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RESEARCH

Association of Urine Heavy Metals with Prevalence of Type 1 Diabetes and Poor Glycaemic Control

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Abstract

Emerging evidence suggests that endocrine-disrupting chemicals specifically heavy metals, may influence metabolic disorders including Type 1 Diabetes mellitus (T1DM). Poor glycaemic control is a key issue in management of T1DM. This cross-sectional study explores the association of toxic heavy metals with prevalence of T1DM and glycaemia. A total of 153 individuals with T1DM with mean age of 13 years and age- and sex matched 60 healthy controls from Coimbatore, South India were recruited. Clinical data including glycated haemoglobin and sociodemographic and environmental exposure data were collected. Urine samples were analysed for Copper (Cu), Zinc (Zn), Cadmium (Cd), Arsenic (As), Barium (Ba) and Lead (Pb), which are all known endocrine-disrupting chemicals. Urinary concentrations of all heavy metals were normalized to urine creatinine and expressed as *ug/mg creatinine. The levels of all analyzed metals* were significantly higher in T1DM compared to controls. Correlation analysis revealed the positive association between glycaemia and heavy metals. Arsenic and lead showed significant trend with T1D prevalence on comparison to control while zinc and cadmium showed significant trend with uncontrolled glycaemia. This study reveals the association of heavy metals exposure on the etiology and pathophysiology of T1DM. In addition, this study highlights the need of screening of urinary heavy metals as part of metabolic risk assessment and development of targeted therapies for heavy metal detoxification for achieving better glycaemia in T1DM.

Keywords Type 1 diabetes mellitus · Heavy metals · Endocrine-disrupting chemicals · Poor glycaemia · Uncontrolled diabetes · Glycated hemoglobulin

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Introduction

Type 1 diabetes mellitus (T1DM) is a chronic metabolic disorder that occurs during childhood and adolescence, posing a significant social and economic burden on families and nations. Globally, it is estimated that T1DM accounts for approximately 5–10% of all diabetes cases [1] and in the general population, the global prevalence ranges between 0.8 and 4.6 per 1,000 individuals [2]. These data may not truly reflect the actual cases in low- and middle-income countries (LMICs) due to limited access to healthcare facilities and health awareness [3]. During the last decade, there has been a three- to five-fold increase in the incidence of T1DM in children, particularly in LMICs [4]. This sudden escalation of T1DM cannot be attributed merely to genetically related auto-immune factors [5]. The global prevalence of T1DM incidence coincides with a period where there has been tremendous increase in the production and release of endocrine-disrupting chemicals (EDCs) into the environment [6]. Studies have documented the association between T1DM incidence and exposure to different EDCs including persistent organic pollutants, bisphenol A, plasticizers, pesticides, disinfectants, and toxic heavy metals [5, 7]. Although data on the mode of action of EDCs on triggering T1DM are sparse, studies indicate these chemicals could cause impairment of pancreatic beta cells, directly contributing to insulin deficiency or modulation of immune cell functions that lead to immune system-mediated insulin deficiency [8]. Among the EDCs, heavy metals are unique as they are naturally occurring unlike other EDCs, which are man-made and some of them have essential functions in body physiology. Heavy metals such as zinc, nickel, selenium, and copper are essential elements and they become toxic at higher levels while other heavy metals like arsenic, cadmium, lead, are non-essential and toxic. Several studies have documented the association of heavy metals with type 2 diabetes mellitus (T2DM) prevalence across different regions of the world [9, 10]. In contrast to T2DM, very few studies have explored the role of toxic elements in T1DM. The levels of essential elements (selenium, zinc, magnesium, copper, nickel, manganese) are significantly lower in the blood of individuals with T1DM and are associated with increased oxidative stress markers [11, 12]. An interesting study revealed the detection of aluminium, mercury, and arsenic above detection limits in the cord blood of children who later developed T1DM, indicating gestational exposure to heavy metals could contribute to the etiology of T1DM [13]. Studies have unveiled the association of toxic heavy metals in drinking water with the prevalence of T1DM in Canada [14] and Poland [15]. Altogether, though studies reported the association of toxic metals with T1DM, no study has investigated their levels in the bodily fluids of individuals with T1DM.

In comparison with T2DM, the prevalence of poor glycaemic control is very high among individuals with T1DM. This situation is worse in LMICs, where the resources are limited and maintaining adequate glycaemic control is a huge challenge [16]. Different studies have documented nearly two-thirds prevalence of poor glycaemic control among individuals with T1DM are in LMICs [17–19]. A longitudinal study revealed the strong association of poor glycaemic control and increased cardiovascular mortality in individuals with T1DM [20]. Though sociodemographic factors, lack of awareness and resources are attributed to the poor glycaemic control, the etiology of uncontrolled glycaemia remains poorly understood. In recent years, studies have highlighted the possible association of heavy metals with prevalence of poor glycaemic control among T2DM patients [21, 22] Click or tap here to enter text. A three-year follow-up in individuals with T2DM reported the association between urine heavy metals (arsenic, lead, cadmium, nickel and tin) and faster increases in measures of glycaemia [23]. Despite the increased recognition of toxic heavy metals as contributors to metabolic diseases, their association with prevalence and progression of T1DM remains largely unexplored. Furthermore, no study has comprehensively assessed urinary heavy metal levels in individuals with T1DM and glycaemic control from LIMCs. Therefore, this study aims to understand the association of urine heavy metals with T1DM prevalence and poor glycaemic control in South Indian population.

