Research article

Concentration of serum trace elements in leukemia and lymphoma: A case-control study

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A B S T R A C T

Objective: Trace elements (TEs) have electrochemical and catalytic effects and play a crucial role in metabolism. A change in the concentrations of specific TEs may be associated with the incidence of various diseases such as solid tumors and hematological malignancies. By comparing the concentrations of TEs in the cases and controls, this study aims to provide insights into the possible impacts of TEs concentration on the incidence of leukemia and lymphoma.
Materials and methods: In the current study, the serum concentrations of Zn, Cu, Cd, Fe, and Se were analyzed for 20 patients with leukemia and lymphoma and 20 healthy individuals. Those concentrations were measured by atomic absorption spectroscopy.
Results: The serum Zn concentration in the cases was significantly lower than that in the controls (P < 0.05). The serum concentrations of Cu, Cd and Fe were also lower in the cases than in the controls. However, no significant difference was found (P > 0.05). Also, the serum concentration of Se was higher in the patients than in the controls, but no significant difference was found (P > 0.05).
Conclusion: The results indicate that a low serum concentration of Zn may be associated with the incidence of leukemia and lymphoma. The assessment of TEs in hematological malignancies may be of a prognostic value and provide knowledge about the side effects of alterations in the concentration of those elements. It may also lead to the use of suitable strategies to better manage the clinical conditions of patients.

1. Introduction

The optimal concentration of trace elements (TEs) is required for various metabolical and physiological processes in the human body [1]. The World Health Organization (WHO) has introduced nineteen elements, such as arsenic (As), cadmium (Cd), nickel (Ni), chromium (Cr), selenium (Se) and zink (Zn), as the most important TEs found in the body [2]. In addition to playing molecular and chemical roles, TEs can serve as cofactors for enzymes in many biological processes [2]. Some TEs bind to rare proteins or membrane receptors and control the movement of materials in and out through the cell membrane, thus maintaining the normal physiological function of the cells [3]. Any imbalance in the optimal concentration of TEs may adversely affect significant biological processes and predispose various diseases such as nutrition-related disorders as well as cancers such as leukemia [4]. Generally, cancer is considered

as a major cause of death worldwide, and leukemia, also known as the cancer of the bone marrow or blood cells, is a serious threat to human life. There are two types of blood cancer, leukemia and lymphoma. Depending on its clinical symptoms, leukemia is sub-categorized into acute and chronic types. The former is either acute myelogenous leukemia (AML) or acute lymphoblastic leukemia (ALL), and the latter may be chronic myelogenous leukemia (CML) or chronic lymphoblastic leukemia (CLL) [5]. The occurrence of infections in leukemia patients and their mortality are mainly due to the failure of the bone marrow to generate blood cells and the congestion of atypical cells in the blood and the bone marrow. Like leukemia, lymphoma stems from the bone marrow, but it usually affects the lymphatic system. This disorder is of two major types, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) [6]. While HL regularly moves from one lymph node to another, NHL moves irregularly and destroys the immune system over time [6]. According to epidemiological studies, these disorders are induced by numerous environmental and genetic factors considered as potential risk factors, one of which is imbalanced TEs [7]. The International Agency for Research on Cancer (IARC) has introduced Cd, As and Ni as the major TEs the high concentration of which is carcinogenic [8]. In this regard, numerous studies in recent decades have proved the significant relationship of TEs to the incidence of cancer [9–11]. For instance, the research on the relationship of TEs and leukemia has shown that an increased concentration of copper (Cu) induces acute leukemia and aggravates malignancies like that, while convalescing patients have almost the same concentration of this element as normal individuals [12]. Indeed, the concentration of TEs serves as a predicting factor with which to evaluate the risk of cancer and take appropriate clinical measures for patients.

Despite the rather high incidence of blood cancer in Hamadan Province, little research has been done to assess TEs in patients and compare them to healthy ones. In this regard, the present study seeks to compare the serum concentrations of TEs (Fe, Cd, Cu, Zn, and Se) in leukemia and lymphoma patients and healthy individuals. These comparisons can be helpful to determine the causal relationship between the concentration of these elements and the incidence of hematological malignancies. Also, specifying the association between the serum concentration of TEs and clinical findings can be of help to make suitable treatment decisions. The insight provided helps the health system adopt proper policies to prevent exposure to the poisonous concentrations of those elements and, thus, lower the risk of cancer in the society.

