Selenium and exposure to fibrogenic mineral dust: A mini-review

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A B S T R A C T

Individuals exposed to fibrogenic mineral dust may exhibit an impaired antioxidant system and produce high levels of reactive oxygen and nitrogen species through immune cells, contributing to the perturbation of immune cell function, inflammation, fibrosis and lung cancer. The lung diseases which are caused by inhalation of fibrogenic mineral dust, known as pneumoconioses, develop progressively and irreversibly over decades. At the moment there is no known cure. The trace element selenium has potent antioxidant and anti-inflammatory properties mediated mainly through selenoproteins. Research has demonstrated that selenium has the ability to protect against cardiovascular diseases; to kill cancer cells in vitro and reduce cancer incidence; and to immunomodulate various cellular signaling pathways. For these reasons, selenium has been proposed as a promising therapeutic agent in oxidative stress associated pathology that in theory would be beneficial for the prevention or treatment of pneumoconioses such as silicosis, asbestosis, and coal worker’s pneumoconiosis. However, studies regarding selenium and occupational lung diseases are rare. The purpose of this study is to conduct a mini-review regarding the relationship between selenium and exposure to fibrogenic mineral dust with emphasis on epidemiological studies. We carried out a systematic literature search of English published studies on selenium and exposure to fibrogenic mineral dust. We found four epidemiological studies. Reviewed studies show that selenium is lower in individuals exposed to fibrogenic mineral dust. However, three out of the four reviewed studies could not confirm cause-and-effect relationships between low selenium status and exposure to fibrogenic mineral dust. This mini-review underscores the need for large follow-up and mechanistic studies for selenium to further elucidate its therapeutic effects.

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1. Introduction

1.1. Background

Occupational exposure to fibrogenic mineral dust is associated with the development of pneumoconiosis; fibrogenic dust refers to dust that causes fibrosis. Fibrosis is derived from the Latin word fiber for filament or thread; as a sequela of various persistent inflammatory pathologies, it refers to an increased accumulation of extracellular matrix (ECM) components, such as collagens and fibronectin, in organs and tissues resulting from proliferation and activation of fibroblasts and myofibroblasts (Wick et al., 2013). Lung fibrosis is a chronic lung disease characterized by an increased accumulation of ECM accompanied by remodeling of the lung with physiologic, clinical and radiographic features (Todd et al., 2012). During lung fibrosis, there is a wound-healing process in the lung that leads to a persistent inflammation cascade coupled with lymphocyte–monocyte crosstalk that withstands growth factor release, proteolytic enzyme production and fibrogenic cytokine release, leading to the accumulation of connective tissue and a remodeling of the lung architecture destroying the normal lung structure irreversibly (Wynn, 2004). Fibrotic diseases are a major issue of public concern since efficacy of available drugs is very poor (Scotton and Chambers, 2007). However, these diseases have been neglected worldwide; for example, in the United States, fibrotic diseases are responsible for 45% of deaths (Wick et al., 2013; Wynn, 2004). Fibrotic diseases such as pneumoconioses also remain an issue of occupational concern because they are among the leading causes of morbidity and mortality. Approximately 125,000 lives are lost every year due to pneumoconioses (Lozano et al., 2012). Although pneumoconioses can be prevented by controlling exposure to hazardous dust, they still remain a significant problem worldwide. For this reason, increased awareness of occupational vulnerability to pneumoconioses is required. This will help in preventive measures for pneumoconioses. Pneumoconiosis is a broad term that refers to a range of diseases due to the inhalation and accumulation of dust in the lungs (Chong et al., 2006), leading to interstitial fibrotic disease or non-fibrotic pneumoconiosis (Chong et al., 2006; McLoud, 1991). Fibrotic pneumoconioses have similar clinical patterns such as pulmonary fibrosis characterized by lung function decline, and respiratory symptoms that can lead to premature death (Wang and Christiani, 2000). Pneumoconioses are disabling and they lead to clinical symptoms including dyspnea, dry cough, poor appetite, chest pain and pulmonary cachexia (Mossman and Churg, 1998; Zare Naghadehi et al., 2014). Fibrotic pneumoconioses include common ailments such as asbestosis, silicosis, and coal worker’s pneumoconiosis (CWP) and the rarer types of pneumoconiosis such as berylliosis and talcosis (Chong et al., 2006). Non-fibrotic pneumoconioses include siliosis, siderosis and baritosis. Silicosis and asbestos-related lung diseases remain an issue of major concern due to past exposure to silica dust and to the huge amount of asbestos fibers used during the 20th century. Symptoms of chronic phases normally develop many years after exposure; the latency period may take up to 40 years from the time of initial exposure (Kamp, 2009). Fibrotic pneumoconiosis has a progressive and irreversible development and there is no currently known effective treatment (Attfield and Kuempel, 2003). Previous studies have demonstrated that individuals exposed to fibrogenic dust exhibit an impaired antioxidant system while producing high levels of reactive oxygen species contributing to the initiation and development of inflammation, fibrosis and lung cancer (Kamp et al., 1992; Quinlan et al., 1994).