Materials and Methods

Study Population

The study participants were part of the Microbiota-Environmental chemicals orchestration on type 1 diabetes (Micro-Eco-T1D) study. This cross-sectional study include 153 individuals with T1DM attending endocrinology clinics of Kovai Medical Center and Hospital and Madhuram Diabetic and Thyroid Centre, Coimbatore, Tamil Nadu India. T1DM patients with pregnancy, chronic diseases and other complications were excluded from the study. 60 Nos of age and sex matached healthy controls also included in the study. Complete blood anthropometry included glycated hemoglobulin was performed in the healthy controls and those with any self-reported chronic conditions and/on regular medications were excluded. All participants had established T1DM and are on insulin therapy. Individuals who were pregnant and had life-threatening illnesses, or underwent recent surgeries were excluded. Age- and sex- matched healthy controls

were also included in the study. The study protocol was approved by Institute Human Ethics Committee (Reference no: EC/AP/535/05/2017). Written informed consent was obtained from the parents or legal guardians of participants aged below 18 years and directly from participants aged above 18 years. Demographic details and disease history were collected from all participants using a standard questionnaire. Fasting blood and spot urine samples were collected and stored under appropriate conditions. The blood samples were processed for serum and plasma segregation as per standard protocols and stored at −80 °C.

Biochemical Measurements

Peripheral blood samples were collected separately in clot and EDTA tubes were immediately processed for serum and plasma separation respectively as per standard protocols. The plasma and serum were stored at −80° C deep freezer (Thermo Scientific™ TSX70086FA. The spot urine samples were collected and an aliquot is and stored at −80 °C in deep freezer) for further elemental analysis and creatinine analysis was performed immediately. Whole blood were analysed for Glycated haemoglobin (HbA_{1c}), which was measured using the D-10® Haemoglobin Testing System (Bio-Rad Laboratories, Hercules, CA, USA). Based on HbA_{1c} values, individuals with T1DM were categorized as controlled glycaemia [≤8.5% (69 mmol/mol)] or uncontrolled glycaemia [>8.5% (69 mmol/mol)]. Urine samples were analysed for spot creatinine using the Cobas® e 601 module of the Cobas 6000 analyser series (Roche Diagnostics, Germany).

Urine Heavy Metal Analysis

Urine samples were analysed for Copper (Cu), Zinc (Zn), Cadmium (Cd), Arsenic (As), Barium (Ba) and Lead (Pb) by Inductively coupled plasma mass spectrometry (ICP-MS) (NexION® 300X; PerkinElmer Inc.) as per standard protocols [9]. The ICP-MS (NexION 300X, PerkinElmer) was calibrated using multi-element standard solutions prepared from a certified stock standard [Multielement calibration standard 3 (No Hg); Catalogue No. HNO_3 (7697-37−2); Perkin Elmer Inc., USA]. Quantification was performed using a four-point calibration curve with a correlation coefficient (R^2) greater than 0.999. The limits of detection (LOD) and quantification (LOQ) for the elements were determined to be 0.01 ppb and 10 ppb, respectively. Method accuracy was assessed by analyzing a standard solution as a sample, yielding recovery values between 90% and 98%. Analytical precision was evaluated through triplicate measurements, with relative standard deviations (RSD) below 5%. Procedural blanks and spiked samples were routinely analyzed to maintain data quality and ensure reliability of the results. 200 µl urine sample was diluted with 1.8 mL diluent (5% nitric acid + 1.5% ethanol) and filtered through a 20 µm nylon-66 membrane filter. The filtrate was subjected to ICP-MS analysis. The concentrations of metals were normalised to urinary creatinine and expressed as µg/mg creatinine.

Statistical Analysis

All statistical analyses were conducted using SPSS Version 26.0 (IBM Corp., Armonk, NY, USA) and R programming language V 4.1.0 (R Core Team, 2021). Continuous variables were presented as mean ± standard error (SE), and categorical variables as counts and percentages. To minimize the influence of extreme outliers, urinary metal concentrations were subjected to winsorization at the 5th and 95th percentiles. Values below the 5th percentile were set to the 5th percentile value, and those above the 95th percentile were set to the 95th percentile value. Comparison between individuals with T1DM and healthy controls was done using the Mann-Whitney test for continuous variables and Pearson's chi square test for categorical variables. The dot and violin plots were generated using ggplot2, R-package [24]. Spearman's correlation coefficient was calculated between metals and HbA_{1c} values. Urine metal concentrations were categorised into quartiles based on the weighted sample distribution. The association between risk factors and disease outcomes was studied. For each metal, we used logistic regression to estimate odds ratios (ORs) and confidence intervals (CIs) levels for T1DM and glycaemic control by comparing each quartile with the lowest quartile. Our logistic regression models were fitted with appropriate degrees of adjustment. In each analysis, we also evaluated the significance of the differences of the average proportion of T1DM across the four quartiles of the model by a generalised maximum likelihood Wald $\chi 2$ test. Subsequently, we tested for linear trends across quartiles of urine metals by including the median of each quartile as a continuous variable in logistic regression models. Statistical significance was determined on the basis of two-sided p values of < 0.05.

