Original Article

# Effects of STZ-Induced Diabetes on Zinc, Boron and Antioxidant Defense Mechanisms in Rats

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**Abstract**

**Background:** Diabetes mellitus (DM), characterized by dysregulation of glucose metabolism, is a significant global health issue. This study aims to investigate the effects of DM, induced with streptozotocin (STZ), on serum zinc and boron levels as well as antioxidant defense mechanisms in rats. **Materials and Methods:** In this study, a rat model was utilized where rats, after an overnight fast, were administered a single intraperitoneal dose of STZ to induce type-1 diabetes. Diabetic status was confirmed three days post-STZ administration with fasting blood glucose levels exceeding 300 mg/dL. Six rats were assigned to the STZ-induced diabetic (DM group) and control groups (C group). Inductively coupled plasma mass spectrometry (ICP-MS) was used to analyze serum samples treated with hydrogen peroxide and nitric acid. Furthermore, serum samples were analyzed using ELISA to measure total oxidant-antioxidant status (TOS-TAS). **Results:** The ICP-MS method was validated with validation parameters including method linearity (10–500 ng/mL), precision (≤ 3.25% RSD), accuracy (≤ ±2.58% RE), and recovery (98.2 ± 4.53% for zinc and 101.4 ± 5.46% for boron). Our results showed significantly decreased serum levels of both zinc and boron in the DM group compared to the C group ($P$ = 0.001), suggesting a possible link between trace element dysregulation and DM pathogenesis. The DM group showed a statistically significant increase in TOS ($P$ = 0.006); and a decrease in TAS ($P$ = 0.001) compared to the C group. Assessment of oxidative stress parameters demonstrated an imbalance in oxidative stress homeostasis in diabetic rats, further implicating the role of trace elements in DM-associated complications. **Conclusion:** These findings contribute valuable insights into the complex interplay between trace elements and oxidative stress in DM.

**Keywords:** *Boron, diabetes mellitus, ICP-MS, TAS-TOS, zinc*

**Received:** 28-Aug-2024;
**Revision:** 18-Dec-2024;
**Accepted:** 28-Dec-2024;
**Published:** 27-Mar-2025

## Introduction

The chronic illness known as diabetes mellitus (DM) is characterized by elevated blood glucose levels caused either by the body's inefficient use of insulin or by the pancreas' incapacity to make adequate insulin. The three primary forms of DM are insulin-dependent type-1, non-insulin-dependent type-2, and gestational diabetes. Insulin-producing beta cells in the pancreas are destroyed, resulting in inadequate insulin secretion and the development of type-1 DM. The incapacity of the cells to react to insulin as intended is a characteristic of type-2 diabetes. Higher than normal blood glucose levels characterize gestational diabetes, which occurs during pregnancy.[1] According to the World Health Organization, 1.5 million deaths worldwide in 2019 were directly attributed to diabetes, and its incidence has been increasing in recent years.[2]

Oxidative stress induces cellular dysfunctions, contributing to diabetes progression and β-cell

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_566_24

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**How to cite this article:** Demirkaya Miloglu F, Gundogdu G, Bayrak B, Kadioglu Y, Yuksel B. Effects of STZ-induced diabetes on zinc, boron and antioxidant defense mechanisms in rats. Niger J Clin Pract 2025;28:248-54.

damage.[3,4] In addition, reactive oxygen species (ROS) also activate numerous stress-sensitive cellular pathways and contribute to cellular degradation, decreasing insulin secretion and insulin resistance.[5] Studies have shown that ROS production occurs in various tissues under diabetic conditions.[6,7]

Trace elements are key as enzyme components and catalysts in biochemical reactions. While their influence on diabetic patients has been attributed to mechanisms such as activation of insulin receptor sites, serving as cofactors or components for enzymes in glucose metabolism, and acting as antioxidants to improve insulin sensitivity, the specific effects of individual trace elements remain incompletely understood.[8] As a result, variations in the levels of these trace elements can trigger various diseases.