1.2. Common forms of pneumoconiosis

1.2.1. Silicosis

Silicosis is a fibrotic lung disease due to the inhalation of respirable crystalline silicon dioxide (silica) (Leung et al., 2012), the most common quartz, in occupational settings such as tunneling, mining, sandblasting, and quarrying (McLoud, 1991; American Thoracic Society, 1986). Respirable crystalline silica refers to particulates having a diameter of < 10 μm, the range most likely to reach the lung alveolus while escaping retention in the upper respiratory airways such as the nose or throat. Silicosis often develops progressively and irreversibly over decades even after exposure has ceased. Clinical features of silicosis include simple silicosis, silicoproteinosis (acute silicosis), complicated silicosis (progressive massive fibrosis), and interstitial fibrosis. Radiographic features of silicosis include rounded opacities (1–10 mm) in the upper zones of both lungs (Greenberg et al., 2007). Silicosis may develop in some cases together with a variety of diseases including tuberculosis (Xia et al., 2014); CWP and autoimmune diseases (Maeda et al., 2010). Silica exposure is still prevalent in low and middle income countries, and developed countries also are not immune to new silica exposure (Steinland and Ward, 2014).

1.2.2. Asbestosis

Asbestosis is a bilateral diffuse lung fibrosis due to the inhalation and accumulation of asbestos fibers in the lungs (Mossman and Churg, 1998; American Thoracic Society, 1986) during asbestos production, use, removal, or disposal. Occupational exposure occurs, for example, during the manufacture or installation of asbestos-containing building materials (Cullinan and Reid, 2013). Asbestos is a sexedet of naturally occurring silicate minerals grouped in serpentine (chrysotile), and amphibole (amosite, crocidolite, tremolite, anthophyllite, and actinolite) (Kanarek, 2011). Asbestos is characterized by physical properties that make it commercially useful for builders; these physical properties include resistance to fire, heat, electrical and biochemical alterations. For safety reasons, most developed countries have fully banned the use of asbestos in construction; however, some developed countries such as the USA and many developing countries still use asbestos (Prazakova et al., 2014). Radiographic features of asbestosis include ground glass opacities, small nodular opacities, pleural plaques, “Shaggy” cardiac silhouette, ill-defined diaphragmatic contours, honey combing and volume loss (Roach et al., 2002).

1.2.3. Coal workers’ pneumoconiosis

Coal is a natural brownish black or black graphite-like material which is a fossil fuel for producing energy such as electricity. CWP, which is known also as a black lung disease, is due to the inhalation and accumulation of coal mine dust in the lungs (Castranova and Vallyathan, 2000). Radiographic appearance allows classifying CWP into simple pneumoconiosis and progressive massive fibrosis. Simple CWP is characterized by small rounded lung opacities in the upper zones of both lungs, while progressive massive fibrosis features large
conglomerate lung opacities (Davis et al., 1983; Soutar and Collins, 1984; Young et al., 1992). Two types of coal mining exist, surface coal mining and underground coal mining. Miners working in both surface and underground coal mining are likely to be exposed to silica, with underground coal mining being the most well-known source of coal dust exposure and more commonly associated with silicosis (Castranova and Vallyathan, 2000).