Results

Participant Characteristics

A total of 213 individuals were enrolled in the study, including 153 participants with T1DM and 60 healthy controls. The healthy controls were age- and sex- matched. Sociodemographic and exposure characteristics are represented in Table 1. There has been relatively increased incidence of T1DM among the females (63.4%) in our study area. 79% of the T1DM population fell within the age group of 07–18

Table 1 Demographic characteristics of children with type 1 diabetes (T1DM) ($n=153$) and healthy controls ($n=60$)

		Control *n* (%)	T1DM *n* (%)	*p*-value
Sex	Male	28 (46.67%)	56 (36.60%)	0.213
	Female	32 (53.33%)	97 (63.40%)	
Age Group	< 6 yrs	13 (21.67%)	9 (5.88%)	0.005
	7–12 yrs	21 (35.00%)	65 (42.48%)	
	13–18 yrs	15 (25.00%)	56 (36.60%)	
	> 18 yrs	11 (18.33%)	23 (15.03%)	
Residence area	Urban	35 (58.33%)	58 (37.91%)	0.007
	Rural	25 (41.67%)	95 (62.09%)	
Presence of farmland near residence	Yes	32 (53.33%)	84 (54.90%)	0.836
	No	28 (46.67%)	69 (45.10%)	
Presence of industries near residence	Yes	13 (21.67%)	26 (17.00%)	0.436
	No	47 (78.33%)	127 (83.00%)	
Presence of farmland or industries near residence	Yes	34 (56.67%)	93 (60.00%)	0.542
	No	26 (43.33%)	60 (40.00%)	
Drinking Water Source	Ground water	9 (15.25%)	26 (14.44%)	0.356
	Piped river water	42 (71.19%)	92 (51.11%)	
	Processed water	9 (15.25%)	35 (19.44%)	

years indicating higher prevalence in these age groups. It is interesting to note that 62% of the T1DM population were from rural areas and living near farm lands or industries that could be potential sources of heavy metals. Only 19.44% of the population uses processed drinking water. The healthy controls were matched for all the demographic variables.

Association of Urine Heavy Metals with T1DM on Comparison to Healthy Controls

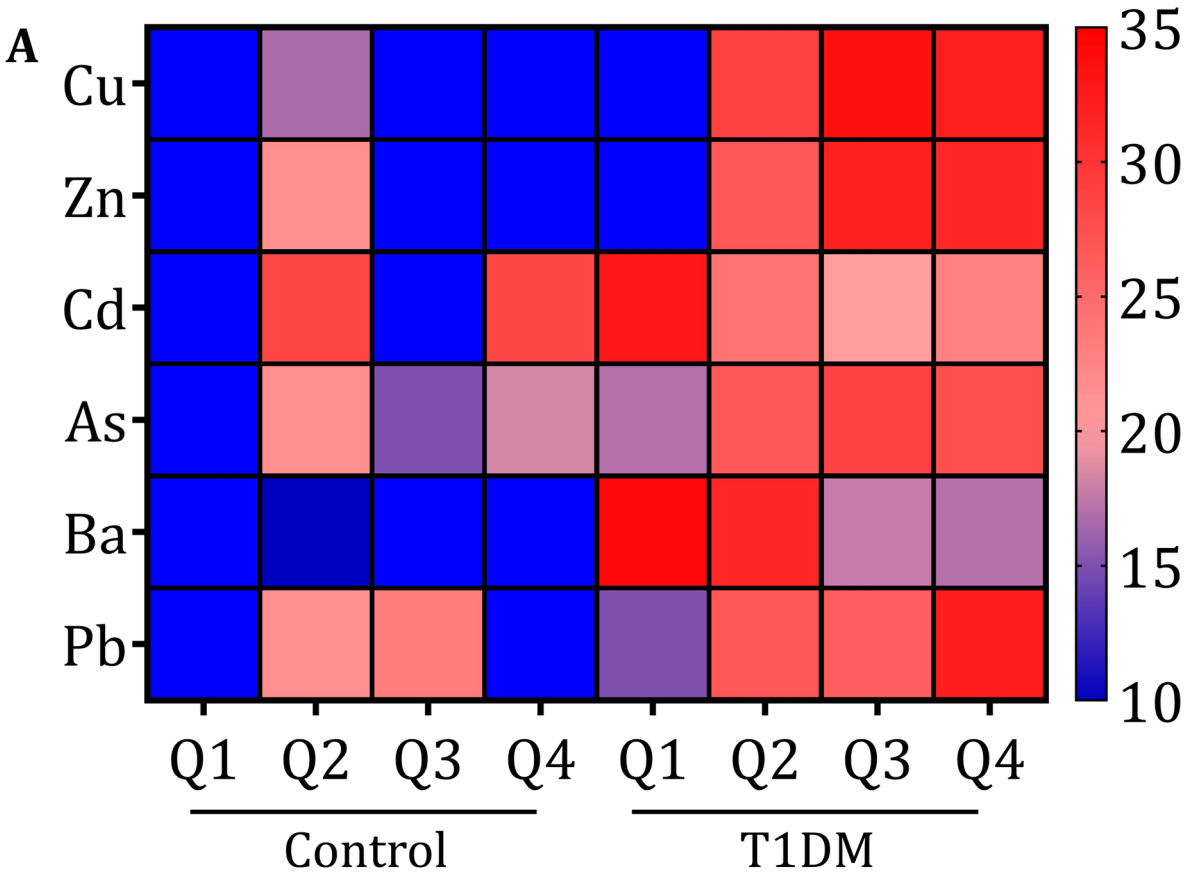
The levels of all the urine heavy metals analysed (Cu, Zn, Cd, As, Ba, Pb) are significantly higher in individuals with T1DM compared to controls (Fig. S1). Based on metal accumulation, the population was divided into quartiles and logistic regression analysis was performed between the quartiles, using the lowest quartile as reference group. More than 50% of healthy controls falls within the lowest quartiles for all heavy metals analysed while in case of T1DM, more than 50% of population fell within the highest quartiles (Fig. 1A and Supplementary Table S1). Urinary concentrations of all six metals showed statistically significant differences between T1DM and control participants ($p<0.001$; Fig. 1A and Supplementary Table S1). Copper and zinc were markedly elevated in the T1DM group, with 32.0% and 31.4% of participants falling in the highest quartile (Q4), respectively, compared to only 6.7%

