



Serum levels of essential and non-essential trace elements in type 2 diabetic patients with rheumatoid arthritis in Western Iran

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Keywords	Abstract
Diabetes mellitus type 2 Rheumatoid arthritis Serum Trace elements	Background and Objectives: Type 2 diabetes mellitus (T2DM) and rheumatoid arthritis (RA) are chronic inflammatory diseases with significant comorbidities. Trace elements play vital roles in metabolic and immune functions, and their imbalance may contribute to disease pathogenesis. This study aimed to evaluate serum levels of essential and non-essential trace elements in T2DM patients with RA in western Iran. Methods: This case-control study included 100 T2DM patients, 100 T2DM patients with RA, and 100 healthy controls aged 35–65 years from Ravansar city in western Iran. Serum concentrations of arsenic (As), cadmium (Cd), lead (Pb), and zinc (Zn) were measured using inductively coupled plasma mass spectrometry (ICP-MS). Moreover, statistical analyses were performed using IBM SPSS Statistics version 25 and R version 4.5.2. Results: Our findings showed that T2DM patients had significantly higher age and BMI ($p = 0.014$ and $p < 0.001$, respectively). In T2DM patients without RA, serum arsenic, cadmium, copper, and lead concentrations were significantly higher, while zinc was lower, compared with controls (all $p < 0.05$). A similar pattern was observed in the small RA-positive subgroup (higher As, Cd, Cu, and Pb; lower Zn), but due to the very small sample size (10 vs. 5), these findings are merely descriptive and exploratory, and no conclusion regarding statistical significance can be drawn. Conclusion: Serum arsenic, cadmium, and lead were higher, and zinc was lower, in T2DM patients compared with healthy controls. However, due to the small sample size and limited complete cases, these findings should be considered exploratory and interpreted cautiously.
Highlights 	• Higher serum As, Cd, Cu, and Pb, and lower Zn in T2DM patients. • Higher RA prevalence in T2DM patients than controls, but not significant. • Similar trace element patterns in the small RA-positive subgroup. • Findings are exploratory and need confirmation in larger studies. Citing Bahirae O., Babaei S., Manoochehri Z., Ahmadi Joybari T., Mansouri B., Mansourisarabbadi A. Serum levels of essential and non-essential trace elements in type 2 diabetic patients with rheumatoid arthritis in Western Iran. Environ Med Toxicol. 2026;():e254817. doi: 10.22034/emt.2026.601747.1004

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Introduction

Type 2 diabetes mellitus (T2DM) and rheumatoid arthritis (RA) are major chronic health challenges that significantly affect healthcare systems and diminish the quality of life for millions [1, 2]. T2DM is a complex metabolic disorder characterized by chronic hyperglycemia due to insulin resistance and declining pancreatic beta-cell function. Its development results from a combination of genetic factors, environmental influences, and lifestyle choices, such as obesity and poor diet [3]. The global prevalence of T2DM is alarming, with approximately 537 million adults affected in 2021, and projections indicating that this number could reach 783 million by 2045 [4]. T2DM leads to serious complications, including cardiovascular disease and nephropathy, contributing to premature mortality [5]. Rheumatoid arthritis is a destructive autoimmune disorder that primarily affects the synovial joints, resulting in persistent inflammation, pain, and joint damage [6]. It commonly impacts the small joints but can also involve larger joints and other organs. While the exact causes of RA are not fully understood, it is linked to genetic predispositions and environmental triggers [7]. Beyond joint pain, RA is associated with systemic complications such as fatigue, increased cardiovascular risk, and osteoporosis, all of which significantly interfere with daily life [8]. Notably, T2DM and RA share underlying mechanisms like chronic inflammation and oxidative stress, explaining the increased prevalence of diabetes among RA patients. This interconnection underscores the importance of integrated management strategies to improve health outcomes for individuals facing these chronic conditions [9].

