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ORIGINAL ARTICLE

Clinical Significance of Elevated Serum Chromium Levels: A Retrospective Study of Serum Chromium Concentrations and Clinical Toxicity

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Abstract

***Background*:** Elevated serum chromium levels are occasionally detected during clinical evaluation; however, their relationship with clinical toxicity remains uncertain. Potential confounders, including complementary and alternative medicine (CAM) use and underlying comorbidities, may influence the interpretation of elevated chromium concentrations. Hence, we aim to evaluate the association between serum chromium levels and clinical manifestations in these patients.
***Methods*:** We performed a retrospective analysis of 22 patients with elevated serum chromium levels (>10 µg/L) at a tertiary care hospital in South India from January to December 2015. Clinical records were reviewed for symptoms associated with chromium toxicity and possible confounders. Correlation analyses were used to examine links between chromium concentrations and clinical findings.
***Results*:** Only 2 of 22 patients (9.1%) exhibited symptoms considered attributable to chromium exposure. Mean serum chromium concentrations were similar in symptomatic and asymptomatic patients (40.45 µg/L vs. 35.16 µg/L; p = 0.83). Stratified analyses demonstrated no serum concentration–response relationship between chromium levels and symptom prevalence. CAM use was reported in 36.4% of patients and was associated with significantly higher chromium concentrations than in non-users (53.40 ± 34.55 µg/L vs. 25.50 ± 25.68 µg/L; p = 0.0185). Comorbidities were present in 50.0% of patients and may have contributed to clinical manifestations independently of chromium exposure.
***Conclusion*:** No significant association was observed between elevated serum chromium levels and clinical toxicity in this cohort. Clinical interpretation should therefore rely on comprehensive assessment rather than serum chromium concentrations alone.

Keywords: Chromium; Heavy Metal Toxicity; Complementary and Alternative Medicine; Occupational Exposure; Environmental Exposure

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INTRODUCTION

Chromium is a naturally occurring trace element present in soil, water, and a variety of foods. Occupational exposure occurs in several industrial settings, including stainless steel welding, leather tanning, and chrome plating, while non-occupational exposure may arise from environmental sources and complementary and alternative medicine (CAM) preparations [1]. Chromium can be absorbed through ingestion, inhalation, or dermal contact. Among its various oxidation states, trivalent chromium (Cr III) is generally considered less toxic, whereas hexavalent chromium (Cr VI) is a well-established carcinogen with greater oxidative potential and systemic toxicity [2]. Both forms can accumulate in biological tissues and contribute to cellular injury through oxidative stress, mitochondrial dysfunction, and inflammatory pathways.

The toxicological profile of chromium spans multiple organ systems. Chronic exposure to hexavalent chromium is strongly associated with contact dermatitis, type IV hypersensitivity reactions, chronic respiratory diseases, and bronchogenic carcinoma. Conversely, acute ingestion can precipitate severe gastrointestinal injury, acute kidney injury (AKI), and fulminant hepatic necrosis. While peripheral neuropathy and myopathy have also been documented, these neurological and neuromuscular

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manifestations remain relatively underrecognized in clinical practice [3].

Despite the established toxicological effects of chromium, the clinical significance of elevated serum chromium concentrations remains uncertain. Most available evidence is derived from experimental studies or occupational exposure settings, and data correlating serum chromium levels with clinical manifestations are limited [2,4]. When elevated chromium levels are detected in patients without clear occupational exposure, interpretation becomes particularly challenging. Furthermore, potential confounders such as CAM use and comorbid conditions including diabetes mellitus, chronic kidney disease, and hypertension may contribute to clinical manifestations independently of chromium exposure.

To date, no study has systematically evaluated the relationship between elevated serum chromium concentrations and overt clinical toxicity within an Indian cohort. Therefore, this retrospective observational study aimed to evaluate the association between elevated serum chromium concentrations and clinical manifestations in patients with elevated serum chromium levels, while identifying potential confounding factors that may influence the interpretation of serum chromium concentrations in clinical practice.