Fig. 1 Distribution of urinary metal concentrations categorized across quartiles. (**A**) T1DM and Controls. (**B**) T1DM with controlled and uncontrolled glycaemic control

and 8.3% of controls. Conversely, the lowest quartile (Q1) for copper and zinc included 73.3% and 63.3% of controls, but only 5.9% and 9.8% of T1DM individuals, respectively. Cadmium also showed an increased distribution in T1DM, with 32.7% in Q1 compared to just 5% in controls. Arsenic concentrations were similarly higher in T1DM, with 56.2% occupying Q3 and Q4, compared to 33.3% of controls; only 17% of T1DM participants were in Q1 compared to 45% of controls. Urinary barium levels were 33.9% in Q1 compared to 1.7% of controls. Lead concentrations were higher in T1DM, with 58.2% of individuals in Q3 and Q4, while half of the control group clustered in Q1. Logistic regression was performed with adjusted models included age and sex as covariates, and quartile 1 (Q1) served as the reference group. T1DM participants were substantially overrepresented in the highest quartiles of copper and zinc. The odds of T1DM increased sharply across quartiles for both metals. Particularly, individuals with T1DM in Q4 had significantly higher odds of disease for copper (adjusted odds ratio = 0.020 vs. Q1; CI: 0.001–0.568), same trend was seen for zinc, where T1DM participants in Q4 had an OR of 0.035 ($p<0.025$ and 0.011, respectively). Arsenic showed a strong association with individuals in the highest quartile (Q4), which is found to be having 15.62-fold higher odds of developing T1DM compared to those in the lowest quartile (Q1) (95% CI: 1.952–101.25; $p<0.002$). A similar pattern was observed in lead (Pb) with T1DM participants in Q4 showing increased odds compared to those in lower quartiles ($p<0.016$). Altogether, upon logistic regression analysis, significant trends were obtained for the highest quartiles for Cu, Zn, As and Pb on comparing the odds ratio of T1DM with controls (Table 2).

Heavy Metals and Glycaemic Control in T1DM

To assess the relationship between urinary metal concentrations and HbA_{1c} among individuals with T1DM, Spearman's rank correlation analysis was performed (Table 3). Significant positive correlations were found between HbA_{1c} and the urinary levels of zinc ($\rho=0.181$, $p=0.025$), lead ($\rho=0.185$, $p=0.022$), and barium ($\rho=0.174$, $p=0.032$). Though cadmium and arsenic also showed positive correlations with HbA_{1c}, they did not reach statistical significance. Participants were stratified by glycaemic control using an HbA_{1c} threshold of 8.5% [69 mmol/mol] (controlled ≤ 8.5% [69 mmol/mol]), uncontrolled > 8.5% [69 mmol/mol])), and metal concentrations were assessed across quartiles (Fig. 1B and Supplementary table S2). For copper, individuals with uncontrolled glycaemia were more frequently


A
Cu
Zn
Cd
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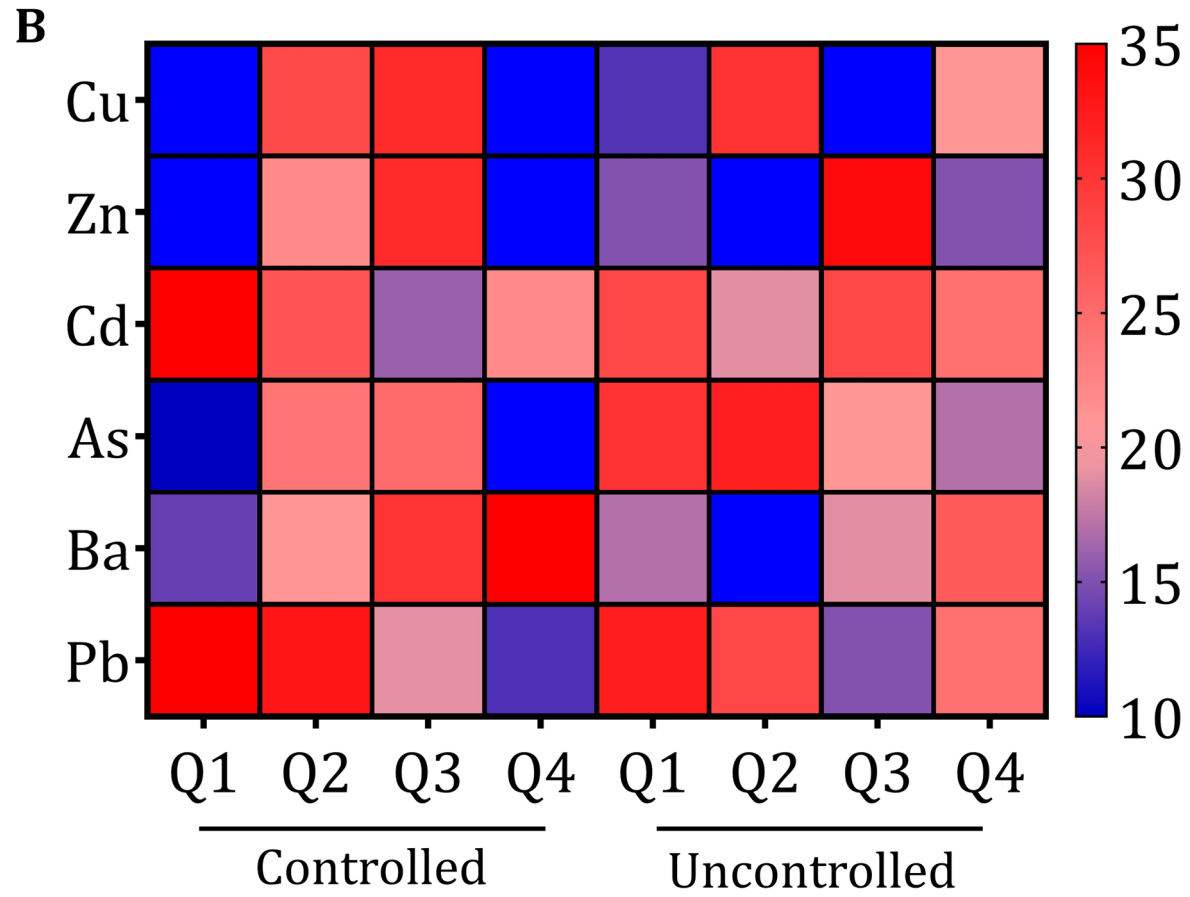
B
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Controlled
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35
30
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20
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10