1.3. Selenium and selenoproteins

Selenium (Se) is an essential micronutrient having potent antioxidant and anti-inflammatory properties mediated through selenoproteins (such as glutathione peroxidase, thioredoxin reductases, selenoprotein P, selenoprotein 15, etc.) most of which are oxido-reductase, playing a crucial role in scavenging hydrogen peroxide and in boosting immunity (Look et al., 1997; Hatfield and Gladyshev, 2002; Muzembo et al., 2013; Rayman, 2012; Burk and Hill, 2009; Hatfield et al., 2014). Selenoproteins are a family of proteins containing in their primary structure selenocysteine (Sec) as the 21st amino acid in the genetic code. Sec is an analog of cysteine in which the sulfur-containing side chain is replaced by a Se-containing side chain (Burk et al., 2003). Sec cotranslationally incorporates into a nascent polypeptide chain in a manner dependent on Sec tRNA decoding for the UGA codon which normally has a role in stopping translation for non-selenoprotein genes (Labunsky et al., 2014). To decode the UGA as Sec, selenoprotein mRNAs contain a Sec insertion sequence site (SECIS) element in the 3′-untranslated (3′-UTR) region of mammalian selenoprotein mRNAs. SECIS is then recognized by the SECIS binding protein 2 (SBP2) (Hatfield et al., 2014). To date, in humans, there are 25 identified and characterized selenoprotein genes distributed in almost all cells and tissues and having various functions (Koyukov et al., 2003), with some functions, such as the promotion of cancer, being dangerous for the human body (Yoo et al., 2012). For example, selenoprotein 15 (Sep 15) and thioredoxin reductase 1 (TR1) have dual functions in promoting cancer in tumor cells and preventing cancer in normal cells, a subject for molecular and cellular studies before the conduct of large studies concerning Se supplementation (Hatfield et al., 2009).

Se is an important dietary component, and the recommended dietary intake for Se is 55 μg per day for adults. There is no international agreement regarding serum or plasma Se needed for the optimal activity of selenoproteins (Muzembo et al., 2013) and serum Se levels of 100 μg/l are required for the full expression of selenoproteins (Thomson et al., 1993). Adequate Se status is fundamentally important for human health (Nogueira and Rocha, 2011). However, many of the biological and biomedical beneficial effects of Se are relatively unknown to those not directly working with Se (Hatfield et al., 2014). Se has been proposed as a promising therapeutic agent for use in conditions associated with oxidative damage (Wojewoda et al., 2010) that in theory would be beneficial for the prevention or treatment of occupational lung diseases such as silicosis, asbestosis, and CWP.

From the recent past until today, Se has been receiving increasing attention in medicine and biology because of its potent antioxidant properties; for this reason, Se has been studied for its ability to kill cancer cells in vitro and for its properties as a chemo agent for cancer and muscle disorders in animals, and to prevent cardiovascular diseases and protect against viruses (for example, it can delay the onset of AIDS in people affected with human immunodeficiency virus) (Hatfield et al., 2014; Dunn, 2012; Clark et al., 1996). The main source of Se for humans comes from food intake. Dietary Se has various forms, the form most commonly ingested being selenomethionine, which is transformed into selenocysteine (Sec) as follows: selenomethionine is transformed into the intermediate selenocystathionine through the action of cystathionine β-synthase and then selenocystathionine is transformed into Sec through cystathionine γ-lyase (Fairweather-Tait et al., 2011). Se concentration in food varies by country, and depends on the concentration of Se in the soil where crops are grown or where animals are raised (Thomson and Robinson, 1980; Thomson et al., 2008; Rayman, 2000; Rayman et al., 2008). As for Se status, it correlates with Se intake (Rayman, 2000), with some countries having a higher intake (Canada, Japan, Venezuela, and the USA), a lower intake (Eastern Europe) and both higher and lower intakes (China) (Rayman, 2012). Lack of Se reduces the synthesis of selenoproteins, may alter the host immune response against inflammation, and is involved in the pathogenesis of both Kashin–Beck disease (osteoarthritis) (Zou et al., 2009), and Keshan disease (cardiomyopathy), which was first discovered in 1935 in Keshan County, Heilongjiang Province, China, where the soil is poor in Se (Gee et al., 1983). At present, there is no universally accepted method to determine Se status in an individual. Se status can be assayed in a single specimen of plasma, serum, toenail, or urine (Goodman et al., 2001; Longnecker et al., 1996).