Zinc is critical in insulin synthesis, crystallization, secretion, function, and storage.[9] Studies on zinc have demonstrated its ability to increase insulin secretion and sensitivity in pancreatic β-cells with zinc supplementation. Inside the cell, insulin monomers are stored as zinc crystals and in dimeric form for secretion in the presence of zinc. In addition, insulin complexes with two zinc molecules form a hexameric zinc-2-insulin-6, which is required for secretion after maturation. Zinc stimulates the phosphorylation of the β-subunit of the insulin receptor, facilitating glucose transport into cells by activating protein kinase B and phosphatidylinositol 3-kinase.[10] Zinc is also involved in the molecular signaling pathways of insulin, increasing the transcription of the insulin receptor gene by zinc finger proteins of the insulin receptor gene and regulating glucose uptake. Thus, zinc deficiency causes glucose intolerance and insulin resistance.[9,11] Moreover, antioxidant enzymes such as catalase and superoxide dismutase have zinc in their structures. Insufficient zinc levels lead to increased generation of ROS and tissue damage in diabetes. Depletion of intracellular zinc stores makes it more difficult for the cell to defend itself against this oxidative stress, which may contribute to the progression of type-1 diabetes. Moreover, zinc promotes glucose storage as glycogen and prevents this monosaccharide from being produced, helping maintain glucose homeostasis.[11,12]

Boron is an essential trace element with a partially understood biochemical role. It is theorized to influence several vital functions, including bone and mineral metabolism, endocrine activities, energy regulation, oxidative stress response, wound healing, and Vitamin D metabolism.[8,13,14] It has been suggested in various studies that boron shows a decrease in oxidative stress and prevents damage by increasing glutathione stores and inhibiting other ROS species,[15] as in zinc. Boron concentrations in human tissues are typically low, leading to nutrient deficiencies when below optimal levels and potential toxicity at high concentrations, highlighting the narrow margin between deficiency and excess.[16] Daily boron intake by humans mainly depends on dietary intake from fruits and vegetables.[17]

However, it is noteworthy that there currently need to be more studies in the literature that focus on the simultaneous assessment of zinc and boron levels. Despite extensive research into the individual roles of these trace elements, there still needs to be a gap in understanding their combined effects, particularly in the context of DM. This study uses ICP-MS methodology to assess zinc and boron levels in rat serum with STZ-induced experimental DM, focusing on the role of oxidative stress in their involvement in diabetes pathogenesis.

## Material and Methods

### Model of type-1 diabetes in experimentation

The Animal Experimentation Ethics Committee of Atatürk University (date: 28.02.2022, number: HADYEK-2022/2, 39) approved the methods and ethical standards that were strictly followed when conducting animal experiments. The Laboratory Animal Teaching and Research Centre of the Laboratory of Laboratory Animals (Ataturk University) provided twelve male Sprague-Dawley rats, weighing 268 ± 24 g and around 12 weeks old. These rats were provided water and normal rodent feed on an as-needed basis after being acclimated to the laboratory setting. They were kept in cages with carefully regulated humidity and temperature, as well as a 12-h light-dark cycle designed to replicate the cycles of the natural world.

In the experimental rats, type-1 DM was induced using STZ. A meticulously mixed solution of 65 mg/kg of the drug, freshly dissolved in cold citrate buffer, was used to give STZ. To guarantee uniform circumstances, the rats were given a 12-h fast before receiving a single intraperitoneal dosage of the STZ solution. Following the administration of STZ, the rats were closely observed. An Accu-Chek glucometer was used to assess blood glucose levels three days following the injection of STZ. Rats that tested more than 300 mg/dL for fasting blood glucose were categorized as diabetic and added to the study group. Rats with diabetes conditions that are clinically relevant were selected for further investigations thanks to this stringent criterion.