Table 2 Binomial logistic regression analysis comparing the odds of having T1DM across increasing quartiles of urinary metal concentrations

Metal	Model	Q1	Q2	Q3	Q4	P_{trend}
Cu	Unadjusted	1	0.027 (0.003–0.266) **	0.013 (0.001–0.218) **	0.014 (0.001–0.258) **	**0.025**
	Model 1	1	0.030 (0.002–0.377) **	0.015 (0.001–0.327) **	0.019 (0.001–0.466) *	
	Model 2	1	0.042 (0.023–0.456)**	0.018 (0.001–0.235)*	0.020 (0.001–0.568)*	
Zn	Unadjusted	1	0.053 (0.006–0.464) **	0.008 (0.000–0.233) **	0.030 (0.001–1.186)	**0.011**
	Model 1	1	0.045 (0.004–0.504) **	0.006 (0.000–0.245) **	0.020 (0.000–1.451)	
	Model 2	1	0.012 (0.005–0.483) **	0.005 (0.001–0.315)*	0.035 (0.001–1.548)	
Cd	Unadjusted	1	5.923 (0.612–57)	0.573 (0.012–27.781)	10.227 (0.159–658.675)	**0.711**
	Model 1	1	6.338 (0.620–64)	0.882 (0.012–62.296)	8.586 (0.101–727.684)	
	Model 2	1	6.584 (1.025–41.0)	0.954 (0.012–34.523)	7.561 (0.201–523.0)	
As	Unadjusted	1	0.473 (0.012–18.328)	4.184 (0.326–53.752)	12.765 (1.012–161.053) *	**0.002**
	Model 1	1	0.813 (0.015–44.189)	4.006 (0.270–59.361)	17.879 (1.259–253.983) *	
	Model 2	1	1.023 (0.020–35.641)	4.521 (0.549–39.152)	15.625 (1.952–101.25)*	
Ba	Unadjusted	1	11.686 (0.207–659.437)	20.812 (0.261–1661.516)	72.213 (0.746–6993.940)	**0.262**
	Model 1	1	15.720 (0.198–1250.860)	38.262 (0.283–5167.881)	220.090 (1.081–44806) *	
	Model 2	1	18.112 (0.568–715.0)	28.353 (0.315–1654.0)	132.0 (1.284–1002)*	
Pb	Unadjusted	1	0.350 (0.026–4.633)	1.035 (0.016–66.445)	0.121 (0.001–22.661)	**0.016**
	Model 1	1	0.193 (0.011–3.388)	1.976 (0.022–179.931)	0.143 (0.001–40.095)	
	Model 2	1	0.254 (0.235–5.325)	1.890 (0.050–77.253)	0.152 (0.002–28.99)	

ORs and 95% CIs are shown for both unadjusted and adjusted models. Q1 (lowest quartile) is the reference group. Model 1 adjusted for age and sex while model 2 adjusted for age, sex, presence of industries and farmlands near residence and drinking water source

Table 3 Spearman's rank correlation coefficients between metals and HbA_{1c}

Variable	Spearman ρ (*p*-value)
Cu	0.098 (0.227)
Zn	0.181 (0.025) *
Cd	0.143 (0.078)
As	0.101 (0.213)
Ba	0.174 (0.032) *
Pb	0.185 (0.022) *
BMI	−0.114 (0.162)
No. of Hospitalizations	0.241 (0.003) **

Values represent Spearman's correlation coefficient (rho) between HbA_{1c} and each parameter. *$p<0.05$, **$p<0.01$, ***$p<0.001$

distributed in the lower quartiles. A greater proportion of uncontrolled participants were present in the first quartile (13.2%) and third quartile (35.8%), while only 20.8% fell into the highest quartile. In contrast, 38% of those with controlled glycaemia were in the highest quartile, indicating a statistically significant shift in distribution ($p=0.013$). Zinc showed a similar pattern in uncontrolled individuals more frequently found in the second (35.8%) and third (34.0%) quartiles, while the fourth quartile comprised only 15.1% of this group compared to 40.0% among those with controlled glycaemia. For arsenic, a higher proportion of uncontrolled individuals were found in the second (32.1%) and fourth (19.0%) quartiles, whereas it was 24.0% and 9.0% in controlled group. Urinary metal concentrations were associated with uncontrolled glycaemia ($HbA_{1c}\geq 8.5\%$ [69 mmol/mol])) among T1DM participants using binomial logistic regression. Lowest quartile (Q1) was considered the reference group and odds ratios (ORs) were calculated for both unadjusted and age- and sex-adjusted models (Fig. 2 and Supplementary table S3). In the adjusted model, urinary zinc levels were associated significantly with glycaemic control status (p trend=0.015). For zinc, an odds ratio of 0.242 (95% CI: 0.060–0.983) for having uncontrolled glycaemia was observed in the highest quartile (Q4) compared to those in the lowest quartile. A significant association was also shown by cadmium levels, with increased odds of uncontrolled glycaemia (OR=4.023, 95% CI: 0.991–12.361; p trend=0.017) being exhibited by participants in the highest quartile (Q4). No statistically significant associations were found for copper, arsenic, barium, and lead in the adjusted models. However, the unadjusted model showed reduced odds in some quartiles (e.g., Q3 for arsenic), these associations were not sustained after adjustment for age and sex.

