RESEARCH ARTICLE

Editorial Process: Submission:09/02/2024 Acceptance:09/23/0000 Published:10/16/2025

Molybdenum Deficiency among Esophageal Cancer Patients

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Abstract

Background: Emerging evidence suggests that deficiencies in trace elements, particularly molybdenum, may contribute to Esophageal Cancer (EC) pathogenesis. Molybdenum is an essential micronutrient that plays a key role in detoxifying carcinogenic compounds through its involvement in enzymatic pathways, including xanthine oxidase activity. This study aims to evaluate serum molybdenum levels in patients with histologically confirmed EC and compare them to healthy controls to assess the association between molybdenum deficiency and EC incidence. **Materials and Methods:** This prospective, single-center observational study was conducted at a regional cancer center in Srinagar, Kashmir, India from June 2021 to June 2023. Patients with histologically confirmed EC were included as the study group, while age- and gender-matched healthy volunteers served as controls. Serum molybdenum levels were measured using atomic absorption spectrophotometry. **Results:** A total of 400 participants were enrolled. The study group had a mean age of 62.1 ± 12.61 years, with 58.5% males. The mean serum molybdenum level in esophageal cancer patients was significantly lower than that of the control group (0.79 ± 0.452 vs 2.33 ± 0.707, $p < 0.001$). The gender-based comparison showed that males in the study group had a significantly lower mean serum molybdenum level than male controls ($p <0.001$), with a similar trend observed in females. **Conclusion:** Molybdenum deficiency may be associated with an increased risk of EC by impairing carcinogen detoxification. Further research is needed to explore its preventive and therapeutic potential.

Keywords: Esophageal cancer- Molybdenum deficiency- Trace elements- Xanthine oxidase- Carcinogenesis

Asian Pac J Cancer Prev, **26 (10)**, 3599-3602

Introduction

A growing body of epidemiological and laboratory research on essential trace elements has demonstrated their protective association against the development of various cancers, including esophageal cancer (EC) [1]. EC is the seventh leading cause of cancer death worldwide, and sixth most common in India, accounting for 46, 504 deaths annually [2]. Trace elements were essential micronutrients that form an integral part of our daily diet. Although needed in small quantities, they play a vital role in numerous biological processes [3, 4]. They play a crucial role in various biological processes, such as serving as structural nutrients, supporting normal healing, regulating the metabolism of genetic material for growth and differentiation, facilitating programmed cell death and necrosis, protecting against oxidative damage, and exhibiting anti-inflammatory and anti-carcinogenic effects [5].

Comparative studies of trace elements between areas with high and low incidences of EC have revealed an inverse association between mortality due to EC and the levels of zinc, selenium, molybdenum, and other trace elements in crops, soil, and foodstuffs [6]. The etiology of EC is multifactorial, involving genetic, dietary, and environmental factors, with increasing evidence pointing to the role of trace elements in its pathogenesis. Among these, molybdenum has gained attention due to its potential protective role against EC through its involvement in enzymatic pathways that detoxify carcinogenic compounds, particularly nitrosamines.

Molybdenum is an essential trace mineral that plays a critical role in various biological processes for both mammals and plants. It is primarily acquired through diet, with significant sources including legumes, grains, and organ meats. Despite its importance, molybdenum's availability in the earth's crust is limited, which can occasionally lead to deficiencies [7]. Komada et al. [8] investigated the impact of dietary molybdenum on esophageal carcinogenesis induced by V-methyl-V-benzylnitrosamine (2.5 mg/kg body weight administered subcutaneously once a week for 20 weeks) in male

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F344 rats. The study revealed that the incidence and development of esophageal tumors were significantly lower in the high-molybdenum diet group (2 ppm) compwered to the low-molybdenum diet group (0.032 ppm), with tumor rates of 44.4% (0.6 ± 0.8) and 73.2% (2.2 ± 2.0), respectively [8]. A prospective observational study by Ray S et al (2017) concluded that low concentrations of molybdenum in soil and water were associated with a higher prevalence of EC [9].

