated silicosis and who were referred for consideration of transplantation have been identified between 1997 and 2015, and all cases were workers who had been involved in the manufacturing of artificial stone benchtops.[45] At least 18 workers have undergone lung transplantation, representing a 15-fold increase in the expected rate of transplant for this condition.[46]

In Australia, a case series of seven artificial stone-associated silicosis patients has been reported over a 5-year period, six with PMF and one requiring lung

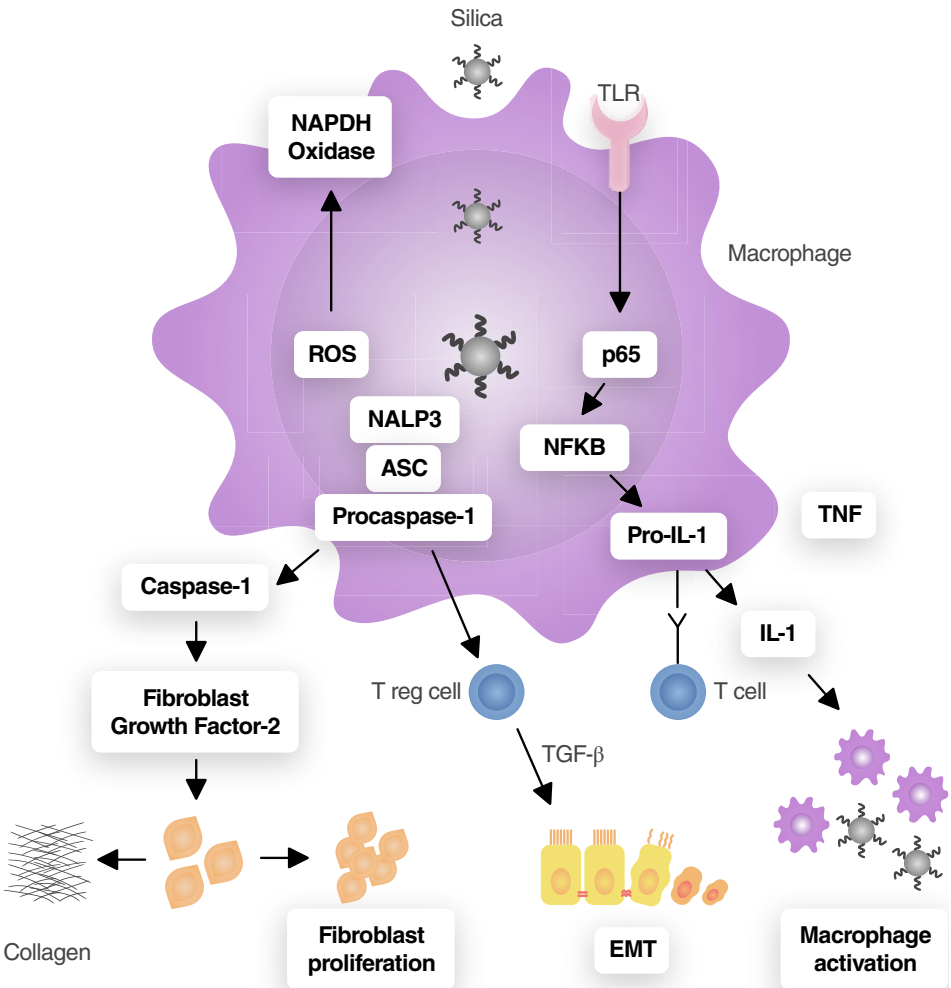

Figure 1 Biological pathways in silicosis. NALP3 (NACHT, LLR and PYD domains containing protein 3), ASC (apoptosis-associated speckle-like protein containing a CARD) and procaspase-1 form the inflammasome. EMT, epithelial mesenchymal transition; IL, interleukin; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; TLR, toll-like receptor; TNF, tumour necrosis factor.

transplantation. Over a follow-up period of 24 months (range: 8–47 months), these patients had a significant decline in lung function, with the mean rate of pre-bronchodilator forced expiratory volume in 1 s (FEV_1) reduced at 429 mL/year (range: 246–788 mL) and forced vital capacity (FVC) reduced per year at 503 mL/year (range: 180–994 mL).[49] A subsequent report in Australia published in February 2019 detected a further 98 cases of silicosis in just 4 months.[63]