Trace elements, or micronutrients, are essential inorganic minerals needed in small amounts for various physiological functions, including enzyme activity, hormone synthesis, immune response, and DNA repair. Key trace elements like zinc (Zn), copper (Cu), iron (Fe), and selenium (Se) must be obtained through diet or supplements, as the body cannot produce them [10, 11]. Zinc acts as a cofactor for over 300

enzymes and is vital for immune function and healing [12]. In contrast, non-essential trace elements such as arsenic (As), lead (Pb), and mercury (Hg) have no beneficial effects and can be toxic even at low levels, linked to health issues like cardiovascular and metabolic diseases [13-15]. Maintaining a balance of trace elements is crucial for health; deficiencies or excesses can have serious consequences. For example, zinc deficiency can impair immune function, while excess can hinder copper absorption [11]. Chronic exposure to toxic metals can cause oxidative stress and contribute to insulin resistance and metabolic disorders [16, 17]. Recent studies suggest that these toxic metals are associated with increased risks of type 2 diabetes (T2DM), highlighting the importance of considering environmental factors alongside genetic predispositions in understanding health impacts [18-20].

Despite evidence linking trace element imbalances to Type 2 Diabetes Mellitus (T2DM) and Rheumatoid Arthritis (RA) individually, few studies have examined their profiles in patients with both conditions. This comorbidity poses significant challenges in clinical management, as affected individuals often experience more severe disease progression, increased cardiovascular risks, and lower treatment efficacy than those with only one condition [21]. There is also a notable lack of research on the Iranian population, particularly in western regions where environmental and lifestyle factors may differ. With the rising prevalence of T2DM and RA in Iran, understanding the influence of regional factors on trace elements in this population is crucial for public health. This study aims to fill these gaps by analyzing both essential and non-essential trace elements in Iranian patients with concurrent T2DM and RA.

Materials and Methods

Study population

This investigation was a case-control study utilizing data from the Ravansar Non-Communicable Diseases (RaNCD) cohort which includes over 10,000 adults in Iran. Participants included 100 patients with type 2 diabetes

mellitus (T2DM), 100 with concurrent T2DM and rheumatoid arthritis (RA), and 100 healthy controls, all aged 35 to 65 years, matched by age, sex, and location. The detailed methodology of the RaNCD cohort has been described extensively in previous publications [22, 23]. The population in this area has been followed longitudinally for various health outcomes, and extensive data on demographic characteristics, medical history, lifestyle factors, and laboratory parameters have been collected systematically [22]. The Ravansar cohort is located in western Iran, featuring a predominantly rural population. Participants were selected based on confirmed diagnoses and were contacted by trained staff. Informed consent was obtained in line with the Declaration of Helsinki and approved by Kermanshah University of Medical Sciences' ethics committee (Ethics Code: [IR.KUMS.MED.REC.1404.172](https://doi.org/10.22034/emt.2026.601747.1004)).

Inclusion and Exclusion Criteria

We developed a comprehensive set of inclusion and exclusion criteria to ensure the validity and reliability of the study findings. Participants were eligible for inclusion if they had a confirmed diagnosis of type 2 diabetes mellitus (T2DM) verified by a specialist physician, were aged between 35 and 65 years, had been permanent residents of the Ravansar region for at least five years, and provided written informed consent. For the T2DM+RA group, participants also needed a confirmed diagnosis of rheumatoid arthritis verified by a specialist physician. Control participants were healthy individuals with no history of T2DM, rheumatoid arthritis (RA), or other chronic metabolic or autoimmune diseases. Exclusion criteria included the presence of other chronic diseases such as cardiovascular disease, chronic kidney disease, chronic liver disease, malignancy, occupational exposure to heavy metals, use of medications that affect trace element metabolism (e.g., diuretics, chelating agents), pregnancy or lactation, recent major dietary or lifestyle changes, chronic alcohol consumption, and incomplete data. We applied these criteria rigorously to minimize confounding factors and improve comparability between study groups.