Despite these findings, data on molybdenum levels in EC patients remain limited, particularly in India. Given the geographical variation in EC incidence and the potential influence of environmental trace element availability, further research is necessary to determine whether serum molybdenum levels differ significantly between EC patients and healthy individuals. This study aims to evaluate molybdenum levels in patients with histologically confirmed EC and compare them to healthy controls. By analyzing the association between serum molybdenum levels and EC incidence, this study seeks to contribute to the growing body of evidence on the role of trace elements in cancer prevention and pathogenesis.

Materials and Methods

Study Design and Setting

This was a prospective, single-center observational study conducted at a regional cancer center in Srinagar, Kashmir, India. The study aimed to investigate molybdenum levels in patients with histologically confirmed carcinoma of the esophagus. Patients were registered and enrolled between June 2021 and June 2023.

Study Population

The study included 200 patients diagnosed with EC as study group and 200 healthy volunteers as controls. Patients were selected based on histological confirmation of carcinoma, while healthy volunteers were matched for age and gender where possible.

Eligibility Criteria

Patients with histologically confirmed carcinoma of the esophagus, who had not received any prior cancer treatment were included in the study group, along with healthy volunteers with no history of systemic illnesses, were included in the control group. Patients were excluded if they had a history of taking minerals, vitamins, or other drug combinations within the six months prior to enrolment, or if they had co-morbid conditions that could interfere with the analysis of trace elements.

Sample Collection and Processing

Venous blood samples (5 ml) were collected from the antecubital vein of each participant between 8 and 10 a.m. after overnight fasting. Samples were collected in plain screw-cap specimen tubes and left to retract for 30 minutes. They were centrifuged at 3000g for 5 minutes, and the supernatant serum was aspirated using a Pasteur pipette into a clean plain tube.

The supernatant was pooled and stored at -20°C until analysis. At the time of analysis, 2 ml of the thawed serum sample was mixed thoroughly, transferred to a clean 10 ml centrifuge tube, and diluted to 10 ml with hydrochloric acid. The diluted serum was centrifuged for 3 minutes at 3000 revolutions per minute to remove cellular debris. The resulting serum was analysed for molybdenum levels using atomic absorption spectrophotometry.

Outcome Measures

The primary outcome was serum molybdenum levels in EC patients compared to healthy controls. Secondary outcomes included analysis of patient demographics (age, gender, and locality) and clinical characteristics.

Statistical Analysis

All statistical analyses were performed using SPSS software version 20. Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Comparisons between groups were made using the Student's independent t-test for continuous variables and the Chi-square test for categorical variables. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants before inclusion in the study. The study protocol was reviewed and approved by the Institutional Ethics Committee.

Results

Out of the 400 patients, the mean age of patients was 62.1 ± 12.61 years. Dysphagia was the most common presenting symptom, observed in 92% of cases (Table 1).

The study group presented (patients with esophageal carcinoma) 0.79 ± 0.452 µg/dL mean serum molybdenum levels, which was significantly lower than that in the control group (2.33 ± 0.707 µg/dL), with a p-value < 0.001, indicating a statistically significant difference between

Table 1. Baseline Characteristics of Study and Control Groups

Age (years)	Study group	Control group	P-value
< 50, n (%)	42 (21)	58 (29)	0.096
>50, n (%)	158 (79)	142 (71)	
Gender, n (%)			
Male	117 (58.5)	131 (65.5)	0.181
Female	83 (41.5)	69 (34.5)	

SD, Standard Deviation

Table 2. Mean Serum Molybdenum Levels

Gender	Study Group	Control Group	P-value
Male, mean ± SD	0.74 ± 0.417	2.34 ± 0.703	<0.001*
Female, mean ± SD	0.85 ± 0.492	2.28 ± 0.725	<0.001*

SD, Standard Deviation

the two groups. Given that the normal reference range for serum molybdenum levels is 1.2–3.6 µg/L, it was evident that patients with esophageal cancer had a notable molybdenum deficiency, whereas levels in the control group remained within the normal range.