METHODS

Study design

This retrospective observational study was conducted at a tertiary referral hospital in South India, between January and December 2015. Electronic medical records were systematically reviewed to identify all adult patients (≥18 years) with elevated serum chromium levels (>10 µg/L) detected during routine clinical evaluation. Chromium measurements were obtained as part of heavy metal screening in physician-directed evaluation of specific symptoms. Among patients undergoing heavy metal screening during the study period, 211 were identified with elevated levels of one or more heavy metals. Of these, 22 patients had elevated isolated serum chromium concentrations (> 10 µg/L) and fulfilled the study inclusion criteria. Patients with insufficient symptom documentation were excluded. This study utilized archived, fully de-identified registry data from 2015. Institutional Review Board approval was secured retrospectively in 2024 (IRB Min. No. 2407164 dated 24.07.2024), prior to data extraction, ensuring complete alignment with the Declaration of Helsinki.

Materials

Clinical data were extracted from electronic medical records at the time of patient evaluation. Variables collected included demographic characteristics, exposure history (including occupational exposure and CAM use), comorbidities, laboratory investigations, and clinical examination findings. This study included all eligible patients found in the record review during the study period. Geographic distribution was recorded to reflect the diverse referral population represented in the cohort, as the study was conducted at a tertiary referral centre that receives patients from multiple regions across India and neighbouring countries.

Definitions

In this study, elevated chromium was defined as a serum chromium concentration > 10 µg/L measured by Ion Chromatography-Inductively Coupled Plasma Mass Spectrometry. The assay quantified total serum chromium, and chromium speciation was not performed. Serum chromium was selected as the biomarker because it reflects recent systemic chromium exposure and is the standard assay available in our institutional laboratory [5]. No universally accepted serum chromium concentration has been established to define clinical toxicity, as reported reference values vary widely according to analytical methods, sample contamination, and study populations. Previous studies have suggested that serum chromium concentrations < 2 µg/L are generally of limited clinical significance, while pragmatic thresholds of 5–10 µg/L have been used in clinical practice to prompt further evaluation [6,7]. In our institution, > 10 µg/L is the laboratory reporting threshold for an elevated serum chromium concentration and was therefore used as the study inclusion criterion. This threshold served solely as the study inclusion criterion and was not intended to represent a validated threshold for clinical toxicity.

Serum chromium concentrations were categorized as mild (≤ 20 µg/L), moderate (20–50 µg/L), and severe (> 50 µg/L) for descriptive analysis. These categories were defined a priori to facilitate comparison across increasing serum chromium concentrations and do not represent validated clinical severity classifications.

Clinical toxicity was defined as the presence of symptoms documented by the treating physician as being compatible with chromium toxicity after clinical evaluation and exclusion of alternative diagnoses, based on previously reported manifestations in the literature, while asymptomatic patients had incidentally detected elevated chromium levels with explicit documentation of the absence of such symptoms [2–4, 8].

CAM exposure was defined as documented use of complementary and alternative medicine for more than three months. Available medical records identified traditional native medications; however, detailed information regarding product composition, manufacturer, or chromium content was not available because of the retrospective study design.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (range), while categorical variables are expressed as frequencies and percentages. Associations between serum chromium concentrations and clinical variables were assessed using Pearson or Spearman correlation coefficients, as appropriate. Comparisons

between groups were performed using non-parametric methods when data distribution assumptions were not met. All analyses were exploratory. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Baseline Characteristics

Baseline characteristics are summarized in Table 1. The mean (Standard Deviation) age was 43.9 (10.9) years with male predominance (63.6%). Only 2 patients (9.1%) had symptoms considered attributable to chromium exposure, while the majority (90.9%) were asymptomatic despite elevated chromium levels. Serum chromium ranged from 11.20 to 128.60 µg/L (mean 35.65 ± 31.54). Mean serum chromium concentrations did not differ significantly between symptomatic and asymptomatic patients (40.45 µg/L vs 35.16 µg/L; p = 0.83). Individual patient data points spanned the full range of chromium concentrations, with symptomatic patients not confined to higher levels (Figure 1).