The true prevalence of silicosis is likely to be much higher than that reported in the literature. WorkCover Queensland (Australia) performed a random screening programme with just 10 stone benchtop fabrication workplaces and identified 36 workers with silicosis—one-third of the screened workforce. Half of those diagnosed with silicosis had PMF.[64]

Furthermore, in many of the international cited outbreaks, some affected individuals are employed as undeclared workers without or with limited access to health care, living far from home, working long hours and without any respiratory protection or engineering controls demonstrated to reduce silica exposure.[37]

Denim jean sandblasters

Denim sandblasting utilizes silica-containing sand as an abrasive on the blue jean surface to produce a 'worn-out' look.[65] In 2007, a series of 50 denim jean sandblasters with silicosis was reported in Turkey (53% of 145 screened workers). In this cohort, with a mean age at presentation of 19 years and exposed to silica for only a mean duration of 3 years (±2.2 years), 7 workers had acute silicosis and 43 accelerated silicosis. Sixteen cases subsequently developed PMF and three young workers had already died at the time of follow-up.[37] A follow-up study of the same cohort published in 2011 found that despite the cessation of denim sandblasting or any other work involving silica exposure, the prevalence of silicosis had increased to 96%. In addition, radiographic progression and pulmonary function decline had occurred in 82% and 66% of workers, respectively, with a further nine workers deceased.[20]

Jewellery polishers

Workers involved in semi-precious stone production have seen an increase in accelerated silicosis, particularly in China and India.[34,56,66] Cutting and polishing of agate and other gemstones, and the use of silica-containing chalk moulds in jewellery casting produces high concentrations of silica dust (98–99% silica combined with aluminium and iron oxide). In India, 20 workers from different jewellery polishing factories were screened, and 8 workers were found to have silicosis confirmed by chest radiography

Table 2 Recent silicosis cases in non-traditional industries

Country	Cases	Age	Duration of exposure (years)	Deaths
Slate pencil workers				
India (1985–1987)[26]	148 (54.6% of workers surveyed)†	26 (13)	7 (4.6)	23 (15%)
Stonemasons				
UK (1984–1989)[27]	3‡	40–52	—	2 (67%)
Iran (2000–2007)[28]	23§	29 (13.7)	2 (0.6)	10 (43%)
Italy (2004–2008)[29]	1¶	54	4	1
UK (2015)[30]	6‡	33.8 (5.9)	13 (5.3)	0
Iran (2017)[31]	48§	38 (14.20)	3.0 (1.19)	44 (92%)
Spain (2018)[32]	143§	53 (10.7)	—	13 (9%)
Metal grinder				
Israel (1999)[33]	1¶	34	13	1
Agate mill workers				
China (1998–1999)[34]	32 (60% of workers surveyed)†	30 (4.50)	3.5 (1.70)	3 (9%)
Denim sandblasting				
Turkey (2001–2009)[35]	32§	31.5 (5.6)	3.7 (3.49)	6 (5%)
Turkey (2007)[36]	2‡	24 (1.4)	2.2 (1)	0
Turkey (2015)[20,37,38]	83§	23 (5)	4	9 (11%)
Dental supplies				
USA (2004)[39]	5‡	51 (9)	21 (10)	2 (40%)
Electrical cable manufacturers				
Turkey (2007)[40]	4‡	30 (2)	7 (1.5)	1 (25%)
Artificial stone benchtop manufacturing				
Spain (2014)[41]	46§	33 (29–37)	11 (9–17)	1 (2%)
USA (2014)[42]	1¶	37	10	0
USA (1999–2003)[43]	35§	—	—	35 (100%)
Italy (2015)[44]	3‡	48 (3.5)	13 (6)	0
Israel (2016)[45,46]	82§	47 (11.38)	19.8 (4.47)	13 LTx, 3 died (20%)
Spain (2018)[47]	19§	47 (13.33)	11 (3.58)	—
Belgium (2018)[48]	2‡	—	<10	0
Australia (2018)[49]	7§	44 (26–61)	7 (4–10)	1 LTx (1%)
Sandblaster				
Spain (2015)[50]	1¶	27	5	1
Czech Republic (2015)[51]	1¶	38	3.2	1
Turkey (2018)[52]	1¶	28	2	0
USA (2018)†† [53]	101§	—	—	—
Stone crusher				
India (2015)[54]	1	28	1	0
India (2015)[55]	1	35	2	0
Jewellery and semi-precious stone workers				
India (2015)[56]	19	—	3.4 (1.7)	12 (63%)
Brazil (2017)[57]	57	32	12.5	6 (11%)
China (2018)[34]	15 (47% prevalence)	29 (4.9)	3.5 (1.7)	3 (20%)