Se ranks 34th in the periodic table and has an atomic mass of 78.96. The word Se is derived from the Greek word selene for “moon goddess”; the element was discovered in 1817 by the Swede Jöns Jakob Berzelius, who confounded it with Tellurium while looking for the causes of disease in workers at a sulfuric acid manufacturing plant. In that period Se was considered to be a toxic element or even a carcinogen. For example, Se was implicated in causing ‘alkali disease’ in livestock that pastured in the Nebraska and Dakota plains (Hatfield et al., 2014), and this was confirmed in 1934 by Franke (Franke, 1934), who demonstrated that the ‘alkali disease’ in livestock was caused by plants growing in soil rich in Se rather than alkali salt or water. However, in 1957, Schwartz and Foltz were the first researchers to report on the health benefits of Se; they reported that Se salts protect against necrotic liver degeneration in vitamin E-deficient mice. Later, in 1973, Rotruck JT et al. found that Se is the active component of glutathione peroxidase. As a component of an antioxidant system such as glutathione peroxidase, it appears reasonable to think that Se might play an important role in the protection of the lungs against environmental exposure to silica, asbestos or coal dust. In this line, previous studies have reported that very low levels of Se were a risk factor for the development of lung cancer, even if Se increases the risk of lung cancer mortality in people having high Se (Knekt et al., 1998; Fritz et al., 2011; El-Bayoumy, 2001; Suadicani et al., 2012). In vitro and animal studies have generated controversial data regarding the protective antioxidant effect of Se in fibrotic lung diseases (Robinson et al., 2012; Gabor et al., 1985; Janssen et al., 1990; Rose et al., 2014). Moreover, a great number of workers exposed to silica, asbestos, and coal dust are smokers (Wang and Christiani, 2000). Tobacco smoking and exposure to mineral dust lead to inflammation and secretion of oxidants. Tobacco smoking has been found to be associated with low Se status (Goodman et al., 2001; Oryszczyn et al., 1996). Accordingly, human studies regarding Se and common fibrotic pulmonary diseases (silicosis, asbestosis, and CWP) are scant. This mini-review focuses on the reported relationship between Se and exposure to dust that can lead to common fibrotic pulmonaryosis. Because of the higher risk of lung cancer due to asbestos, silica, or CWP, this mini-review will allow us to take a step in understanding whether Se dietary supplements should be used by individuals with silicosis, or asbestosis or CWP with hyposelenemia for lung cancer prevention.

1.4. Common fibrotic pulmonaryoses and oxidative stress

The immune response upon inhalation of silica, asbestos, or coal is the secretion of reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Mossman and Churg, 1998; Shulda et al., 2003). Many ROS are generated upon silica, asbestos, or coal inhalation; these ROS include hydrogen peroxide (H2O2), superoxide anion (O2•−), and the hydroxyl radical (OH•) (Kimula et al., 2005). The reactive oxygen species are mainly released by phagocytes, polymorphonuclear, alveolar, bronchial and endothelial cells after lung injury (Bargagli et al., 2009). The generation of ROS in the human lungs is realized by various pathways that include nicotinamide adenine dinucleotide phosphate (NADP)
oxidases, the mitochondrial electron transport chain, xanthine oxidase, myeloperoxidase and eosinophil peroxidase (Kinnula et al., 2005). ROS not only plays a crucial role in intracellular and extracellular signal transduction pathways implicated in diverse functions including the maintenance of homeostasis and eliminating pathogens, but also plays a crucial role in the pathogenesis and progression of various diseases including lung fibrosis (Kinnula et al., 2005; Bartz and Plantadosi, 2010). The secretion of ROS and reactive nitrogen species upon mineral dust (silica, asbestos, or coal) exposure can cause oxidative damage to the lungs orchestrated directly through hydroxyl radical formation via the Haber–Weiss reaction with fiber surface iron, and indirectly by activation of cells from the innate immune system such as macrophages (Shukla et al., 2003; Pelclova et al., 2008; Dostert et al., 2008; Hornung et al., 2008).