2. Materials and methods

2.1. Study design

The study was conducted on 14 patients with AML and 6 patients with NHL as well as a control group of 20 healthy individuals from September 2019 to October 2022. The healthy individuals were selected through convenience sampling. The patients and the healthy individuals had referred to Shahid Beheshti Hospital of Hamadan University of Medical Sciences. The inclusion criteria were the diagnosis of cancer (leukemia or lymphoma) by a specialist physician, being over 18 years of age, no invasive procedures such as surgical operations within a month before the sampling, no history of diabetes, and taking no chemotherapy or radiotherapy when entering the study. Leukemia was diagnosed by bone marrow aspiration. Also, flow cytometry and real-time polymerase chain reaction (RT-PCR) techniques were used to detect leukemia phenotypes [13]. In addition, immunohistochemistry (IHC) served to diagnose various types of NHL [14]. The exclusion criteria were diseases such as diabetes, taking a blood product, drug or supplement, chemotherapy, radiotherapy and a surgical operation within a month before participating in the study. An informed consent was obtained from each of the participants, and their personal data (e.g., first name, surname, age, and gender) was obtained through questionnaires and interviews. This study was approved by the ethics committee of Hamadan University of Medical Sciences (IR. UMSHA.REC.1398.144).

2.2. Chemical analysis

Nowadays, there are numerous techniques for the analysis of TEs. Electrochemical methods including atomic absorption spectrophotometry (AAS), inductively coupled plasma mass spectrometry (ICP- MS), instrumental neutron activation analysis (INAA), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), inductively coupled plasma optical emission spectroscopy (ICP-OES), flame atomic absorption spectrometry (FAAS), and total X-ray reflection fluorescence (TXRF) are routinely used to trace up different TEs in biological samples [10,15–20]. The peripheral blood, serum, plasma, urine, hair and, nail are the biological samples that are used in TEs analysis [15,19,21,22]. Due to the sensitivity and capability of measuring the total content of elements within a sample, the AAS technique was used in this study.

To measure TEs, 5 cc of 12-h fasting peripheral blood was collected from the individual members of both the case and control groups. The blood samples of the patients were taken before the first chemotherapy session. Then, the blood serum was derived from the collected samples and kept at $-80\,^\circ$C for the next biochemical experiments. The TEs were measured by AAS, which is an accurate, sensitive, compatible and highly repeatable method of measuring different elements in a solution qualitatively and quantitatively.

Through ICP-OES, the conditions for the measurement of the studied elements were optimized to achieve the maximum signal-to-background ratio. Linearity was conducted to specify the elements analyzed, and the detection limits were determined through the measuring of the TEs absorbance in standard solutions for three times; thus, the LOD was calculated. Different concentrations (0.5, 1.0, 2.0, 5.0, 10.0, and 20.0 µg/dL) of TEs were utilized to calibrate the standard graphs. To verify the assay accuracy and to maintain the quality, the standard solutions were run 10 times for each sample [23]. All the reagents were of analytical steps and were utilized without additional purification. Double-purified water was also used for dilutions. H2SO4, HCl, H2O2, and HNO3 were bought from Merck (Germany). All the glassware was washed by being soaked in diluted nitric acid overnight and rinsed with double-purified water before use. Stock element standard solutions (1000 ppm mL-1) were prepared by dissolving suitable amounts of chloride salts, and

working solutions were made through the daily dilution of metal ions stock solutions [24].

One milliliter of each serum sample was put in a porcelain crucible at a temperature that was slowly raised to 650 °C in an hour. The sample was burned to ash for 2 h until a greyish or white precipitate was obtained. The precipitate was disbanded in HNO3 (5 ml of 25 % v/v) and then warmed for better dissolution. Next, it was digested with an acidic combination of H2O2:H2SO4: HNO3 (1:1:3). The mixture was warmed up to 120∘C for 2 h. The obtained solution was moved into a 25-ml volumetric flask, and its volume was raised to the intended value with double-purified water [24,25]. Ultimately, the concentrations of Zn, Se, Cu, Fe, and Cd were measured with a 400p-novAA atomic absorption spectrometer (Analytik Jena, Germany).