### Experimental groups

A total of twelve rats were used in the experimental groups; six of the rats were given STZ to induce diabetes (DM group), while the other six rats were used

as controls (C group). At the end of the experimental procedure, the rats were sacrificed under general anesthesia induced by intraperitoneal administration of ketamine hydrochloride and 2% xylazine hydrochloride. Blood samples were then taken from the abdominal aorta of each rat to ensure the accuracy and consistency of the information collected.

### Blood samples were immediately centrifuged to separate the serum from the cellular components

The serum obtained was carefully transferred into small polypropylene test tubes to maintain sample integrity and avoid contamination. The tubes were then sealed and stored at -80°C to preserve the stability of the serum components until further testing. This methodical approach to sample collection and processing was designed to preserve the biochemical composition and integrity of the serum samples for further investigation.

### Analytical analysis

***Instrument and method conditions:*** The levels of zinc and boron in serum samples were measured using an Agilent 7800 Inductively Coupled Plasma Mass Spectrometer (ICP-MS) in Waldbronn, Germany. The manufacturer's recommended experimental settings were followed throughout the analysis. High-purity argon gas was used to prepare the serum medium in which the analysis was performed. Reactive gases such as helium and methane were used to facilitate the measurement process. The instrument settings were as follows 18 L/min for the plasma gas, 1.0 L/min for the auxiliary gas, and 1550 W for the radio frequency (RF) power.

The chosen parameters of the instrument were carefully selected to provide the best possible performance and precision in the determination of zinc and boron levels in the serum samples.

***Reagent and Sample Preparation:*** Nitric acid was purchased from Fisher Scientific (Pittsburgh, PA) and hydrogen peroxide from Merck-Millipore (Darmstadt, Germany) for acidification of standards. Milli-Q deionized water with a resistivity of 18 MΩ/cm was purchased from Millipore (Bedford, MA) for sample preparation and analysis. ICP-MS zinc and boron standard solutions (Merck VI, Darmstadt, Germany) were used to generate calibration to ensure the analytical method. The Milestone ETHOS UP high-performance microwave digestion system was used for sample preparation. One mL samples were mixed with 9 mL nitric acid and 1 mL hydrogen peroxide. The samples were then digested using the blood method at 1800 W power, 190°C temperature, and a sample-to-sample time of fifteen minutes. After digestion, the samples were adjusted to a final volume of 15 mL.

### Analyses of the Oxidative Stress Index (OSI), Total Antioxidant Status (TAS), and Total Oxidant Status (TOS)

The serum sample was measured using the Rel Assay Total Oxidant Status commercial kit (Mega Tıp, Gaziantep, Turkey) to determine the TOS concentration. The measurement is based on the principle of the supernatant causing an increase in absorbance by converting the $Fe^{2+}$ complex to $Fe^{3+}$ and reacting with chromogen in an acidic environment. The absorbance increase, monitored spectrophotometric method, is directly proportional to the oxidant molecules in the sample. The color change was evaluated by measuring absorbance at a wavelength of 530 nm. The measurement was calibrated with hydrogen peroxide, and the results were expressed as μmol $H_2O_2$ Equiv/L. The TAS concentration of serum was measured using the using the Rel Assay Total Antioxidant Status commercial kit (Mega Tıp, Gaziantep, Turkey). The measurement is based on the principle of all antioxidants in the sample converting the blue-green 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical to colorless reduced ABTS. The absorbance value is proportional to the level of antioxidants in the sample. The color change was evaluated by measuring absorbance at a wavelength of 660 nm, and the results were expressed as mmol Trolox equivalent/L.

The Oxidative Stress Index (OSI) is a measure of oxidative stress degree, calculated by multiplying the value obtained by dividing TOS by TAS by 100.

OSI = TOS (μmol $H_2O_2$ equiv./L)/TAS (μmol Trolox equiv./L) ×100.

