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LETTER TO THE EDITOR

The Essential Role of Club Cell Protein 16 (CC16) rapid kit in Silicosis Prevention in Iran

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Silicosis remains one of the most devastating occupational lung diseases afflicting workers exposed to crystalline silica dust. Despite modern industrial safety standards, Iran continues to face rising cases among miners, construction workers, ceramic manufacturers, and sandblasting operators. Silica is a major component of the Earth's crust. Therefore, any occupational activity that destroys the Earth's crust exposes workers to silica during work with rocks. Extraction and work with rocks such as granite and rocks in general, coal, industry, minerals (gold, arsenic, tin, precious stones, glass and rubber, production, ceramics, building materials (phosphorus rocks), casting and talc production, sandblasting operations, etc. can cause a risk.

Based on the results of a related study, the geometric mean concentration for workers' exposure to crystalline silica was reported to be in the range of 0.0212-0.2689 mg/m^3 [1]. In addition, the mean concentration of crystalline silica was reported to be in the range 0.1476 ± 0.1628 mg/m^3 in Iranian industries, which was higher than the recommended exposure standard limit by the American Conference of Governmental Industrial Hygienists (ACGIH), and Iran's national occupational exposure limits (0.025 mg/m^3), NIOSH (0.05 mg/m^3), as well as OSHA (0.01 mg/m^3) [2].

Silica has various polymorphs such as quartz, tridymite, cristobalite, coesite, stishovite and several others. Among them, quartz is the most common form of silica polymorphs. Exposure to RCS can occur in many activities and occupations like construction, drilling, foundry, abrasive drilling and sandblasting, mixing silica flour, sand and clay, and casting, polishing and molding of dental and jewelry materials [3]. Moreover, most of the workers of open-pit and underground mines are exposed to free crystalline silica dust, as it is likely to be present in the site soil and to be released in the course of mining operations. However, this is of greater importance for silica mines, where workers are generally exposed to high concentrations of silica dust. A wide range of health problems have been reported for workers exposed to free crystalline silica, including respiratory problems, heart disorders, kidney problems, autoimmune diseases, and genetic effect (DNA damage). Exposure of workers in silica mines is much higher than in other mines. [4-6]. The fact that the International Agency for Research on Cancer (IARC) has classified silica as a group 1 carcinogen further underscores the necessity of monitoring silica dust level in working environments. According to the American Conference of Governmental Industrial Hygienists (ACGIH), the 8-hour working exposure limit for silica is 0.025 mg/m^3

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(ACGIH, 2015). In Iran, the Ministry of Health has also set this limit to 0.025 mg/m^3 [3]. Silicosis, one of the most common types of pneumoconiosis worldwide, is a fibrotic lung disease that usually occurs due to chronic inhalation of respirable crystalline silica by workers in mining, quarrying, or sandblasting. Although the molecular mechanisms in the pathogenesis of silicosis are still not fully understood, increasing evidence suggests that phagocytosis of RCS causes active inflammation and oxidative stress, which play an important role in various diseases in exposed individuals [7]. Silicosis is recognized as a preventable but not curable disease. Accordingly, disease prevention is primarily based on reducing the exposure of workers in high-risk occupations to silica particles, which is implemented through the use of control methods and personal protection. Sometimes, despite the use of control methods, exposure is still high. For instance, in a recent study, 25 silicosis patients were identified in Hamadan province [8], implying that the use of control measures and personal protective equipment has not been sufficient. In this regard, especially in developing countries essential to propose an identifiable biomarker indicating high exposure or risk of disease. For this reason, various probably biomarkers have been also evaluated and suggested such as blood serum level of copper [9], neopterin [10], selenium [11], zinc [12], heme oxygenase-1 [13], and Clara cell protein (CC16) [14]. However, there are conflicting results regarding their use as a reliable biomarker.

In recent years, several studies in India have focused on the use of a rapid point of care CC16 kit for screening of occupational silica dust exposed workers [15]. It is noteworthy that CC16 is a marker of Clara cell protein and can reflect lung changes; it has been proposed for early screening. In previous studies it has been reported that the serum CC16 levels were highest in healthy individuals, lower in workers exposed to moderate silica dust, and lowest in patients with advanced silicosis. So that mean serum CC16 concentrations were 16.7±3.81 ng/mL in healthy controls, 10.2±1.77 ng/mL in moderately silica dust-exposed workers, and 4.7±3.07 ng/mL in X-ray confirmed advanced silicosis patients without any smoking habit [16]. The same range has been reported for the serum CC16 level in non-exposed, silica-exposed and silicosis confirmed patients by previous studies [17]. The kit is used to test the level of human CC16, based on the principle of double antibody sandwich technology enzyme linked immunosorbent assay (ELISA). Due to the fact that silicosis is clinically diagnosed by chest X-ray along with history of silica dust exposure, diagnosis is invariably made at an advanced or end stage when it is irreversible. On the other hand, using X-rays is a high-risk diagnostic method that can lead to serious complications during periodic examinations, and it is not possible to early detect the disease. In this regard, using a method to reflect high exposure in workers who are routinely exposed especially in high risk occupations is necessary. It is recommended that these commercially available rapid tests and diagnostic kits be studied and used to screen a group of personnel in Iran, and if the results are useful, they should be included as a periodic monitoring in all silica-related occupations. Sensitivity and specificity of CC16 values were also found to be ≥83 per cent for screening all categories of individuals [16]. It should be noted that the CC16 kit is not independently accepted as a definitive diagnostic or screening method and its performance (sensitivity/specificity) can vary by population and assay design and hence, before implementation in large population of exposed workers in Iran it is recommended:

- Validate in the target population
- Ensure test quality and standardization
- Integrate results with occupational health systems (periodic examinations, imaging as needed)
- Obtain regulatory approvals, assess cost-effectiveness, and establish follow-up protocols for positive results.

However, since the low level of serum CC16 level reflecting the early initiation of the process of lung damage, it can be useful in lung damages caused by silica dust exposure. Further studies on large workers population are required to reflect the early initiation of the process of lung damage caused by silica dust exposure. In conclusion, it can be expressed that the use of this method (determining serum CC16 level can be considered as a potential biomarker of exposure to free crystalline silica dust not as a diagnosis or even pre-screening silicosis method in high risk industries.

Conflict of Interest
The authors declare no conflict of interest.

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Author's Contributions
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AI Statement
The authors confirm that no AI tools or services were used during the preparation of this work.

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