3. Statistical analysis

In this study, frequencies and percentages were used as statistical indices to report the qualitative variables, while the quantitative variables were defined with means and standard deviations (mean ± SD). The normality of the quantitative variables was evaluated using the Shapiro-Wilk test. For the normally distributed variables, the mean values of the two groups were compared using the independent *t*-test. For the non-normally distributed variables, a non-parametric analysis, particularly the Mann-Whitney *U* test, was performed. In addition, the relationship between the qualitative variables and the group levels was analyzed using either the chi-square test or Fisher's exact test. The analyses were conducted with the Statistical Package for Social Sciences (SPSS) software (version 22, IBM, USA), and the p-value of <0.05 was regarded as the level of statistical significance for all the tests.

4. Results

This study was conducted to measure the concentration of TEs in 40 people including 20 healthy individuals as the control group and 20 patients (12 males and 8 females) newly diagnosed with AML and NHL. The basic information about the patients is presented in Table 1. To determine the possible effect of TEs concentration on the incidence of cancer, the serum concentrations of TEs in the case and control groups were compared before the chemotherapy of the patients. Due to the low number of the patients, the serum concentrations of Zn, Cu, Fe, Cd and Se were compared regardless of the type of cancer. The comparative data for the mean concentrations of TEs are presented in Table 2. As the results showed, the mean serum concentration of Zn in the leukemia patients (57.76 ± 20.04 μg/dL) was considerably lower (P = 0.001) than that in the control group (86.92 ± 7.87 μg/dL) (Fig. 1). The serum concentration of Cu was also lower in the patients than in the controls, but the difference was not significant (P > 0.05) (Fig. 2). The same difference was found between the two groups in terms of the serum concentration of Cd (P = 0.946) (Fig. 3). Furthermore, as presented in Fig. 4, the serum concentration of Se was higher in the cancer patients than in the controls, but insignificantly (P > 0.05). In contrast, as Fig. 5 indicates, Fe was found to be insignificantly lower in the cases than in the controls (P = 0.839). In the present study, the patients had a significantly higher number of lococytes than the control individuals (P < 0.001). The two groups were also significantly different in that the patients had a lower mean number of platelets as well as a lower mean concentration of hemoglobins (P < 0.05) (Table 2).

5. Discussion

Based on the outcomes of the current study, the serum concentration of Zn is considerably lower in patients with leukemia and lymphoma than in healthy people. This finding is in concurrence with some previous studies that have shown the relationship of Zn deficiency and malignancies [26]. By impacting the function of various transcription factors, Zn plays a crucial role in cell division and differentiation [27]. Moreover, studies have shown that Zn interferes with solid tumor cell growth, possibly due to the induction of apoptosis and cell-cycle arrest [28]. Owing to its antioxidant effects, Zn also serves as a protection against carcinogenesis [27]. According to the results of the current study regarding Zn, a decrease in the serum concentration of Zn may be associated with the incidence of hematological malignancies.

As it emerged, the patients in this study had a lower serum concentration of Cu than the healthy ones, but the difference was not significant. In agreement with this finding, Akhgarjand et al. reported a noticeable reduction of the Cu concentration in the serum
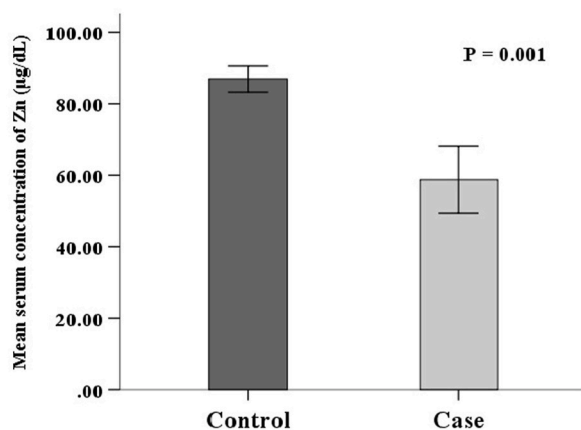
Table 1
Basic data of the patients.