### Statistical analyses

Software from IBM SPSS Statistics 23 was used to examine the data. The mean ± standard deviation was used to represent continuous variables. If parametric assumptions were not met, non-parametric tests were applied. Group comparisons were performed using the Kruskal-Wallis variance analysis, followed by the Mann-Whitney U test with Bonferroni correction for pairwise comparisons. A *P*-value of <0.05 was considered statistically significant.

## Results

### ICP-MS method development and validation for zinc and boron analysis in serum samples

ICP-MS is a sophisticated method for the simultaneous analysis of multiple elements in different samples because of its multi-element capability, wide linear dynamic range, and high sensitivity.[18] However, challenges arise from interferences caused by sample components, which

can affect the reliable detection of trace elements. To ensure the high sensitivity and accuracy of ICP-MS, it is imperative to validate the method used for specific analytical purposes, thereby confirming its effectiveness in achieving the intended objectives.[19] Therefore, The ICP-MS method employed in this study demonstrated its efficacy in accurately determining the levels of zinc and boron in serum samples and the proposed method was validated according to the guidelines of the FDA Elemental Analysis Manual (EAM 4.7).[20]

By utilizing specific isotopes (64Zn for zinc and 11B for boron), we ensured selectivity and minimized interference from sample components. The dilution of serum samples by a factor of 15 effectively mitigated the matrix effect, allowing for reliable measurements without interference from serum components. Thus, no interference from serum components was observed.

The linearity of the ICP-MS method was assessed by constructing calibration curves for both boron and zinc standards over a concentration range of 10–500 ng/mL. The resulting equations for the calibration curves were Y = 3758.18x + 6308.2 (R: 0.9990, n: 7) for boron and Y = 2385.83x + 6588.43 (R: 0.9993, n: 7) for zinc [Figure 1]. These equations exhibited high correlation coefficients ($R^2 \geq 0.9990$), indicating excellent linearity and statistical reliability, consistent with the criteria proposed.

The precision and accuracy of the ICP-MS method were evaluated by analyzing quality control (QC) samples covering high, medium, and low concentrations (25, 100, and 500 ng/mL) for each element. Relative standard deviation (RSD %) and relative error (RE%) were used as metrics to assess precision and accuracy, respectively. The results indicate that the method has excellent precision and accuracy with RE ≤ ±2.58% and RSD% ≤ 3.25% for both boron and zinc. These values meet the criteria for satisfactory method performance that %RSD should be less than or equal to ± 20 for both elements [Table 1].