Discussion

Our study reports a comprehensive analysis of urinary trace element concentrations among T1DM participants and healthy controls, with a focus on their association with HbA_{1c}. In our cohort there was a slightly increased proportion of females compared to male T1DM participants though it is not statistically significant. This pattern is supported

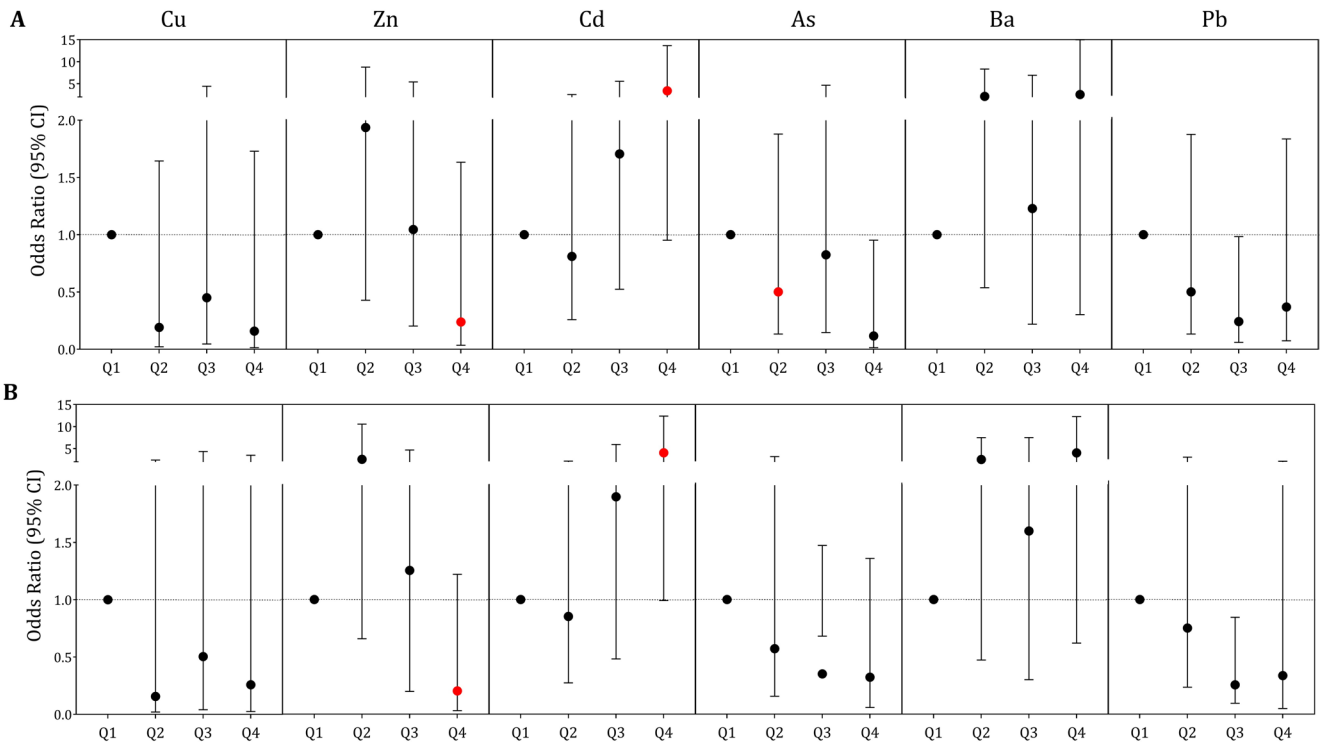

Fig. 2 Odds ratio (95% CI) for glycaemic control associated with the quartiles of heavy metals. The red colour indicates statistical significance. (**A**) Unadjusted model (**B**) Multivariate adjustment included age, sex, presence of industries and farmlands near residence and drinking water source