Sample Collection and Biochemical Analysis

Blood samples were collected from all participants after an overnight fast of at least 8 hours. For diabetic patients, blood collection was scheduled before their morning dose of glucose-lowering medication to ensure comparable conditions. Approximately 10 mL of whole blood was drawn using sterile venipuncture techniques into trace element-free vacuum tubes. The samples were allowed to clot for 30 minutes at room temperature and were then centrifuged at 3000 rpm for 10 minutes at 4°C to separate the serum. The resulting serum was aliquoted into sterile tubes and stored at -70°C until analysis to maintain the integrity of the trace elements and prevent degradation. For the determination of trace elements, the serum samples were thawed and subjected to acid digestion. One milliliter of serum was mixed with 3 milliliters of concentrated nitric acid (65%) and 1 milliliter of hydrogen peroxide (30%), and the mixture was digested in a water bath at 96°C until a clear solution was obtained. After cooling, the samples were diluted to a final volume of 10 milliliters with ultrapure water. The concentrations of arsenic, cadmium, lead, and zinc were measured using inductively coupled plasma mass spectrometry (ICP-MS). Quality control measures included the use of certified reference materials, reagent blanks, and recovery calculations ranging from 92% to 105%. Each sample was measured in triplicate, and the results were expressed as parts per billion (ppb) with the mean $\pm$ standard deviation.

Statistical analysis

Quantitative variables were expressed as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), as appropriate based on their distribution. Categorical variables were summarized as frequencies and percentages. Between-group comparisons of quantitative variables were performed using the independent-samples t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Serum concentrations of arsenic (As), cadmium (Cd), copper (Cu), lead (Pb), and zinc (Zn) were specifically compared between patients with type 2 diabetes mellitus (T2DM) and healthy controls.

Comparisons involving subgroups with rheumatoid arthritis (RA) were considered exploratory and were interpreted descriptively because of the limited sample size. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 25 and R version 4.5.2.

Results

Descriptive Characteristics of the Study Population

A total of 200 individuals participated in the study, which included 100 patients with type 2 diabetes and 100 individuals in a control group. According to the results shown in Figure 1, among the 100 patients with type 2 diabetes, only 10% had rheumatoid arthritis, compared to 5% in the control group. Although the prevalence of rheumatoid arthritis was higher in the diabetes group, this difference was not statistically significant (p -value = 0.179). The demographic and clinical characteristics of participants in both groups are summarized in Table 1. The mean age of individuals with type 2 diabetes was significantly higher than that of the control group (48.04 ± 7.34 years vs. 45.42 ± 7.60 years; p -value = 0.014). Additionally, the mean body mass index (BMI) in the diabetes group was significantly higher than in the control group (30.79 ± 4.40 kg/m² vs. 27.25 ± 4.43 kg/m²; p -value < 0.001). Regarding education, a higher proportion of individuals in the diabetes group were illiterate compared to the control group (58% vs. 38%), and the distribution of education levels differed significantly between the two groups (p -value = 0.016). Furthermore, a greater percentage of individuals living in rural areas was observed in the diabetes group compared to the control group (31% vs. 7%; p -value < 0.001). Conversely, no significant differences were found between the two groups concerning gender (p -value = 0.202), marital status (p -value = 0.340), or employment status (p -value = 0.157).

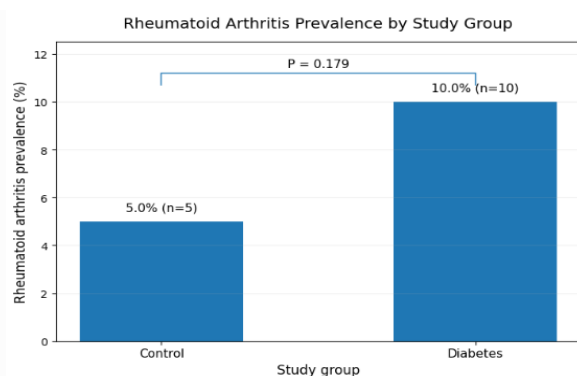


Fig. 1 Prevalence of Rheumatoid Arthritis in Diabetic and Control Groups

Table 1 Demographic and Clinical Characteristics of the Study Participants by T2DM Status