Oxidative stress is defined as a mismatch between oxidants released and antioxidant defenses due to the excessive production of ROS, which can affect proteins, lipids, carbohydrates and deoxyribonucleic acid (DNA) in the human body. The assessment of oxidative stress in body fluids relies on the measurements of oxidative stress biomarkers, and the antioxidant activity against oxidation. This is because the half-lives of reactive oxygen species are usually very short, and therefore, difficult to measure (Bartz and Plantadosi, 2010; Day, 2008; Halliwell and Gutteridge, 1999). An imbalance between antioxidants and pro-oxidants has been implicated in the initiation or progression of cancer (Bargagli et al., 2009; Klaunig et al., 2011; Bargagli et al., 2008). Due to their large surface area and function, the lungs are susceptible to high oxidative damage; however, the lungs are equipped with an efficient system against reactive oxygen species (Bargagli et al., 2009; Kinnula, 2005; Rahman et al., 2006). To protect against oxidative stress, the human body has a defense system including antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, catalase, and low-molecular weight antioxidants such as beta-carotene and tocopherols, located in the lung tissue, interstitial fluid, and erythrocytes (Engelen et al., 1990). As an example, serum superoxide dismutase, glutathione, and malonaldehyde were found to be higher in patients with silicosis compared to controls (Zhang et al., 2010). After inhalation, dust particles are taken up by macrophages leading to the release of free radicals, and activation of the Nalp3 inflammasome. This triggers the maturation of proinflammatory cytokines (IL–1beta, IL–18, etc.) and apoptosis, and subsequently to lung inflammation (Dostert et al., 2008; Engelen et al., 1990; Fubini and Hubbard, 2003). Excessive reactive oxygen species attack the polyunsaturated fatty acids (PUFAs) in cell membranes in the lungs and cause damage to the lung tissue. PUFAs have a link with lung inflammation because PUFAs are a precursor of eicosanoids through arachidonic acid. Eicosanoids play a crucial role in modulating lung inflammation, for example, by helping platelets to aggregate by the secretion of growth factors and chemotactic factors. PUFAs come from dietary lipids and provide arachidonic acid, which is a polyunsaturated omega-6 fatty acid found in the phospholipids of cell membranes. Phospholipid membranes are the predominant lipids of cell membranes and are extremely sensitive to ROS attack; phospholipid attack by ROS leads to the secretion of highly reactive free radicals which in turn oxidize adjacent polyunsaturated fatty acid side chains, thus damaging cell membrane structures, leading to lung injury and thus promoting lung fibrosis (Ciofu and Lykkesfeldt, 2014; Calder, 2006).

2. Methods

This mini-review focuses on silicosis, asbestosis and CWP. We reviewed English published studies in PubMed concerning the antioxidant effects of Se and exposure to fibrogenic mineral dust as of July 2014 with the following keywords: Selenium, silicosis, asbestosis, CWP, mesothelioma and fibrotic pneumoconiosis.

All published epidemiological, experimental animal in vivo and in vitro studies were considered for inclusion. All English published studies were included because of the paucity of studies regarding Se and exposure to fibrogenic mineral dust, and the absence of randomized controlled clinical trials. We emphasized on epidemiological studies. For each study, the following parameters were recorded: the year of publication, the country where the study was conducted, the study population, biological fluid used and the findings.

3. Results

Our search yielded two studies on experimental animal in vivo, one in vitro study and four epidemiological studies.