by recent literature, attributing to difference in the immune regulatory effects of genes on the X chromosome and sex-specific immune responses. There are also certain conditions like systemic lupus erythematosus (SLE), rheumatoid arthritis and multiple sclerosis where the presence of estrogen influences the degree of immune response [25, 26]. On the contrary other studies have reported equal or increased male population in their cohort [27, 28]. While this pattern in T1DM remains incompletely defined, further studies in sex-specific investigation in the South Asian population is required. Our results demonstrated differences in urinary metal levels across HbA_{1c}, with several trace elements, particularly zinc and cadmium showing significant associations with glycaemic outcomes. Copper (Cu) levels were found to be significantly elevated in T1DM participants, with a greater number of individuals classified into the higher urinary Cu quartiles, and this pattern was confirmed by regression analysis, which indicated a strong association between increased Cu excretion and T1DM status. Individuals with uncontrolled HbA_{1c} were found more in the highest Cu quartiles and although correlation and regression were not significant, the pattern reinforced the link between elevated Cu and poorer glycaemic control. These findings are consistent with the literature in which Cu dysregulation is linked to T1DM pathophysiology. β-cell function has been shown to be impaired by excess Cu through oxidative stress, disruption of Cu transporter activity, and activation of inflammatory pathways [29–31]. These mechanisms may underlie the observed association between elevated copper levels and poorer glycaemic control in our cohort. Zinc (Zn) plays an important role in synthesis of insulin [32] and acts as antioxidant [33], was considerably elevated in individuals T1DM, indicating increased renal Zn loss. Logistic regression model reveals higher Zn quartiles is associated with increased odds of T1DM. Additionally, individuals with T1DM with elevated Zn tend to have a controlled glycaemia, suggesting a complex interplay between insulin regulation, glycaemic control, and disease severity. These findings are similar with a condition called “hyperzincuria” reported in T1DM [34–36] Urinary Zn can also serve as biomarker for metabolic stress. Galvez-Fernandez et al. [36] further demonstrated that adequate zinc status is associated with better glycaemic outcomes in children with T1DM. The interplay between Zn and Cu was an interesting observation in our study. It is known that both these elements share common transporters and regulatory pathways, so any disruption can affect the homeostasis of these elements. Dinicolantonio et al. [37] emphasized that excessive copper can inhibit zinc

absorption and impair glycaemic control via altered redox signalling. In this study, the dysregulated zinc-copper axis was suggested by the inverse relationship between zinc and HbA_{1c}, in parallel with elevated Cu contributing to impaired β-cell function.

A more complex relationship was shown by cadmium (Cd), though it was not considered to be statistically significant among the different groups; a greater odds of uncontrolled glycaemia was observed in individuals with higher urinary Cd. This observation is similar to previous reports claiming its effect on insulin resistance [38], it also plays a role in oxidative stress and other metabolic pathway. Cd levels can serve as stress biomarker for pancreatic beta cell [39]. Hong et al. [40] showed that cadmium disrupts β-cell function by impairing mitochondrial pathways, reducing insulin secretion, and altering lipid metabolism. Wen et al. [41] reported that cadmium exposure elevates oxidative stress and inflammatory signalling, aggravating glycaemic instability. Buha et al. [38] further emphasized cadmium's ability to interfere with insulin sensitivity and impair pancreatic health even at low environmental levels. Arsenic (As) is known for its diabetogenic role and has been a public health concern. There was a strong and statistically significant association with T1DM with highest quartile urinary As being 18-fold increase in odds of T1DM, even after adjusting for possible confounders. Cameran et al. [42] reported that chronic arsenic exposure is associated with disruption of insulin signalling pathways and induction of oxidative stress, which contribute to pancreatic β-cell dysfunction. Arsenic's ability to impair glucose uptake and promote the production of inflammatory cytokines was demonstrated by Liu et al. [43]. While Pánico et al. [44] have shown that arsenic impacts endothelial and immune pathways involved in metabolic dysregulation. Additionally, extensive agricultural usage of arsenic-containing fertilizers has been reported, and arsenic occurs naturally as a contaminant in groundwater, often as a result of geogenic factors or anthropogenic activities such as mining. Prolonged exposure to arsenic-contaminated groundwater, which is a global issue, continues to pose substantial risks to public health due to the widespread reliance on these water sources for drinking and agriculture [45].

Barium (Ba) is a non-essential element with limited biological function. Ba levels were significantly elevated in T1DM cohort and showed a positive association with HbA_{1c}, pointing its role in glycaemic dysregulation. However, Evidence linking glucose dyshomeostasis is underreported [46]. Acute barium poisoning can lead to "hypokalemia" as it interferes ion channel as reported by Tao et al. [47]. Lead (Pb) is widely known for its versatility, but it is also known for its toxicity which, upon exposure, can inflict damage to pancreatic beta cell, promotes oxidative stress, and plays a major role in activation of immune system [48]. Elevated level of Pb was observed in T1DM population and positively correlated with glycaemic level, which is consistent with prior research that states exposure to Pb is associated with elevated blood glucose. Participants in the highest quartile of urinary lead has significantly increased odds of T1DM. These exposures stem from contaminated sources such as water, air, and cooking utensils and industrial residues in our environment [49–51]. In overall, the heavy metals can induce the pancreatic beta cell destruction through immune and non-autoimmune pathways mediated through reactive oxygen species and oxidative stress (Fig. 3).

This study has limitations, adjustment for urine concentration variability was achieved using creatinine; however, the long-term or cumulative exposure may not have been accurately reflected by spot urine sampling. While a more reliable estimate could have been provided by a 24-hour collection, this was not practically feasible in our paediatric T1DM outpatient setting. Additionally, more robust data could have been obtained if complementary analysis of blood and hair samples had been performed. The detailed information on the longitudinal history of exposure to environmental chemicals, metal speciation, and data on dietary intake were also limited.

Conclusion

Our study reveals significant associations between urinary metals and T1DM status in South Indian children. Elevated levels of heavy metals were linked to both disease risk and glycaemic control. Despite the limitations, this study provides important preliminary insights into the relationship between environmental metal exposure and glycaemic health in the T1DM cohort. Future studies should include prospective cohort designs and mechanistic approaches to determine pathways followed by interventions like dietary modification and chelation therapy for better glycaemic control among heavy metal-exposed T1DM population.