Quantitative features		Control (n=100)	T2DM (n=100)	P-value
Age (year)		45.42 ± 7.60	48.04 ± 7.34	0.014**
BMI (kg/m ²)		27.25 ± 4.43	30.79 ± 4.40	< 0.001**
Qualitative features		Control (n=100)	T2DM (n=100)	p-value
Gender	Female	48 (48)*	58 (58)	0.202
	Male	52 (52)	42 (42)	
Education level	Illiterate	38 (38)	58 (58)	0.016**
	Under diploma& diploma	54 (54)	38 (38)	
	Academic	8 (8)	4 (4)	
Marital status	Married	95 (95)	91 (91)	0.340
	Single	5 (5)	9 (9)	
Employment status	Employee	54 (54)	43 (43)	0.157
	Unemployed	46 (46)	57 (57)	
Residence	Rural	7 (7)	31 (31)	< 0.001**
	Urban	93 (93)	69 (69)	

*Data are presented as n (%) for qualitative features, mean ± SD for quantitative features. ** Indicates p -value < 0.05 .

Comparison of trace element concentrations

The results of comparing serum concentrations of trace elements between individuals with type 2 diabetes without rheumatoid arthritis (T2DM without RA; $n = 90$) and those in the control group without rheumatoid arthritis (Control without RA; $n = 95$) are presented in Table 2. The median arsenic (As) concentration was considerably higher in the diabetes group than in the control group (20.11 vs. 1.36 ppb; p -value < 0.001). Similarly, cadmium (Cd) concentration was higher in the diabetes group (0.83 vs. 0.10 ppb; p -

value < 0.001). The median copper (Cu) concentration was also higher in individuals with diabetes compared to the control group (78.55 vs. 56.95 ppb; p -value = 0.010). Additionally, lead (Pb) concentration was higher in the diabetes group (7.97 vs. 1.74 ppb; p -value < 0.001). In contrast, the median zinc (Zn) concentration was lower in the diabetes group than in the control group (635.28 vs. 787.17 ppb; p -value = 0.015).

The results of comparing metal concentrations between the diabetes group with RA ($n = 10$) and the control group with RA ($n = 5$) are shown in Figure 2. Individuals with type 2 diabetes and RA had higher levels of arsenic (10.51 vs. 4.18 ppb), cadmium (0.84 vs. 0.14 ppb), copper (83.89 vs. 44.69 ppb), and lead (6.61 vs. 2.58 ppb). In contrast, the median zinc concentration was lower in the diabetes group with RA than in the control group with RA (654.69 vs. 868.36 ppb). However, due to the small sample size, these findings should be interpreted with caution and are merely descriptive and exploratory in nature. Therefore, no conclusion regarding the statistical significance of the differences can be drawn from this figure alone.

Table 2 Serum concentrations of trace elements across study groups

Trace element	T2DM without RA (n=90)	Control without RA (n=95)	P-value
As (ppb)	11.20 (8.09)*	1.36 (5.92)	< 0.001**
Cd (ppb)	0.83 (1.89)	0.10 (0.10)	< 0.001**
Cu (ppb)	78.55 (42.32)	56.95 (42.50)	0.010**
Pb (ppb)	7.97 (5.81)	1.74 (1.99)	< 0.001**
Zn (ppb)	635.28 (609.27)	787.17 (471.97)	0.015**

*Values are presented as median (interquartile range, IQR). ** indicates p -value < 0.05.

Discussion

This elevated serum concentrations of arsenic, cadmium, and lead observed in our diabetic patients are consistent with findings from several previous epidemiological studies. A large cross-sectional study using NHANES data reported that higher urinary levels of arsenic and cadmium were associated with increased prevalence of T2DM [24]. Similarly, a systematic review and meta-analysis by Filippini et al. [25] found that exposure to arsenic and cadmium was significantly associated with increased T2DM risk, with pooled odds ratios of 1.52 (95% CI: 1.13–2.05) for cadmium and 1.32 (95% CI: 1.08–1.61) for arsenic. The mechanisms underlying these associations include oxidative stress, inflammation, and interference with insulin signaling pathways [26].