Table 1. Baseline Demographic and Clinical Characteristics of Patients with Elevated Serum Chromium Levels (n = 22)

Variables	Value
Age (years), Mean ± SD	43.9 ± 10.9
Male sex, n (%)	14 (63.6)
***Geographic distribution, n (%)**	
West Bengal	6 (27.3)
Tamil Nadu	4 (18.2)
Andhra Pradesh	4 (18.2)
Jharkhand	3 (13.6)
Bihar	2 (9.1)
Bangladesh	2 (9.1)
Occupation, n (%)	
Housewives	6 (27.3)
Farmers	4 (18.2)
Businesspersons	3 (13.6)
Unemployed	3 (13.6)
Others	6 (27.3)
****Comorbidities, n (%)**	**11 (50.0)**
Diabetes mellitus	7 (31.8)
Hypertension	5 (22.7)
Chronic kidney disease	1 (4.5)
Laboratory parameters	**Mean ± SD (Reference Range)**
Serum chromium (µg/L)	35.65 ± 31.54 (<10)
Serum creatinine (mg/dL)	1.14 ± 0.65 (0.6–1.2)
Potassium (mEq/L)	2.95 ± 1.12 (3.5–5.0)
Creatine phosphokinase (U/L)	134.27 ± 96.8 (<150)
Hemoglobin (g/dL)	12.19 ± 1.39 (13.0–17.0 males; 12.0–15.0 females)

SD = Standard Deviation

Values are presented as mean ± standard deviation (SD) for continuous variables and number (percentage) for categorical variables. Geographic distribution reflects the state or region of residence at the time of presentation.

*Geographic distribution reflects the patient's place of residence at presentation. The study centre is a tertiary referral hospital serving patients from multiple regions of India and neighbouring countries.

**Comorbidities include previously diagnosed chronic conditions documented in medical records. Laboratory parameters represent values obtained at the time of clinical evaluation.

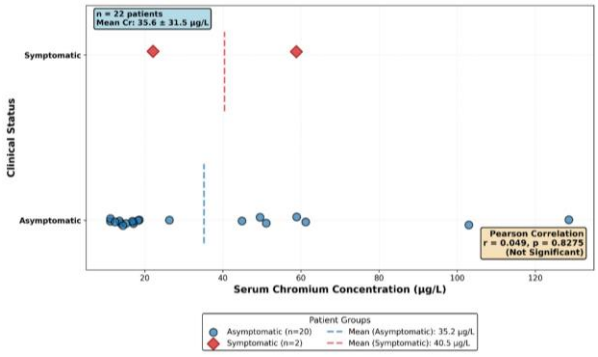

Figure 1. Scatter plot of serum chromium concentrations according to clinical symptom status.
Individual patient serum chromium concentrations are shown for symptomatic and asymptomatic patients (n = 22).
No significant difference in chromium concentrations was observed between groups (40.45 µg/L vs. 35.16 µg/L; p = 0.83), and symptomatic patients were not concentrated at higher chromium levels, indicating no apparent serum chromium concentration-toxicity relationship.

Representative clinical profiles illustrating the spectrum of serum chromium concentrations and clinical manifestations are presented in Table 2. Patients with markedly elevated serum chromium concentrations, including the highest recorded value (128.6 µg/L), remained asymptomatic, whereas the two symptomatic patients had moderate-to-severe elevations and heterogeneous clinical presentations (non-compressive myelopathy and myokymia). These representative cases further illustrate the absence of a consistent relationship between serum chromium concentration and clinical manifestations. Patients were stratified into mild (≤ 20 µg/L), moderate (20–50 µg/L), and severe (> 50 µg/L) chromium elevation categories (Table 3). Symptom prevalence remained low across all categories, with no observed relationship between serum chromium concentration and symptom prevalence.

CAM use was reported in 36.4% of patients (n = 8). CAM users had higher mean serum chromium concentration (53.40 ± 34.55 µg/L) compared with non-CAM users (25.50 ± 25.68 µg/L), representing a 27.90 µg/L difference and approximately a 2.09-fold increase (Mann-Whitney U test: p = 0.0185). None of the patients had documented occupational exposure to chromium in any form or employment in industries traditionally associated with chromium exposure. Electromyography was performed in 19 patients; 6 demonstrated abnormalities, including axonal neuropathy and neurogenic pattern. Eleven patients (50.0%) had documented comorbidities. No significant correlation

Table 2. Representative Clinical Profiles of Patients with Elevated Serum Chromium Concentrations