3.1. Animal experimental in vivo studies and in vitro studies of selenium and common fibrotic pneumoconioses

Results from animal experimental in vivo studies and in vitro studies regarding the effectiveness of Se in controlling diseases related to exposure to fibrotic pneumoconioses are conflicting. A study by Robinson et al. failed to find a beneficial association between supplementing Se in the study outcome; they reported that Se supplementation to mice did not prolong survival after asbestos exposure or reduce the incidence of mesothelioma (Robinson et al., 2012), a lethal cancer due to asbestos exposure (Antman, 1993). However, various studies have demonstrated the increase of the Se-dependent enzyme glutathione peroxidase (hydrogen peroxide scavenging enzyme) or its mRNA upon silica or asbestos exposure as an adaptive response to the secretion of oxidants (Janssen et al., 1990, 1992). Gabor et al. found that nontoxic doses of selenium could reduce quartz toxicity and lipid peroxidation upon co-treatment of guinea pig peritoneal macrophages with quartz and selenium (Gabor et al., 1985). In addition, a study by Apostolou et al. supported the anti-apoptotic effect of Se and its anti-proliferative effect on malignant mesothelioma cells, therefore supporting the hypothesis that Se may be useful in chemoprevention for asbestos-exposed workers with a high risk of malignant mesothelioma (Apostolou et al., 2004).

3.2. Epidemiological studies on selenium and exposure to fibrogenic mineral dust

As for animal studies, there are few epidemiological studies that have investigated levels of Se in silicosis, asbestosis, or CWP in an adult population (Table 1). All these epidemiological studies support the fact that Se is correlated with exposure to fibrogenic dust, principally relating a low Se status in people exposed to fibrogenic dust as compared with controls. We found four cross-sectional studies; of them, one study combined cross-sectional and longitudinal designs. These cross-sectional studies reported that levels of Se were reduced in workers exposed to coal mine dust (Oryszczyn et al., 1996; Nadif et al., 2001) and in patients suffering from silicosis (Muzembo et al., 2013), and in those suffering from asbestosis (Gottschall et al., 2004). A summary of these studies is described below.

3.2.1. Epidemiological study of selenium and silica exposure

3.2.1.1. Muzembo et al. study. We have previously demonstrated that serum Se levels were lower in patients with silicosis, and corresponding selenoprotein P levels were also low in patients with silicosis (Muzembo et al., 2013). We carried out a retrospective case-control study using chest radiographs and serum from 78 patients with silicosis and 20 healthy subjects. Approximately 87% of the patients with silicosis were former tunnel drillers, who had retired after being occupationally exposed to silica dust for an average of 16 years (range 1–44 years). The median age for patients with silicosis was 73.5 years old (range 59–87 years old). Of the 78 patients with silicosis, 88.5% were former smokers with a mean of twenty-seven pack-years of smoking. Eighty percent of the subjects in the control groups were former smokers with a median age of 72.5 years (range 62–81 years old). Se was measured using electrothermal atomic
absorption spectrophotometry, while selenoprotein P was assessed with sandwich Enzyme Immunoassay.

Both Se and selenoprotein P decreased significantly with the radiological severity of the disease. Se was inversely associated with age. The study lacked data on Se intake; however, subjects in this study came from Japan, a country with a high intake of Se (177.5 µg per day for men) (Yoneyama et al., 2008); this was considered a limitation as Se status relies on food intake.

3.2.3.2. Nadif et al. study. This study appealed for Se supplementation for asbestos-exposed people. Nadif et al. conducted a cross-sectional and longitudinal study by interviewing 79 asbestos-exposed workers. The miners were assayed for plasma Se and glutathione peroxidase. Se levels were reduced in asbestos-exposed workers while levels of 8-isoprostaglandin F₂α (biomarker of lipid peroxidation) increased. Se was assayed using fluorometric methods. The authors found that current workers in contact with coal dust had lower Se levels as well as lower activity of glutathione peroxidase. When plasma Se was analyzed in relation to the degree of exposure, they found that serum Se was significantly lower in workers with high exposure when compared with workers exposed to low coal dust. The main finding from this study was that low Se levels are consequence of its use to fight against oxidative stress, concomitantly related to coal dust exposure and smoking.