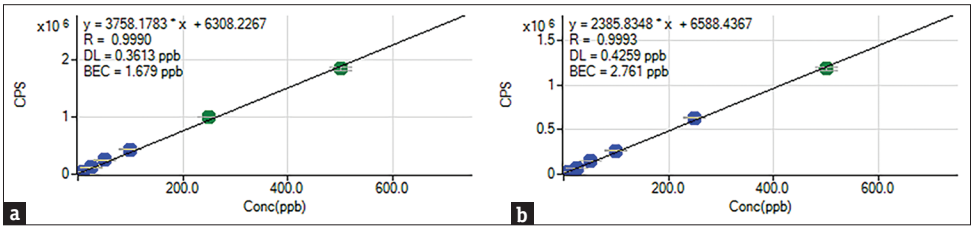


**Figure 1:** Calibration curves obtained with ICP method a) Boron b) Zinc

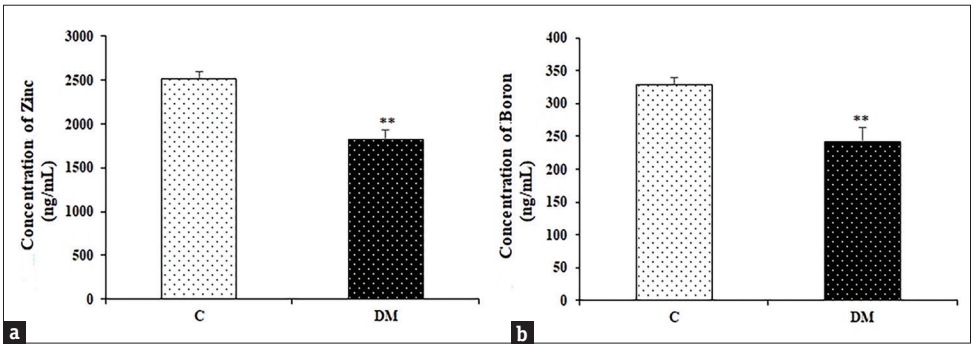


**Figure 2:** Serum Zinc and Boron Concentrations in C and DM Groups. a: Serum Zinc concentrations (ng/mL) in C and DM groups. b: Serum Boron concentrations (ng/mL) in C and DM groups (mean ± SD; n = 6, $^{**}P \leq 0.001$)

**Table 1: Precision and accuracy assessment of the ICP-MS Method for Zinc and Boron Analysis**

| Element | Added (ng/mL) | Intra-day | | | Inter-day | | |
|---|---|---|---|---|---|---|---|
| | | Found±SD (ng/mL) | RE% | RSD% | Found±SD (ng/mL) | RE% | RSD% |
| Zn | 25 | 25.1±0.58 | 0.20 | 2.30 | 25.7±0.42 | 1.64 | 2.42 |
| | 100 | 101.8±1.68 | 1.76 | 1.65 | 102.8±1.13 | 2.58 | 1.09 |
| | 500 | 498.2±3.60 | -0.36 | 0.72 | 499.5±2.96 | -1.02 | 0.59 |
| B | 25 | 25.3±0.14 | 1.30 | 0.57 | 24.6±0.80 | -1.76 | 3.25 |
| | 100 | 101.2±0.75 | 1.22 | 0.75 | 102.9±1.69 | 2.08 | 1.66 |
| | 500 | 499.1±2.59 | 0.18 | 0.52 | 498.3±2.99 | 0.35 | 0.60 |

SD: standard deviation ($n$=6). RE: relative error, RSD: relative standard deviation