Age is presented as mean (SD or range); duration of exposure is presented in years (SD or range).
†Case finding.
‡Case series.
§Retrospective cohort study.
¶Case report.
††Mix of sandblasting and foundry workers, represents silicosis within 1–10 years of exposure;
—, Not stated; LTx, lung transplantation.

(CXR) and presence of intracellular particles within the macrophages of bronchoalveolar lavage (BAL) fluid analysis noted by electron microscopy. Workers were all males, aged between 20 and 29 years, and developed silicosis after only a mean work duration of 3.4 years. All had died by the end of the 3-year follow-up.[56] Thirty-two men screened in a small agate mill in Guangzhou, China, found 15 cases of accelerated silicosis (prevalence of 47%)

with a mean age of 29.8 years (SD: 4.9) and a mean duration of exposure of 3.5 years (SD: 1.7). In a 9-month follow-up, eight developed respiratory failure and three had died. An occupational inspection of the worksite where workers sawed, carved and polished these gemstones found the mean total dust concentration was 3.0–9.9 mg/m^3, far exceeding the Chinese National Maximum Allowance Concentration of 1 mg/m^3. The free SiO_2 content of the agate was 90.5%.[34]

Other industries

A literature review of all published case reports and longitudinal cohort studies of silicosis in modern workplaces is presented in Table 2. Overall, it suggests that in these at-risk occupations, the reported incidence of silicosis in these workplaces is upwards of 50–60% and the mortality rate is 10–100%, exceedingly higher than the prevalence and mortality rates of chronic silicosis in more traditional occupations such as the mining industry (mortality of 6 per 1000 workers). Further concern regarding excessive silica exposure has been raised in the hydraulic fracturing industry,[67] construction (bricklayers, painters and labourers)[68] and highway repair.[69]

DIAGNOSIS OF ACUTE AND ACCELERATED SILICOSIS IN MODERN INDUSTRIES

Whilst current screening recommendations and diagnosis guidelines vary across countries (Table 3), they are based on decades of understanding the natural history of chronic silicosis. Whether these methods are appropriate for the screening of acute and accelerated silicosis need to be assessed.

Diagnosis of silicosis requires a history of adequate silica dust exposure with appropriate radiological ± histopathological findings, and exclusion of other diseases that may mimic silicosis.[3] An 'adequate' exposure history may be more difficult to appreciate in these newer occupations with short duration high-intensity silica exposures. It may also be difficult to distinguish between accelerated silicosis and a silica-exposed worker with a radiologically similar disease such as sarcoidosis, who will have a very different disease trajectory. Further investigations including BAL, lymph node sampling and lung biopsy may be used to detect disease mimics and associated conditions including lung cancer, tuberculosis or sarcoidosis. Further research is required in developing more precise diagnostic and prognostic tools.

Table 3 A comparison of screening recommendations for occupational crystalline silica exposure

Source	Screening requirements	Time interval	Target
Worksafe Australia 2019[70]	Medical and occupational history, questionnaire CXR using the ILO classification Spirometry	Not specified	Numerous workplaces including stone benchtop manufacturing, mining and abrasive blasting
NIOSH (USA) 2002[71]	Medical and occupational history, questionnaire CXR using the ILO classification Spirometry Evaluation for tuberculosis	At employment commencement; 3 yearly thereafter; tuberculosis screening annually	Numerous workplaces including mining, construction and blasting
UK 2016[72]	Medical and occupational history, questionnaire, smoking history CXR according to the ILO classification Spirometry Evaluation for tuberculosis	At employment commencement, after 15 years and then 3 yearly thereafter	Numerous workplaces including construction, stonework, foundries and manufacturing
WHO 1996[71]	Medical and occupational history Medical examination CXR using the ILO classification Spirometry	At employment commencement, 2–3 yearly during exposure and then 3–5 yearly	Silica-exposed workers
Department of Labour, South Africa[71]	CXR using the ILO classification Spirometry	No interval specified	Silica-exposed workers
India (Factories Act) 1987[73]	Medical and occupational history Medical examination CXR using the ILO classification Spirometry	At employment commencement; 5 yearly	Mining, stone crushing and construction

CXR, chest radiography; ILO, International Labour Organization; NIOSH, National Institute for Occupational Health and Safety.