4. Discussion

4.1. Selenium toxicity

Se benefits health in humans in trace amounts but is toxic if a higher amount is ingested (Aldosary et al., 2012; MacFarquhar et al., 2010; Morris and Crane, 2013; Johnson et al., 2010; Muller and Desel, 2010), and can even lead to fatality (Spiller and Pfeifer, 2007). Se toxicity is known as selenosis, with clinical symptoms including gastrointestinal trouble, garlic breath, skin disorders, troubles of the nervous system, nail discoloration, hair loss, poor dental health and paralysis (Johnson et al., 2010). Se has been known in the USA to cause toxicity in animals and plants, and the disease was called “alkali disease” (Nogueira and Rocha, 2011; Moxon et al., 1943). Recently, errors in the formulation of a Se supplement diet resulted in Se poisoning with gastrointestinal symptoms, nail discoloration and hair loss. This happened in the USA in 2008 when some victims as much as doubled the dose of the misformulated product after toxic symptoms appeared, as they did not directly suspect that a dietary supplement could cause toxicity symptoms (MacFarquhar et al., 2010). Selenosis is also found in areas where Se concentration in the soil is naturally high such as in the state of South Dakota in the USA (Wilber, 1980).

Se is a versatile element. Therefore, special caution is required due to the narrow therapeutic range of Se and to the excess of Se which may be positively associated with morbidity and mortality (Bleys et al., 2008; Lippman et al., 2009; Jablonska et al., 2008; Coudray et al., 1997), though Se can also reduce mortality (Bleys et al., 2008; Akbaraly et al., 2005).

4.2. Commentary and perspectives

The literature demonstrated that occupational inhalation of fibrogenic dust such as crystalline silica, asbestos and coal dust can lead to pneumoconioses or malignancies (Dostert et al., 2008). Although the molecular mechanism by which inhalation of the above pollutants can lead to pneumoconioses or malignancies is not fully understood, inflammation and oxidative/nitrosative stress are known to be involved in pneumoconioses and malignancies (Fig. 1). On the positive side, many
dietary nutrients with different mechanisms can modulate diseases involving inflammation and oxidative/nitrosative stress (Dunn, 2012). Se is one of those nutrients with proven beneficial health effects supported by in vitro, animal and human studies. To assess the evidence that exposure to fibrogenic dust might be associated with low Se status, we reviewed published studies related to Se and exposure to fibrogenic mineral dust, emphasizing epidemiological studies. Findings from the reviewed epidemiological studies are consistent. Reviewed epidemiologic studies show that Se is lower in individuals exposed to fibrogenic mineral dust with or without disease. These findings were supported by in vitro