Variables	Frequently: Number (%)
Leukemia	14 (70 %)
AML with t (15; 17) (q24.1; q21.2)	(n = 10)
AML with inv (16) (p13.1q22)	(n = 4)
NHL	6 (30 %)
Males	12 (60 %)
Females	8 (40 %)
Metastasis	
Yes	2 (10 %)
No	18 (90 %)
Splenomegaly	
Yes	2 (10 %)
No	18 (90 %)

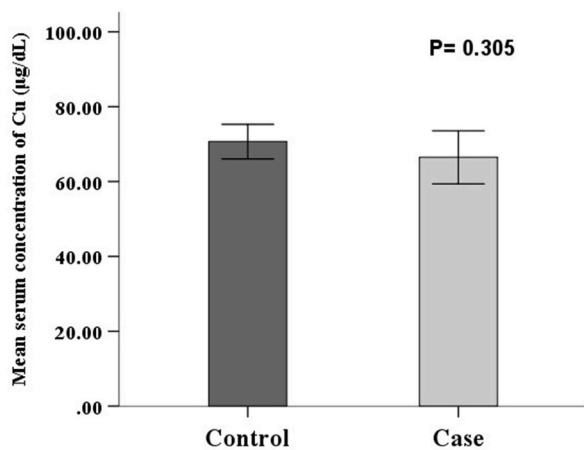**Abbreviations:** AML: acute myeloid leukemia, NHL: non-Hodgkin lymphoma.

Fig. 2. Comparison of the mean Cu concentrations in the cases and the control subjects.
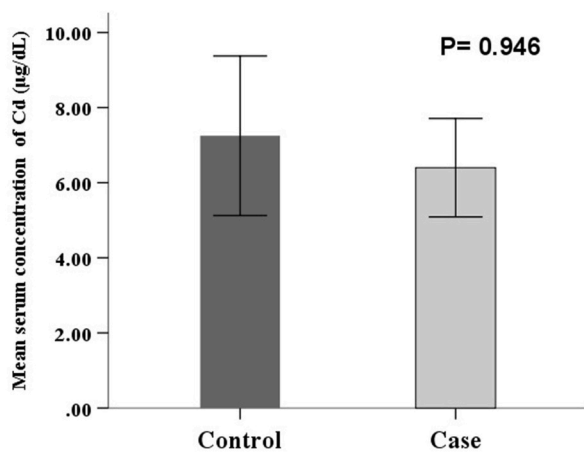

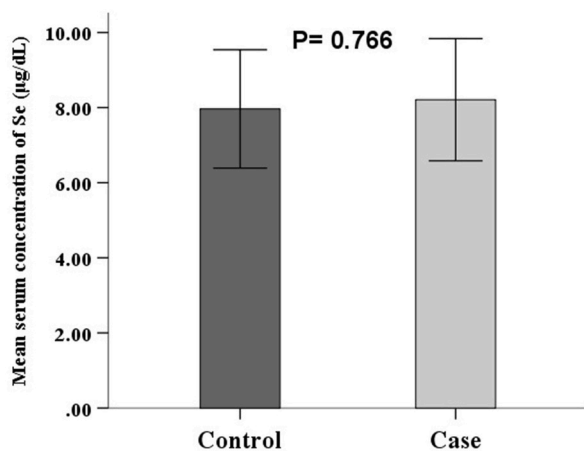**Fig. 3.** Comparison of the mean Cd concentrations in the cases and the control subjects.

Fig. 4. Comparison of the mean Se concentrations in the cases and the control subjects.
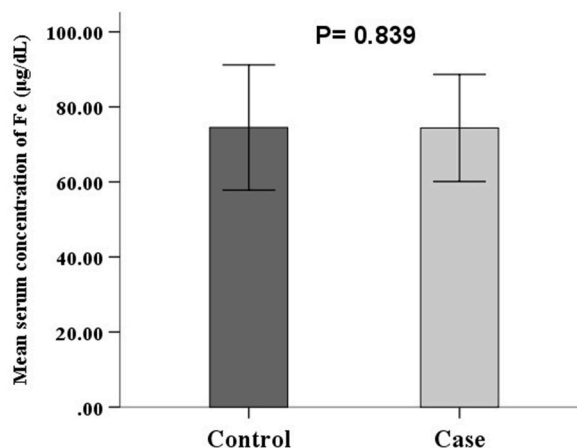
Fig. 5. Comparison chart of the mean Fe concentrations in the cases and the control subjects.