Radiology

Plain CXR using the International Labour Organization (ILO) classification has traditionally been used in the screening and subsequent diagnosis of silica-affected workers (Table 4).[74] There is mixed evidence as to whether this correlates with disease progression and survival.[75] It is unclear how the ILO CXR classification might be applied to screening and diagnosis of silicosis associated with high-intensity exposure, and the interval at which repeat screening should occur. Furthermore, in accelerated silicosis, fibrosis may be irregular and more diffuse, or not apparent on CXR, limiting the reliability of CXR in screening in this setting.[76]

Computed tomography (CT) scan of the chest is superior to CXR in the early detection of the initial phase of silicosis, and is more likely to detect changes in nodular coalescence earlier than CXR.[45] The above-mentioned case reports of acute and accelerated silicosis describe centrilobular nodules, bilateral airspace consolidation (often in a lower zone predominance), calcified lymphadenopathy and pleural thickening as the most common findings on CT (Fig. 2). Nodules and consolidation most commonly involved the posterior portions of the lungs. Crazy-paving pattern was rarely present.[37,65,77] Whether chest CT scans should be used in place of CXR for screening remain to be seen.

Where positron emission tomography (PET) is used, it may demonstrate diffuse increased uptake within the lungs and lymph nodes (Fig. 2), postulated due to the increased respiratory burst activity of neutrophils which rely on glucose as their energy source.[38]

BAL and lung biopsy

BAL fluid analysis may demonstrate lymphocytosis (20% compared to 6% in healthy controls) or neutrophilia (10% compared to 0% in healthy controls) in acute silicosis[78]; however, these findings are non-specific and are noted in other radiologically similar diseases such as sarcoidosis and pulmonary fibrosis. In one study, acute silicotic patients with massive silica dust exposure had more than 70% of BAL macrophages containing dust particles (>70%).[78] It is unclear whether these findings portend a better potential response to whole lung lavage or immunosuppression treatment, or whether they predict overall prognosis.

Although returned lavage fluid from patients with acute silicoproteinosis has classically been reported to be a milky effluent with positive periodic-acid Schiff stain,[2] cases from more recent outbreaks rarely describe this finding.[51,78]

Histology from lung biopsy or explanted lungs in recent silicosis outbreaks typically demonstrate a combination of acute and accelerated silicosis, with silicotic nodules comprised of histiocytes, fibroblasts and birefringent particles in a peripheral and centrilobular distribution, as well as severe patchy pulmonary fibrosis.[41,46]

Respiratory function testing

Spirometry may appear normal in the early stages of disease. As silicosis progresses, obstruction, restriction or a mixed ventilatory defect may develop. Whilst spirometric findings are not specific to the diagnosis of silicosis, results play a role in monitoring progress and prognosis.[2] Declining diffusion capacity of the lung for carbon monoxide (DL_{CO}) appears to correlate with increasing lung opacities and PMF.[79]

Table 4 International Labour Organization classification of radiographs of pneumonconioses[74]

Parenchymal abnormalities	
Small opacities (<1 cm)	
Profusion	
0	0/– 0/0 0/1
1	1/0 1/1 1/2
2	2/1 2/2 2/3
3	3/2 3/3 3/+
Affected zones	Upper/middle lower Right/left
Round shape and size	
p	Opacities with diameters up to 1.5 mm
q	Opacities with diameters 1.5–3 mm
r	Opacities with diameters 3–10 mm
Irregular shape and size	
s	Opacities with widths up to 1.5 mm
t	Opacities with widths 1.5–3 mm
u	Opacities with widths 3–10 mm
Large opacities (>1 cm)	
0	None
A	Up to 5 cm
B	5 cm to the size of the right upper zone
C	Bigger than the right upper zone
Pleural abnormalities	
Plaques (localized thickening)	Yes/no
Diffuse pleural thickening	Yes/no
Costophrenic angle obliteration	Yes/no
Diaphragm involvement	Yes/no
Calcification	Yes/no

Profusion is the frequency or concentration of opacities. Case CXR are read in comparison to reference CXR for each category, whereby 0 indicates no opacity and 3 indicates the most profuse. The first number (i.e. 1 in 1/0) indicates the major category for which the CXR is thought to most likely represent, and the second number (i.e. 0 in 1/0) represents the most plausible alternative category.[74]

CXR, chest radiography.