Case	Age/Sex	Occupation	Serum Chromium (µg/L)	Severity Category	CAM Use	Comorbidities	Presenting Symptoms	EMG Findings*
1	37/M	Business	13.9	Mild	No	Diabetes mellitus	None	Normal
2	46/F	Housewife	18.6	Mild	Yes	Ischaemic heart disease	None	Normal
3	29/M	Computer operator	22.1	Moderate	No	None	Non-compressive myelopathy	Normal
4	48/M	Farmer	49.5	Moderate	Yes	None	None	Normal
5	52/M	Veterinary assistant	51.1	Severe	Yes	None	None	Normal
6	17/M	Unemployed	58.8	Severe	Yes	None	Myokymia	Neurogenic process involving the Cervical and lumbosacral myotomes
7	59/F	Business	103.0	Severe	No	COPD, Diabetes mellitus	None	Not performed
8	46/M	Salesman	128.6	Severe	Yes	Hypertension	None	Normal

CAM = Complementary and Alternative Medicine, EMG = Electromyograph, M = Male, F = Female, COPD = Chronic Obstructive Pulmonary Disease
Cases were selected to represent the spectrum of serum chromium concentrations observed in the study cohort, including mild, moderate, and severe elevations, as well as the two patients with clinical manifestations attributed to chromium exposure and representative asymptomatic patients with markedly elevated serum chromium concentrations. Serum chromium concentrations were measured at the time of clinical evaluation.
*EMG findings are summarized from available neurophysiological evaluations. "Normal" indicates no significant abnormality detected; "Not performed" indicates that EMG was not clinically indicated.

Table 3. Distribution of Patients According to Serum Chromium Severity Categories

Chromium Category	n (%)	Mean Chromium Level (µg/L), Mean ± Standard deviation	Symptomatic Patients, n (%)
Mild (≤20 µg/L)	12 (54.5)	14.98 ± 2.63	0 (0.0)
Moderate (20–50 µg/L)	4 (18.2)	35.70 ± 13.52	1 (25.0)
Severe (>50 µg/L)	6 (27.3)	76.93 ± 31.36	1 (16.7)
Total	22 (100)	35.65 ± 31.54	2 (9.1)

Distribution of patients according to serum chromium severity categories. Symptom prevalence remained low across all chromium categories, with no apparent serum chromium level–toxicity relationship. No significant association was observed between chromium severity category and symptom status.

was observed between serum chromium concentration and the presence of clinical symptoms (Spearman correlation, p = 0.6667).

DISCUSSION

Heavy metal toxicity is a recognized cause of unexplained clinical manifestations, particularly in occupational settings (9). Although the toxic effects of chromium have been extensively described, the relationship between serum chromium concentrations and clinical

toxicity remains poorly defined [10]. To our knowledge, systematic clinical studies evaluating patient-level correlations between serum chromium concentrations and clinical manifestations in non-occupational settings are limited, and no prior Indian cohort has systematically examined this relationship. In this retrospective observational study, elevated serum chromium levels were not consistently associated with clinical toxicity, suggesting that serum chromium concentration alone may have limited utility as a predictor of clinical toxicity.

Despite elevated chromium concentrations in all patients, only 9.1% exhibited symptoms considered attributable to chromium exposure, and mean chromium levels did not differ significantly between symptomatic and asymptomatic individuals (Figure 1). The representative cases shown in Table 2 further illustrate this clinical heterogeneity, with several patients exhibiting markedly elevated serum chromium concentrations in the absence of clinical manifestations, while symptomatic patients did not consistently have the highest serum chromium levels. More importantly, stratified and correlation analyses failed to demonstrate a clear serum concentration–toxicity relationship. Symptom prevalence remained low across all categories, and neither categorical nor correlation analyses identified a significant association between chromium concentration and symptom status (Table 3). These findings are further supported by Figure 1, which demonstrates a scattered distribution of symptomatic and asymptomatic patients across the full spectrum of chromium concentrations, without clustering of symptomatic cases at higher levels.

These observations are noteworthy because a dose–response relationship is a fundamental principle in toxicology. In this cohort, increasing serum chromium concentrations were not accompanied by a corresponding increase in symptom burden. While the modest sample size precludes definitive conclusions, the findings suggest that factors beyond chromium concentration alone are likely to influence the development of clinical manifestations. Interindividual variability in susceptibility, differences in exposure characteristics, nutritional status, and coexisting medical conditions may all contribute to the observed clinical heterogeneity.