Fig. 1. Pathogenesis of common fibrotic pneumoconioses and mechanism by which selenium might be beneficial in an individual exposed to common fibrotic pneumoconioses. Occupational exposure to silica, asbestos or coal dust causes lung injury and activates the immune system and the healing process leading to the differentiation of naive CD4+ into either Th1 or Th2 effectors. Differentiation towards Th1 effectors restores the lung architecture while differentiation towards Th2 and Th17 effectors can cause chronic lung inflammation, lung fibrosis and lung cancer1. Selenium supplementation boosts immune cells by skewing the differentiation of naive CD4+ into Th1 effectors, while selenium deficiency increases Th2 responses113, which can lead to lung fibrosis and lung cancer. (Source: Adapted from Wick G. et al.1 and Huang Z. et al113).
studies. However, three out of the four reviewed epidemiological studies failed to confirm cause-and-effect relationships between low Se status and exposure to fibrogenic mineral dust because of their study design; for this reason, we cannot draw any definitive conclusion regarding low Se status and exposure to fibrogenic dust. This mini-review also highlights that there is a paucity of studies regarding Se and exposure to fibrogenic dust, and an absence of randomized controlled clinical trial studies. Current limited molecular knowledge regarding Se and fibrogenic dust might be one of the reasons justifying why Se has not been widely studied in this area, and why Se supplementation is not recommended in routine care to prevent or delay the onset of pneumoconiosis or malignancies in individuals exposed to fibrogenic dust. As recently highlighted by Delgado et al. (2012), relocation of workers exposed to fibrogenic dust to other jobs after disease development is an important strategy of secondary or tertiary prevention of dust related diseases. Along these lines, it would be meaningful for relocated workers to be assessed individually, since individuals with lower Se status might benefit from Se supplements in order to enhance the effects of other treatment strategies, as it has been reported that genotoxic and fibrogenic effects of mineral dust can lead to the development of lung cancer (Tsuda et al., 2002), and Se might protect against lung cancer (Fritz et al., 2011; Zhuo et al., 2004). The mechanisms by which Se might exhibit antitoxic properties include the ability for Se to induce apoptosis in cancer cells (Sinha and El-Bayoumy, 2004; Brozmanova et al., 2010); its role in preventing DNA damage; in increasing the activity of enzymes implicated in the repair of DNA damaged by oxidative stress such as DNA glycosylases; and its implication in DNA repair pathways involving proteins such as p53, which is often referred as the "guardian of the genome" (Longtin, 2003; Bera et al., 2013). The molecular mechanism by which Se might protect against fibrotic lung diseases is accomplished through selenoproteins which have potential anti-inflammatory and anti-oxidant properties that can mitigate inflammatory signaling pathways. In fact, an adequate Se status has the ability to boost the immune system, leading to an appropriate immune response against foreign particles (McKenzie et al., 1998; Roy et al., 1994), whereas deficiency in selenoproteins can trigger inappropriate immune responses by weakening T Cell Receptor (TCR) signal, producing excessive oxidants in T cells and therefore decreasing proliferation and differentiation of CD4+ T cells in response to TCR stimulation. CD4+ T cells are very important because they play a crucial role in the initiation of immune responses during lung fibrosis (Hoffmann et al., 2010; Shirmali et al., 2008). For example, the involvement of T cells during the lung fibrotic process leads to the differentiation of naïve CD4+ into either Th1, Th2, or Th17 cytokine secretion phenotype; differentiation towards Th1 protects the lung (with secretion of cytokines such as IFNγ) and leads to resolution of the lung injury, whereas differentiation towards Th2 (with secretion of cytokines such as IL-4 and IL-13) leads to the development of chronic inflammation and to lung fibrosis (Wick et al., 2013; Todd et al., 2012). Interestingly, Se can influence the Th1/Th2 balance (Fig. 1) through high levels of free thiols and inhibition of the transcription factor, nuclear factor-kappa B (NF-kB). Higher levels of dietary Se increase GSH mobilization, oxidative burst, and translocation of the nuclear factor of activated T cells (NFAT), resulting in the reductive state of CD4+ T cells that gives rise to Th1 differentiation and enhanced cellular immune responses (Hoffmann et al., 2010; Huang et al., 2012; Norton and Hoffmann, 2012; Ward and Hunninghake, 1998).

The benefits of Se for human health are not in doubt. For this reason Se has been used as a dietary supplement for a healthy diet and in clinical trials for cancer prevention; however, concern had been raised regarding the effectiveness of Se supplementation in diseases prevention. For example, the Nutritional Prevention of Cancer Trial (NPC) showed that a Se supplement decreased the incidence of lung cancer especially in individuals with low Se status at baseline (Clark et al., 1996; Reid et al., 2002) but Se supplementation was ineffective in preventing basal cell carcinoma, while the risk of nonmelanoma skin cancer increased in the studied population (Duffield-Lillico et al., 2003). Moreover, the Selenium and Vitamin E cancer Prevention Trial (SELECT) did not reduce the incidence of prostate cancer and was prematurely discontinued (Lippman et al., 2009), underscoring the need for a better understanding of molecular mechanisms for Se before implementing clinical trial studies on Se supplementation that take into account individual genotype, disease state, and individual Se status (Hatfield and Gladyshev, 2009). Another concern is about the adverse outcomes of higher levels of Se which can increase the risk of type-2 diabetes (Lippman et al., 2009; Laclaustra et al., 2009a; Chen et al., 2003) and hypertension (Laclaustra et al., 2009b).

5. Conclusion

Selenium is found to be at an inadequate level in individuals exposed to fibrogenic mineral dust. However, three out of the four reviewed studies could not show the causal relationships, nor determine the order in which low Se status and exposure to fibrogenic mineral dust occur.

The epidemiologic data reported in this mini-review, the paucity of studies regarding Se and exposure to fibrogenic mineral dust, and the absence of randomized controlled clinical trials using Se as a unique supplement, all highlight the importance for further mechanistic studies to better understand whether Se can be used as a supplement in people exposed to fibrogenic dust with a high risk of lung cancer or mesothelioma.

Conflicts of interest

There is no conflict of interest regarding this review.

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References