ASSOCIATED CONDITIONS

Silicosis may lead to impaired immune function, and an 8–20-fold increased risk of tuberculosis.[80] Silica particles are also carcinogenic, increasing the risk of lung and renal malignancy.[12] Significant silica exposure is associated with the development of pulmonary alveolar proteinosis.[81] Autoimmune diseases including rheumatoid arthritis, scleroderma and mixed connective tissue disease are also

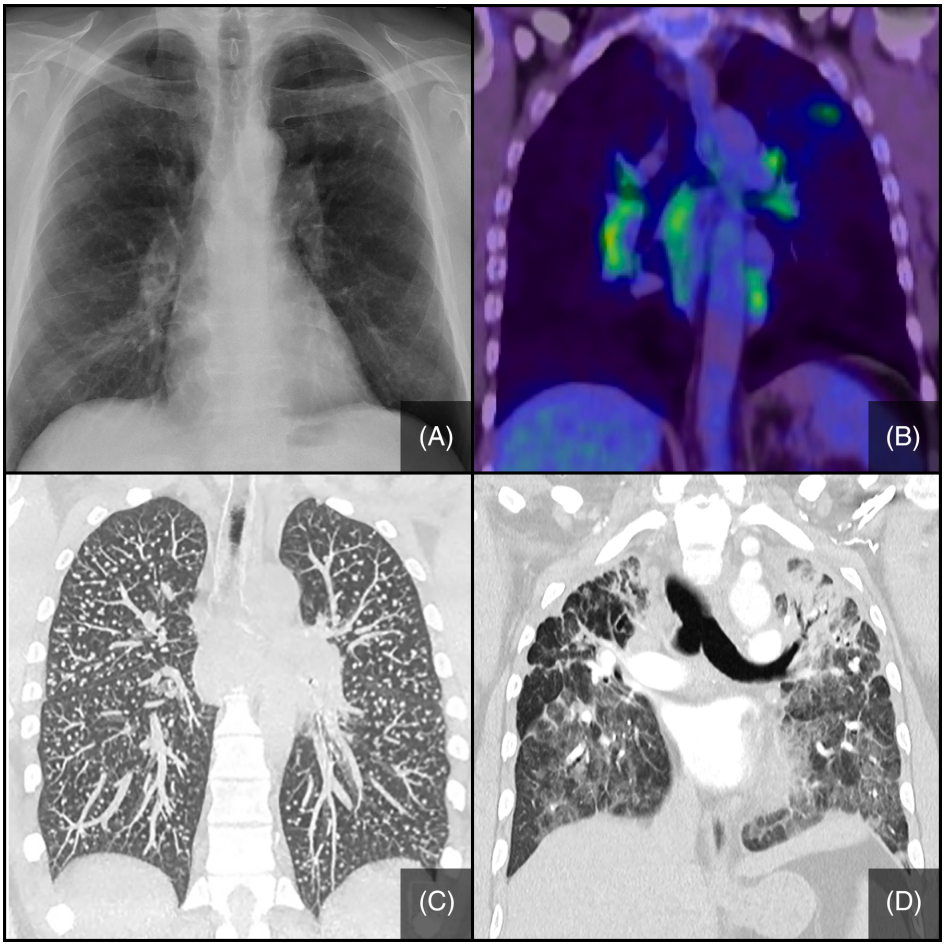

Figure 2 Radiological features of accelerated silicosis. (A) Chest radiography: 2/2 profusion in the left upper zone. (B) Corresponding positron emission tomography scan of (A) with hypermetabolic activity in the affected areas. (C) HRCT demonstrating multiple centrilobular nodules. (D) HRCT with extensive upper zone confluent fibrosis, architectural distortion and hilar elevation, and diffuse ground-glass opacity in the lower zones.