Comorbid conditions were present in half of the study population and may have contributed independently to the observed clinical findings. Conditions such as diabetes mellitus and chronic kidney disease are themselves associated with neurological, metabolic, and renal abnormalities that can mimic manifestations traditionally attributed to heavy metal toxicity. The presence of these comorbidities highlights the complexity of attributing nonspecific symptoms solely to elevated chromium concentrations.

CAM intake is a well-recognized source of heavy metal exposure [11]. In this study, patients reporting CAM use had significantly higher serum chromium concentrations than non-users, demonstrating an approximately twofold increase in chromium levels. This finding suggests that CAM preparations may represent an underrecognized source of chromium exposure in non-occupational settings. Given the widespread use of herbal and traditional medicinal products in many regions, this observation has important public health implications.

However, despite higher chromium concentrations, CAM users did not demonstrate a corresponding increase in symptom prevalence. This discordance further supports the absence of a clear serum concentration–toxicity relationship and suggests that elevated chromium levels do not necessarily translate into clinically significant toxicity.

The relationship between chromium exposure and toxicity remains incompletely characterized in the literature. Most available evidence originates from occupational exposure to hexavalent chromium, where respiratory disease, dermatitis, and carcinogenicity are well established. In contrast, evidence relating serum chromium concentrations to clinical manifestations in environmental or non-occupational exposure settings remains limited and heterogeneous [12]. The present study therefore contributes to a limited body of evidence suggesting that elevated serum chromium concentrations do not reliably predict clinical toxicity in real-world, non-occupational populations.

From a clinical and occupational health perspective, these findings have important implications. Elevated serum chromium levels should be interpreted within the broader clinical context rather than in isolation. Reliance on serum chromium concentrations alone may overestimate toxicity risk and lead to misattribution of symptoms. A detailed exposure history, including CAM use, together with careful assessment of alternative diagnoses and comorbid conditions, remains essential when evaluating patients with elevated chromium levels. Attribution of clinical manifestations to chromium toxicity should therefore be made cautiously and supported by objective clinical evidence.

This study has several limitations. The retrospective design precluded assessment of temporal relationships and causal inference. In addition, the modest sample size and low number of symptomatic patients limited statistical power, increasing the possibility of a Type II error whereby a true association between serum chromium concentrations and clinical toxicity may not have been detected. Chromium speciation was not performed, precluding differentiation between trivalent and hexavalent chromium and limiting interpretation of the observed associations. Furthermore, exposure assessment relied on retrospective clinical documentation, and detailed information regarding the composition and chromium content of complementary and alternative medicine preparations was unavailable. Consequently, these findings should be interpreted as exploratory and hypothesis-generating.

Future studies should employ prospective designs with standardized exposure assessment, chromium speciation, and systematic clinical and neurophysiological evaluation. Larger cohorts are needed to better define potential serum chromium concentration-toxicity relationships and to identify factors influencing susceptibility to chromium exposure. Further investigation of genetic, metabolic, and environmental determinants of toxicity may help explain the marked interindividual variability observed in clinical presentation. Given the widespread use of complementary and alternative medicine preparations, their contribution to heavy metal exposure warrants focused evaluation in future studies.

CONCLUSION

In this retrospective cohort, no significant association was observed between elevated serum chromium concentrations and clinical toxicity, and no clear relationship was identified between serum chromium levels and clinical manifestations. Clinical manifestations appeared to be influenced by alternative factors, including complementary and alternative medicine use and underlying comorbidities. These findings suggest that serum chromium concentrations alone have limited utility in predicting clinical toxicity and should be interpreted in conjunction with clinical assessment, exposure history, and potential confounding factors. Further prospective studies are required to clarify the clinical significance of elevated serum chromium levels.

Declarations

The authors used Claude and Grammarly for language editing, grammar correction, and spelling checks during manuscript preparation. These tools were not used for study design, data collection, data analysis, interpretation of results, or generation of scientific content.

Ethical Considerations

The study was approved by the Institutional Review Board and Ethics Committee of Christian Medical College, Vellore (IRB Min. No. 2407164 dated 24 July 2024).

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Not applicable.

Conflict of interest: The authors declare no conflict of interest.

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