A further gender-based comparison revealed that males in the study group had a mean serum molybdenum level significantly lower than in male controls ($p < 0.001$). Similarly, females in the study group had a mean serum molybdenum level was significantly lower than in female controls ($p < 0.001$) (Table 2).

Although molybdenum deficiency was equally observed in both male and female esophageal cancer patients, there was no major difference in molybdenum levels between genders within the study group.

Discussion

Molybdenum deficiency has been implicated in the increased incidence of EC, studies have suggested that inadequate molybdenum intake may enhance susceptibility to esophageal carcinogenesis by impairing the detoxification of potential carcinogens [10]. In this study, we observed that EC patients exhibit significantly lower concentrations of molybdenum compwered to matched controls ($p < 0.001$), reinforcing the hypothesis that diminished molybdenum reserves may increase susceptibility to environmental carcinogens such as nitrosamines and N-nitroso compounds [11]. The mean age of carcinoma esophagus patients in our study (62.1 years) was slightly lower than the 69.4 years reported by Dietz et al., suggesting that regional and demographic factors may contribute to variations in disease onset [12]. A notable gender disparity was observed in our study, with males accounting for 58.5% of cases compwered to 41.5% in females, a difference that was statistically significant (p-value < 0.05). This aligns with previous research indicating that men were more than three times as likely as women to develop EC [13]. The increasing incidence of esophageal adenocarcinoma and gastroesophageal junction cancer, particularly among white men in Western populations, has also been reported in the literature [14]. Our findings similarly highlight a male predominance in disease occurrence, reinforcing the need for targeted screening and early detection strategies in high-risk populations.

Molybdenum functions as a cofactor for xanthine oxidase (XOD), an enzyme involved in redox reactions [15]. XOD exhibits detoxification properties by reducing organic nitro compounds to hydroxyamino derivatives, which may help prevent the formation of potentially carcinogenic nitroso compounds [16]. A study by Hisanao Komada et al. suggests that xanthine oxidase activity in the esophagus plays a significant role in the inhibitory effect of molybdenum on esophageal carcinogenesis. In our present study, the lower levels of molybdenum observed in EC patients compared to controls further support its antioxidant and protective role in cancer prevention [8]. Yang et al. [6] showed that the molybdenum content of serum, hair, and urine samples from a high-incidence area of EC in China was significantly lower than that of samples from a low-incidence area. He also noted that an inverse correlation was found between the EC mortality rate and the contents of molybdenum, magnesium, and zinc in hair.

This study indicates that EC patients exhibit significantly lower molybdenum levels compared to individuals without tumors, suggesting that molybdenum deficiency may play a crucial role in the development of carcinoma in the esophagus and gastroesophageal junction. These findings emphasize the necessity for further research to elucidate the mechanisms behind molybdenum's inhibitory effects on esophageal carcinogenesis. Understanding these pathways is essential for developing preventive and therapeutic strategies, especially considering the variations in dietary and environmental exposures across different populations.

In conclusion, we observed a deficiency of micronutrients, particularly molybdenum, in the study group, with normal levels observed in the control group. Whether this deficiency is associated as a risk factor for developing esophageal cancer needs to be established by conducting further studies on a larger sample size. Our patients had poor outcomes, suggesting that a deficiency of micronutrients may have prognostic significance. However, this needs to be studied on a larger scale to establish a definitive link

Author Contribution Statement

SS and MAK conceptualized the study, performed the data collection, analyzed the data and prepared the manuscript; AW and PG helped in providing technical inputs to the analysis and assisted in drafting the manuscript. All the authors were involved in all aspects of the conduct of the study and manuscript preparation.

Acknowledgements

None.

Conflict of interest

None.

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