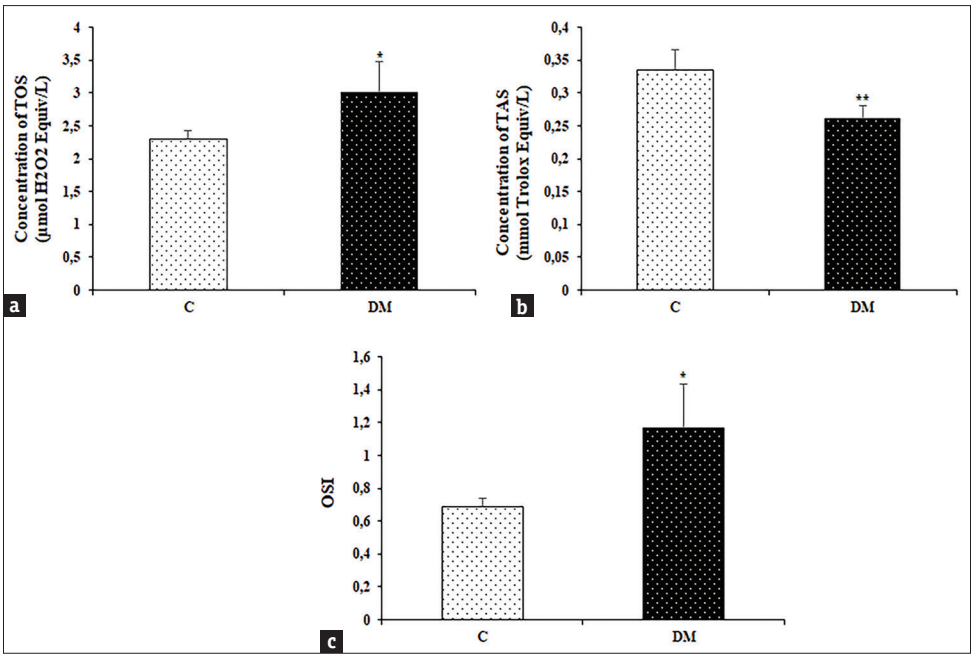


**Figure 3:** Serum TOS, TAS and OSI Concentrations in C and DM Groups. a: Serum TOS concentrations (µmol H2O2 Equiv.) in C and DM groups. b: Serum TAS concentrations (mmol Trolox Equiv.) in C and DM groups. c: Serum OSI concentrations in C and DM groups (mean ± SD; n = 6, $*P < 0.01$, $**P \leq 0.001$)

The limit of detection (LOD) and limit of quantification (LOQ) values for boron and zinc were determined using the calibration curves generated from the data obtained through the ICP-MS method. The calculated LOD values were 1.55 ng/mL for zinc and 2.14 ng/mL for boron, while the LOQ values were found to be 5.11 ng/mL for zinc and 7.06 ng/mL for boron, respectively. These findings validate the robustness and reliability of the ICP-MS method for the simultaneous determination of boron and zinc levels in serum samples.

Serum samples from two groups, DM and C groups, were analyzed using the developed and validated ICP-MS method, which showed exceptional precision and accuracy. The C group represented the baseline, while the DM group represented the experimental group. Zinc levels were determined at 2518 ± 83.46 ng/mL in the C group, while in the DM group, they were found to be 1822.17 ± 102.17 ng/mL. These results indicate that zinc levels are significantly lower in DM group ($P$ = 0.001) [Figure 2a]. Boron levels were found to be 329.38 ± 9.43 ng/mL in the C group and 242.13 ± 20.56 ng/mL in the DM group. These results indicate that boron levels are significantly higher in DM group ($P$ = 0.001) [Figure 2b]. The results of the analysis showed that the zinc and boron concentrations of the two groups were very different, with the serum concentrations of the diabetic rats being much lower than those of the controls.

### Determination of serum TOS, TAS, and OSI levels

The DM group (3.000 ± 0.480 µmol $H_2O_2$ Equiv) showed a statistically significant increase in TOS concentration compared to the C group (2.304 ± 0.117) ($P$ = 0.006), as shown in Figure 3a. Conversely, the TAS concentration in the DM group (0.335 ± 0.030) showed a significant decrease compared to the C group (0.260 ± 0.020) ($P$ = 0.001), as shown in Figure 3b. In addition, the OSI showed a statistically significant increase in the DM group (0.6905 ± 0.052) compared to the C group (1.167 ± 0.267) ($P$ = 0.002), as shown in Figure 3c. These results suggest significant changes in oxidative stress parameters between the DM and C groups.

## Discussion

Our study used the ICP-MS method to determine simultaneously zinc and boron serum concentrations in STZ-induced diabetic and control rats. These findings align with the existing literature emphasizing the role of trace elements in diabetes pathophysiology. DM is a complex metabolic disorder characterized by dysregulated blood glucose levels, and accumulating evidence suggests that alterations in trace element levels may contribute to its pathogenesis.

Zinc, an essential micronutrient, is crucial in insulin synthesis, storage, and secretion. Consistent with our results, studies have shown that zinc deficiency is associated with impaired insulin secretion, insulin

resistance, and increased oxidative stress, all of which are hallmarks of DM.[21] We observed significantly lower serum zinc levels in DM group than in C group, consistent with previous findings in diabetic patients.[21,22] This decrease in zinc levels may be attributed to reduced absorption in the gastrointestinal system and increased urinary excretion.[21] Perez *et al*.[23] reported a positive correlation between serum zinc levels and HbA1c in men, suggesting a potential association between zinc status and glycemic control. However, the relationship between decreased zinc levels and glycated hemoglobin was not significant in their study.