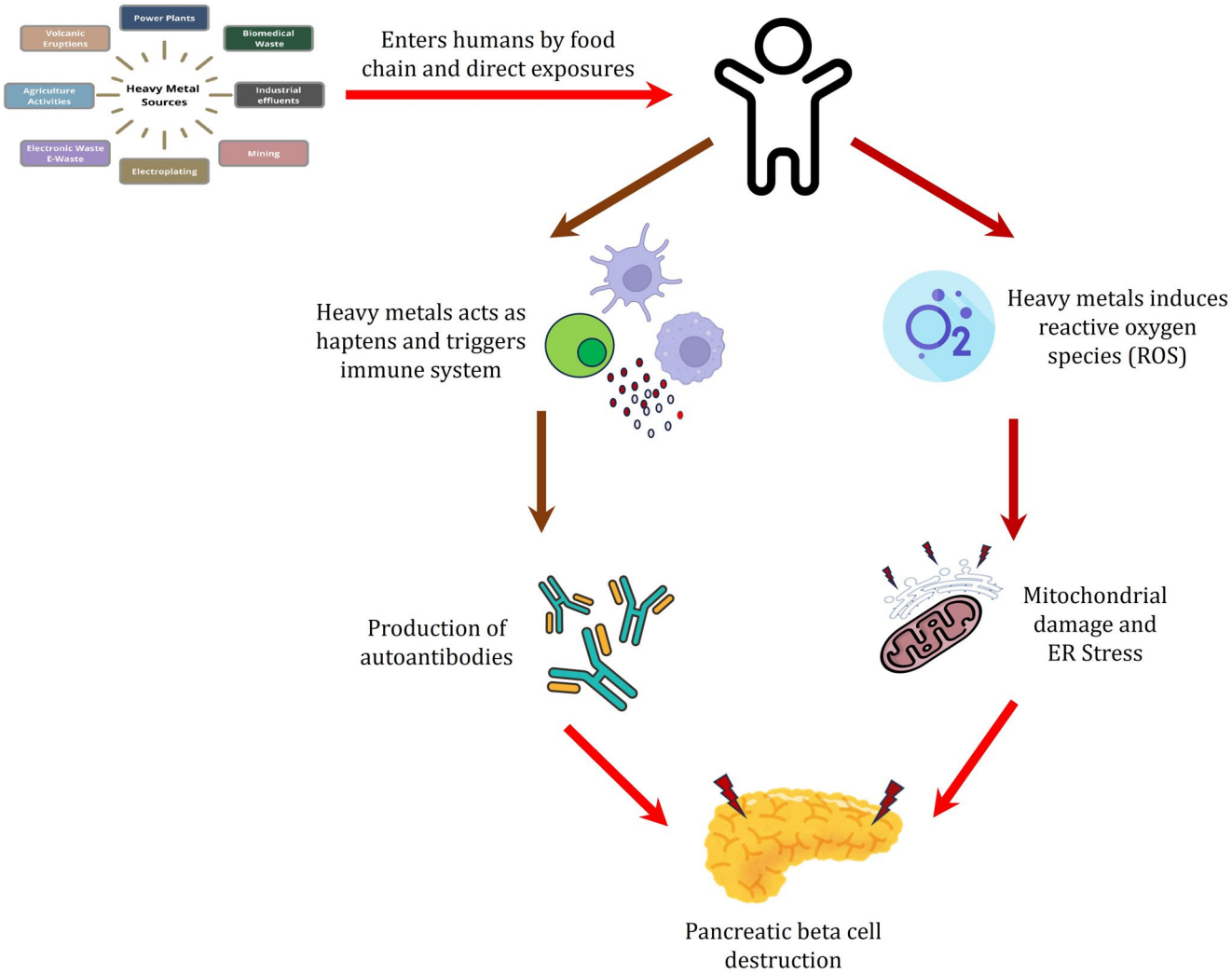

Fig. 3 Schematic illustration of heavy metals-induced beta-cell destruction through immune and non-immune pathway

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Author Contributions Samrat Ashok Vasudevan: Writing – original draft, Validation, Data collection & curation, Methodology, Investigation, Formal analysis. Srinidhi Narayani Seenivasan : Writing – review and editing, Formal analysis, Investigation, Data collection & curation. Avinash Kumar Raghupathy : Writing – review and editing, Formal analysis, Data collection & curation. Dinakaran Vasudevan : Investigation, Data collection & curation. Parthasarathy Ayothi: Investigation, Data collection & curation. Tanmayaa Nayak: Methodology, Investigation. Buvaneswari Gajendran: Data collection & curation. Karthika Durairaj : Data collection & curation. Divya Shree Sathish: Data collection & curation. Srilaxmi Balaji: Data collection & curation. Abisheak Kandasamy: Data collection & curation. Amaravathy P: Writing – review and editing, Formal analysis. Mohanraj Sundaresan: Writing – review and editing, Formal analysis, Data collection & curation, conceptualisation. Shankar Dhandapani: Data collection & curation, conceptualisation. Thalappil Pradeep: Investigation, funding acquisition, conceptualisation. Krishnan Swaminathan: Writing – review and editing, Funding acquisition, conceptualisation, supervision, Project administration. Velmurugan Ganesan: Writing – review and editing, Validation, Methodology, Investigation, Formal analysis, Data collection & curation, Funding acquisition, conceptualisation, supervision, Project administration.

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Data Availability All raw data are available as supplementary materials.

Declarations

Ethics Approval and Consent to Participate The study was conducted in accordance with Declaration of Helsinki and approved by the Institu-

tional Human Ethics Committee (Reference no: EC/AP/535/05/2017) at Kovai Medical Centre and Hospital Limited (KMCH), Coimbatore, India. Informed consent was obtained from the parents or directly from participants aged 18 years and older.

Competing Interests The authors declare no competing interests.

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