associated with silica exposure. Postulated mechanisms include increased levels of autoantibody production, immune complexes and excess production of immunoglobulin. The incidence of autoimmune diseases has increased in artificial stone benchtop fabricators, especially in those with silicoproteinosis.[82] As part of the diagnostic workup for those with suspected accelerated silicosis, it is important to assess for these associated conditions, as treatment for these may alter the disease trajectory.[80]

TREATMENT

There is no current effective treatment for silicosis. For those with near fatal respiratory failure, lung transplantation remains the only option.

Whole lung lavage

Given the pathological similarities with pulmonary alveolar proteinosis, whole lung lavage has been trialled for acute silicoproteinosis.[83] Although it decreases the presence of dust particles, macrophages and cytokines on subsequent BAL analysis, and may decrease lung function decline in the short term, it does not appear to have an impact on long-term outcomes or mortality.[83] Furthermore, potential treatment-related complications including respiratory failure are of serious concern.[84]

Immunosuppression

Immunosuppression has also been trialled in chronic silicosis, with little success. Older studies[85] report a transient improvement in lung function (300 mL FVC) with prednisolone (30 mg daily for 6 weeks followed by a tapering dose) with no apparent sustained benefit or reduction in mortality. There is limited evidence that prednisolone reduces dyspnoea and cough, although benefits appeared to be associated with longer periods of exposure.[85] In a case series of patients with accelerated silicosis undergoing lung transplantation, it was observed that almost all were previously treated with prednisolone that did not change the clinical course. Infliximab reduced the histological inflammatory and fibrotic response in silicosis-induced rats,[86] but this is yet to be translated into human studies.

Antifibrotic therapy

Early studies in silicosis-affected rabbits demonstrated that the presence of aluminium reduced the development of fibrosis, leading to the notion that inhaled aluminium powder may be effective.[87] However, early trials in humans demonstrated not only a lack of benefit, but also there were suggestions that it may even be harmful.[88]

Given the relative success of the use of antifibrotic therapy in idiopathic pulmonary fibrosis, the use of

nintedanib has been tested in experimental animal models,[89] but are yet to progress to human clinical trials. Other antifibrotic agents including tadalafil are also being trialled in animal models.[90]

Cell-based therapy including bone marrow-derived mononuclear cell[91] and mesenchymal cell transplantation[92] have both demonstrated some benefit in animal models and are currently undergoing trials in humans.[93]

FUTURE DIRECTIONS

Novel approaches to effective treatment are urgently needed. Early animal studies have contributed to our understanding of the pathobiology of silicosis and potential therapeutic targets, but more research is required to translate these findings into clinical practice. Until there is effective treatment for silicosis, the mainstay must be identification of high-risk occupations and enforcement of regulated exposure standards and health screening programmes. Cohort studies of workers in high-risk professions will help assess the efficacy of occupational controls such as wet processing, ventilation and respiratory protection. International review and consensus of exposure limits with a specific focus on short-term high-intensity exposure is also required.

CONCLUSION

Silicosis is a rapidly emerging modern-day concern, particularly affecting young and vulnerable workers. The diagnosis should be considered in any occupation where silica is used, in particular sandblasting, stone benchtop fabrication, ceramics, jewellery and glass production. Businesses must consider elimination of high-intensity silica exposure from work practices and, if not feasible, have in place engineering controls such as wet processing, effective ventilation and adequate respiratory personal protective equipment. Periodic, independent assessment of respirable silica levels during typical work activities is also required to ensure the effectiveness of engineering controls. Screening programmes are required to assess the true prevalence and provide workers with adequate medical care. As further workers are diagnosed, more research needs to be undertaken to determine how best to screen and what interval and with what modality. Much of the literature is comprised of case reports and small case series; larger pooled systematic exposure and prospective disease and exposure cohort registries are required to determine risk factors for the development and progression of disease. For those already affected, there is an urgent need to discover effective treatments.

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Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest radiography; FVC, forced vital capacity; HRCT, high-resolution CT; ILO, International Labour Organization; LTx, lung transplantation; PMF, progressive massive fibrosis; TWA, time-weighted average.

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