Boron's involvement in various physiological processes, including bone metabolism and antioxidant defense mechanisms, underscores its potential importance in diabetes pathophysiology.[8,13,14] Our observation of significantly lower serum boron levels in DM group, in line with previous findings of reduced boron levels in diabetic individuals, further supports this notion.[24] Additionally, negative correlations between serum boron levels and total cholesterol, triglyceride, and LDL levels suggest a possible association between boron levels and lipid metabolism during illness.[24] Research by Zhao *et al*.[25] has shown that boron-containing compounds can influence lipid homeostasis by inhibiting SREBP transcriptional activity. Moreover, the inverse relationship between serum boron levels and BMI values implies a connection between boron levels and weight management in diabetes. This suggests that fat accumulation and weight gain impact carbohydrate and lipid metabolisms.[26]

Moreover, our study assessed oxidative stress parameters using ELISA, including TOS, TAS, and OSI, in serum samples from DM and C groups. Maintaining a balance between oxidative stress and the antioxidant system is crucial for overall body redox homeostasis. When this balance is disturbed in favor of oxidants, oxidative stress occurs. Thus, assessing oxidative stress solely based on oxidative stress markers might offer a partial evaluation. Instead, OSI, representing the total serum ratio of TOS to TAS, provides a more accurate estimate of overall redox balance, capturing collective oxidative stress exposure.[27] Indeed, our study calculated the OSI using the antioxidant capacity and found that the DM group had the highest OSI, indicating elevated oxidative stress. Furthermore, consistent with previous literature, the DM group showed markedly lower TAS and higher TOS concentrations than the C group, indicating that DM reduced oxidative activity. These findings suggest a disturbance in oxidative stress homeostasis in diabetes, a phenomenon well-documented in the literature.[28,29] Oxidative stress, resulting from an imbalance between ROS production and antioxidant defense mechanisms, is closely linked to the pathogenesis of diabetes and its complications.[7]

Additionally, the robustness and reliability of our study are further strengthened by the careful development and validation of the ICP-MS method used for trace element analysis. The method underwent rigorous validation procedures, including selectivity assessment, linearity determination, precision and accuracy evaluation, and determination of limits in detection and quantification. By adhering to established guidelines and protocols, we ensured the accuracy and reproducibility of our analytical measurements.[20]

Our study highlights the role of trace elements, particularly zinc and boron, in diabetes. Using reliable analytical methods and evaluating oxidative stress parameters, we provide insights into the relationship between trace elements and oxidative stress in diabetes.

## Conclusion

We conclude that, in comparison to control rats, STZ-induced diabetic rats had significantly different serum zinc and boron levels. These findings underscore the pivotal role of trace elements in diabetes pathophysiology. The assessment of oxidative stress parameters further elucidates the imbalance in oxidative stress homeostasis in diabetes. Developing and validating the ICP-MS method enhances the credibility of our findings. Overall, our study contributes valuable insights into the role of trace elements in diabetes, with potential implications for therapeutic interventions. Further research elucidating the underlying mechanisms linking trace element dysregulation to diabetes-related outcomes may offer novel therapeutic avenues for managing and preventing diabetes and its complications.

### Ethical approval

This study was approved by the Ataturk University Animal Experiments Local Ethics Committee (Date: 28.02.2022, number: HADYEK-2022/2, 39 Number Ethics Committee Decision). In addition, the authors declared that Research and Publication Ethical rules were followed.

### Author contributions

Motivation/Concept: FDM, GG

Design: FDM, GG

Control/Supervision: FDM, GG, YK

Data Collection and/or Processing: FDM, BB

Analysis and/or Interpretation: FDM, GG, BB, BY

Literature Review: FDM, GG, BY

Writing the Article: FDM, GG, BB, YK

Critical Review: FDM, GG, BB, YK, BY


### Financial support and sponsorship

Nil.


### Conflicts of interest

There are no conflicts of interest.

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