Our findings regarding lead exposure are also consistent with the literature. A prospective cohort study reported that higher blood lead levels were significantly associated with increased T2DM risk over a 10-year follow-up period, with a hazard ratio of 1.32 (95% CI: 1.05–1.65) [27]. In our study, although the median serum lead concentration was significantly higher in the T2DM group than in the control group (7.97 vs. 1.74 ppb; p -value < 0.001) according to Table 2, lead showed a marginally significant inverse association in the logistic regression analysis (OR = 0.770, $p = 0.079$). This apparent discrepancy may be explained by the specific outcome variable used in the regression model, the inclusion of patients with both T2DM and RA, the small number of complete cases available for analysis (Valid N = 11), or non-linear dose-response relationships reported for lead and metabolic outcomes [28].

The reduced zinc levels observed in our study are consistent with evidence that zinc deficiency is common in both T2DM and RA. Feng et al. [29] reported that serum zinc concentrations were significantly lower in T2DM patients and correlated with higher levels of inflammatory cytokines, including IL-6 and IL-8. A meta-analysis of 22 studies found that T2DM patients had significantly lower serum zinc levels compared to healthy controls, with a standardized mean difference of -1.07 (95% CI: -1.44 to -0.69) [30]. Zinc deficiency impairs insulin synthesis and secretion, reduces insulin receptor phosphorylation, and increases oxidative stress and inflammation [31]. In RA, zinc deficiency has been associated with increased disease activity and poorer clinical outcomes [32].