As another result of this study, the patients had a higher concentration of serum Se than the healthy individuals, but the difference was not noteworthy. This was in inagreement with the findings of some other studies that reported a reduction of Se in the serum samples of patients with leukemia and lymphoma [35,36]. In addition, in line with our results, lower levels of Se have been found as a risk factor for breast and prostate cancer [37,38]. Selenium is known to have anticancer effects, but an excess of this element may lead to chronic diseases such as hepatitis [39]. The element can curb cancers by providing protection against damages to chromosomes [40].

As for the serum concentration of Fe, the studied patients and the healthy control group were not significantly different. This is in contrast with a previous study which reported a higher serum concentration of Fe for leukemia patients than for healthy people [41]. It is already known that Fe is essential for the advance of blood cancer. In this regard, leukemic cells can continue their fast growth with a ferrous-dependent ribonucleotide reductase (RNR) enzyme needed for DNA synthesis [42]. In fact, Fe is an essential cofactor in the class I RNRs activity [43]. Excessive Fe stimulates the apoptosis of the neighboring natural killer cells, CD4$^+$ T cells and CD8$^+$ T cells, thus making it possible for leukemic cells to escape the immune system [44]. For those who suffer from blood malignancies and have taken allogeneic transplants of hematopoietic stem cells, increased ferritin and serum Fe before transplantation is considered as an undesirable prognostic factor for drug resistance, general survival, and mortality with no relapse [45,46]. Despite there being no significant difference in serum Fe between the leukemia patients and the healthy individuals in this study, measuring Fe shortly after the diagnosis of a hematological malignancy seems to be of prognostic importance to determine the disease severity and the response to treatment [47]. Therefore, it is necessary for future studies to accurately survey the association between the amount of Fe and the incidence of blood malignancies so as to logically design effective therapeutic strategies.

6. Conclusion

In this study, the patients with AML and NHL had a significantly lower serum concentration of Zn than the healthy individuals, but the two groups were not significantly different in terms of Cd, Cu, Se and Fe in their serum samples. The anti-cancer effect of Zn has been shown in many epidemiological studies. This effect is often associated with antioxidant properties. It seems that supplementation and an optimal intake of Zn can improve immune responses and reduce the risk of hematological malignancies [48]. Although this research came up mostly with non-significant comparative results, a good number of previous studies proved the adverse effects of any imbalance (rise or reduction) in the concentration of TEs. Considering the important role of TEs in the physiological activities of the human body, measuring the concentration of those elements can help to identify their possible role in the incidence of malignancies and, subsequently, devise appropriate and timely therapeutic strategies.

It is to be noted that this study is not without limitations. Due to the low number of patients and the short duration of the study, the patients were not followed up to investigate how the concentration of TEs would relate to clinical findings such as relapse, remission, and response to treatment. So, further studies with more extensive sample sizes and longer follow-up periods are required to achieve constructive outcomes in this field. Also, there may be numerous TEs associated with the risk of leukemia and lymphoma, but only a selected few were assessed in this study. Therefore, to fill the gaps, further research is needed with more patients involved and longer follow-up periods. More inclusive research allows one to judge the prognostic role of TEs in hematological malignancies with better certainty. It also presents new perspectives on the management of clinical conditions and the corresponding targeted treatment.

Informed consent

Informed consent was obtained from the individual participants in the study.

Data availability statement

Data supporting this study will be available from "Concentration of serum trace elements in leukemia and lymphoma: A case-control study" at https://doi.org/10.1016/j.heliyon.2024.e33620.

CRediT authorship contribution statement

Hassan Rafieemehr: Writing – original draft, Project administration, Funding acquisition, Data curation. **Naser Kamyari:** Formal analysis. **Masumeh Maleki Behzad:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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