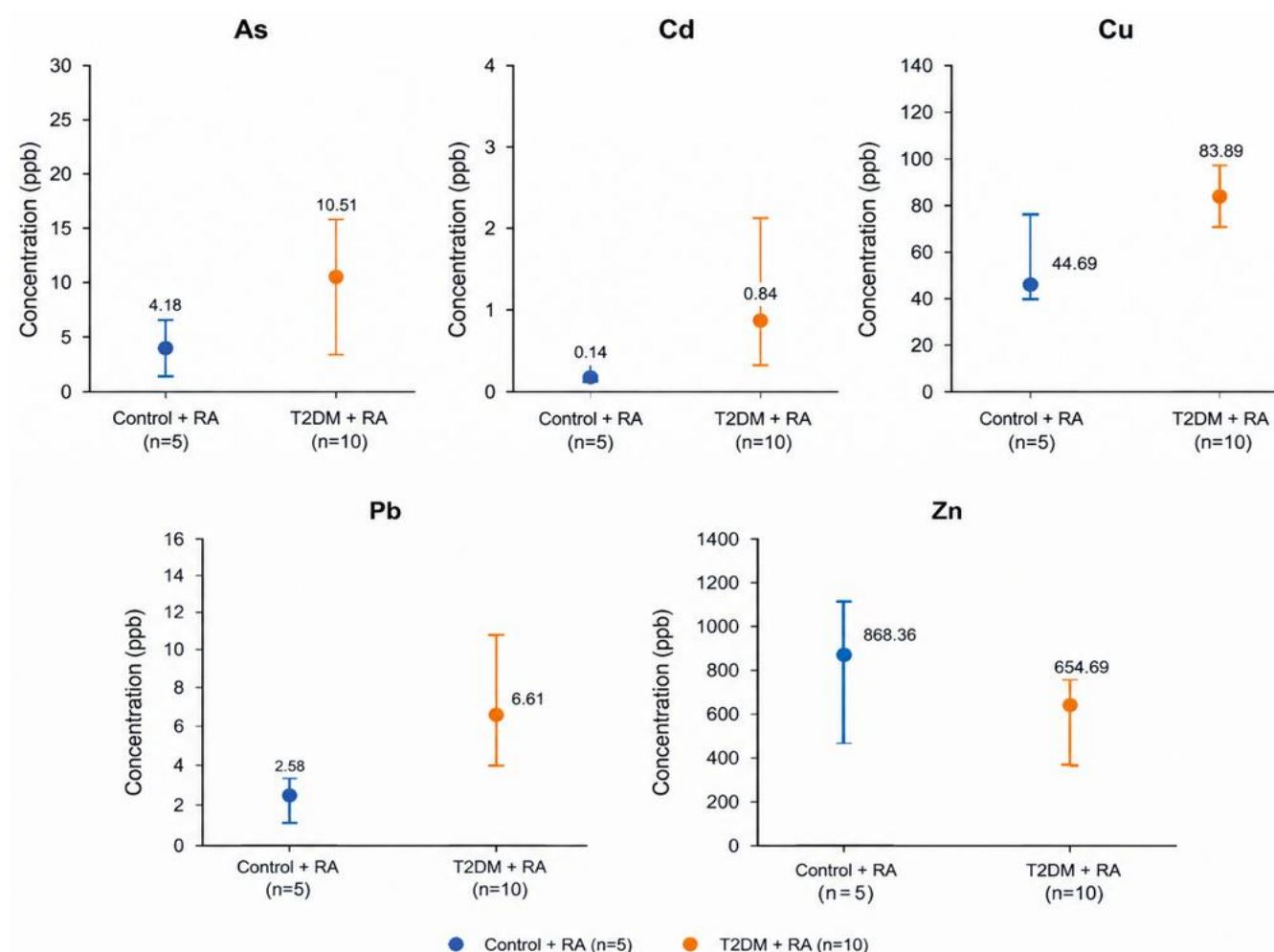


Fig. 2 Serum concentrations of arsenic (As), cadmium (Cd), copper (Cu), lead (Pb), and zinc (Zn) among participants with rheumatoid arthritis (RA) in control and T2DM groups. Points represent medians, and error bars indicate the interquartile range (IQR; Tukey's hinges). The RA-positive control and T2DM groups included 5 and 10 participants, respectively. Findings are descriptive and exploratory given the small subgroup sample sizes.

Mechanistic Insights and Pathophysiological Implications

The mechanisms by which non-essential trace elements, such as arsenic, cadmium, and lead, contribute to the pathogenesis of T2DM and RA are complex and multifactorial. A central pathway is the induction of oxidative stress through the generation of reactive oxygen species (ROS) and the depletion of endogenous antioxidant defenses. Arsenic inhibits key antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, and catalase, while promoting ROS production through the Fenton reaction and disruption of mitochondrial electron transport [33]. The resulting oxidative stress damages cellular proteins, lipids, and DNA, contributing to insulin resistance and pancreatic beta-cell dysfunction [26]. Cadmium similarly induces oxidative stress by interfering with the glutathione system and increasing lipid peroxidation [34]. In RA,

oxidative stress plays a critical role in the inflammatory cascade, contributing to synovial inflammation, cartilage degradation, and bone erosion through NF- κ B activation and pro-inflammatory cytokine secretion [35].

Cadmium and lead also interfere with calcium homeostasis, which has important implications for both insulin secretion and immune cell function. Both metals compete with calcium at various binding sites, including voltage-gated calcium channels and calmodulin, leading to dysregulation of intracellular calcium signaling [36]. In pancreatic beta cells, disturbed calcium signaling impairs glucose-stimulated insulin secretion, while in immune cells, it disrupts the balance between pro-inflammatory and anti-inflammatory responses [37]. Furthermore, cadmium and lead activate the renin-angiotensin-aldosterone system and promote endothelial dysfunction, contributing to hypertension and

cardiovascular disease, common comorbidities in T2DM and RA patients [38].

The observed zinc deficiency in our patients may also contribute to disease pathogenesis through multiple pathways. Zinc is a critical cofactor for numerous enzymes and transcription factors and plays a central role in maintaining the structural integrity of proteins, including insulin and its receptor [39]. Zinc deficiency leads to impaired insulin synthesis, reduced insulin receptor binding affinity, and decreased insulin-mediated glucose uptake [40]. Additionally, zinc is essential for proper immune function, and its deficiency is associated with increased pro-inflammatory cytokine production, decreased natural killer cell activity, and impaired antibody responses [41]. The combination of zinc deficiency and toxic metal accumulation creates a "perfect storm" that predisposes individuals to metabolic dysfunction and inflammatory disease.

The exploratory analysis of the small RA-positive subgroups suggests compelling patterns that align with the main findings. Notably, patients with type 2 diabetes mellitus (T2DM) and rheumatoid arthritis (RA) displayed significantly higher concentrations of arsenic, cadmium, copper, and lead, alongside lower zinc levels, when compared to RA control participants. Although statistical testing was not performed due to the limited sample sizes ($n = 10$ for T2DM + RA and $n = 5$ for controls), these trends strongly echo broader literature. Meta-analyses consistently report elevated copper and decreased zinc levels in RA patients, with copper levels positively correlating with inflammatory markers and overall disease activity [42-44]. Furthermore, RA patients are also found to have increased blood concentrations of cadmium and lead compared to healthy individuals. Given these observations, it is crucial to approach the findings with caution, as they serve mainly as a foundation for future hypotheses. To truly understand the interplay between T2DM and RA, further research with larger sample sizes and sufficient statistical power is vital. Such studies could reveal whether the coexistence of these conditions leads to even more pronounced disruptions in trace element homeostasis than either condition alone.

Limitations

This study has several limitations. The most significant limitation is the small sample size, particularly in the RA-positive subgroups, with only 10 participants for the T2DM + RA group and 5 for

the controls. This small sample size precludes robust statistical testing and restricts the interpretation of the findings to descriptive and exploratory levels. Additionally, the cross-sectional design of the study prevents the establishment of causal relationships between trace element concentrations and disease status. Moreover, the serum measurements primarily reflect recent exposure rather than cumulative exposure over time. The study also did not assess dietary intake, supplementation, or other potentially important factors. Furthermore, residual confounding from environmental and lifestyle factors cannot be completely ruled out. Lastly, the study population was drawn from a single region in western Iran, which limits the generalizability of the findings to other populations. Despite these limitations, this study provides valuable preliminary data that can inform larger, prospective investigations.

Conclusion

This case-control study found that patients with type 2 diabetes mellitus (T2DM) had higher serum concentrations of arsenic, cadmium, copper, and lead, while their zinc levels were lower compared to healthy controls. An exploratory analysis of a small subgroup of rheumatoid arthritis (RA) patients also showed a similar trend: those with T2DM had elevated levels of arsenic, cadmium, copper, and lead, along with reduced zinc concentrations when compared to control participants with RA. However, these findings were not subjected to statistical testing due to the very limited sample size. Given the small scale of the study and the exploratory nature of the subgroup analyses, these results should be interpreted with caution. Larger studies with adequate sample sizes and comprehensive data are necessary to confirm these associations and clarify the potential role of trace elements in T2DM and its comorbidity with RA.

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Authors' Contributions

OB, TAJ and BM conceptualized and designed the study. SB and AM contributed to data collection and laboratory analysis. ZM performed the statistical analysis and interpreted the data. OB, SB, ZM, and BM contributed to writing the initial draft of the

manuscript. OB and BM critically revised the manuscript for important intellectual content and provided methodological expertise. All authors discussed the results, contributed to the final version of the manuscript, and approved it for submission.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no competing or conflicting interests in conducting this study.

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Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Kermanshah University of Medical Sciences (Ethics Code: [IR.KUMS.MED.REC.1404.168](https://doi.org/10.1001/jama.2018.13103)). Written informed consent was obtained from all participants prior to their inclusion in the study.

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