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Original Contribution

SERUM ZINC CONCENTRATIONS IN PATIENTS WITH HIDRADENITIS SUPPURATIVA: A CASE-CONTROL STUDY FROM THE BULGARIAN EXPERT CENTRE

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ABSTRACT

PURPOSE. To evaluate serum zinc (Zn) concentration in patients with hidradenitis suppurativa (HS) and its association with various demographic and clinical characteristics. METHODS. A single-center case-control study included 80 adults (40 HS patients and 40 age- and sex-matched controls) at the Bulgarian HS Expert Centre. HS patients were classified by disease duration, clinical phenotype, severity and comorbidities. Serum Zn concentration was defined as "hypozincemia" (<9 μmol/L), "normal" (9-18 μmol/L) and "hyperzincemia" (>18 μmol/L). RESULTS. Serum Zn concentration displayed a significant difference in patients and controls (mean rank: 47.64 vs 33.36, p=0.006). Hypozincemia was more common (p=0.02) in HS patients (84.6%). Serum Zn was significantly lower in Hurley stage III than in stage II (mean rank: 15.21 vs 26.34, p=0.002) and similarly, it was lower in severe HS than in moderate HS (mean rank: 17.3 vs 27.15, p=0.012) on the IHS4 scale. We found a significant negative correlation between hypozincemia and HS severity assessed by Hurley Stage (τ_c=-0.383, p=0.014) and IHS4 (τ_c=-0.343, p=0.022). No significant associations were found between serum Zn level and sex, smoking, HS family history, duration, or comorbidities. CONCLUSIONS. HS patients have significant hypozincemia compared to controls. A significant negative correlation between HS severity and hypozincemia was established.

Key words: zinc deficiency, hypozincemia, acne inversa, zinc supplementation

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic autoinflammatory disease of terminal hair follicles in apocrine gland-rich skin areas and for this reason in 2017, Chen and Plewig suggested renaming it as "dissecting terminal hair folliculitis" (1). HS is a clinically heterogeneous disease. Treatment of HS patients is a complex long-term process based on the recommendations from international and national guidelines (2–6). The approach is individual and depends on the patient's age, sex, lifestyle, HS duration, phenotype, severity, frequency of flares, comorbidities and compliance. According to the European S2k guidelines (2024), zinc (Zn) supplementation with oral zinc gluconate 90 mg daily may be considered a second-line maintenance treatment in mild-to-moderate HS and can be administered in Zn-deficient patients (6).

Zinc is a divalent heavy metal cation (Zn^{2+}) which is an essential trace element, the second most abundant after iron (7), which constitutes less than 0.005% of total body weight (8). Zn is required for the function of more than 300 metalloenzymes (9) for catalytic, structural, and regulatory functions (10) and approximately 2500 transcription factors (11) that regulate lipid, carbohydrate, protein, and nucleic acid metabolism (8). Zn homeostasis plays a key role in innate and adaptive immune functions and Zn

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is considered a “gatekeeper” of the immune system (12). Due to the complex regulation of Zn homeostasis, Zn status assessment in a clinical or field setting is difficult. Sufficiently sensitive and specific biomarkers have not been identified to date (13-15). It is usually evaluated by measuring Zn concentrations (plasma, serum, blood cells, hair, urine) and serum alkaline phosphatase (16), but their decrease can be detected only in severe Zn deficiency (17, 18). For more precise Zn assessment in the early (marginal) deficiency stage, biomarkers have been proposed, such as metallothionein and Zn transporter expression in circulating human blood cells (19-21), the activity of fatty acid desaturases - FADS1 (Δ5 Desaturase, D5D) and FADS2 (Δ6 desaturase, D6D) (22), linoleic acid: dihomo-γ-linolenic acid (LA/DGLA) ratio and Zn status index (ZSI) concept (21). Evaluating Zn status is essential for identifying Zn deficiency or excess and for assessing interventions to improve it.

In dermatology, zinc is administered to treat conditions caused by zinc deficiency and as an adjunct to the main therapy for several inflammatory and infectious dermatoses (23).

We found only one pilot multicenter case-control study of serum Zn levels in patients with HS (24). Several clinical open-label studies have been conducted to assess the efficacy and safety of Zn supplementation in patients with HS (25-27). The Zn anti-inflammatory effects in HS are probably through different mechanisms of immune system modulation, such as reduction of inflammatory Th-17 responses and neutrophil recruitment (28), activation of NK cells and phagocytic activity of granulocytes (29), inhibition of keratinocyte expression of toll-like receptor-2 (TLR2) (30-32), inhibition of integrin expression (ICAM-1, LFA-1 and VLA3) (33, 34) and modulation of the production of pro-inflammatory cytokines (IL-1β, IL-6 and TNFα) by keratinocytes (35). Zinc also has antioxidant activity reducing the synthesis of reactive oxygen species (ROS) (36), participates in the regulation of matrix metalloproteinases (37), and has an antiandrogenic effect by modulating the expression and activity of 5-α reductase (38).

Our study aims to evaluate the serum zinc (Zn) concentration in patients with hidradenitis suppurativa (HS) and its association with various demographic and clinical characteristics.

MATERIALS AND METHODS

A prospective case-control single center study including 80 subjects (40 HS patients and 40 controls) was carried out among the inpatients and outpatients in the Bulgarian HS Expert Centre at the Clinic of Dermatology and Venereology in the University Multi-profile Hospital for Active Treatment "Prof. Dr. Stoyan Kirkovich", Stara Zagora, Bulgaria. The recruitment period extended from August 2023 to November 2024. Control subjects had no dermatological diseases and were sex and age-matched (± 2 years). The exclusion criteria were: age below 18 years, pregnancy, malabsorption/malnutrition, autoimmune connective tissue diseases, acute and chronic renal or liver failure, severe diabetes, prior malignancy, use of systemic immunosuppressive drugs, alcohol abuse, and consumption of dietary supplements containing Zn during the previous 3 months. The following data was collected and filled in a structured form for each patient: demographics (sex, age), family history, smoking, disease duration, clinical manifestation and concomitant diseases (CDs). According to the history of HS symptoms, patients were divided into two groups: with ≤ 5 years disease duration and > 5 years disease duration. For clinical HS severity assessment, the Hurley staging system, the International Hidradenitis Suppurativa Severity Scoring System (IHS4) and the Hidradenitis Suppurativa Physician's Global Assessment scale (HS-PGA) were applied. HS phenotypes were defined as regular, follicular-furunculous, anogenital/sacrogluteal, conglobate, elephantiasis nostras-like, pyoderma gangrenosum-like, cutis verticis gyrata-like, syndromic and mixed phenotype using the classification of Van der Zee and Jemec et al., 2015 (39, 40), modified by Hristakieva et al. 2023 (41, 42). International Classification of Diseases-10 (ICD-10) was used for coding the main groups of concomitant diseases. Blood samples were collected by venipuncture into serum vacutainer tubes and allowed to clot at room temperature for 30 minutes, followed by centrifugation at 1300 g for 10 minutes. The separated serum was stored in a freezer (–20°C) until analysis. The serum Zn concentration was determined with an automatic atomic absorption spectrophotometer by direct flame atomic absorption spectrophotometry (AAS). AAS is the preferred method for measuring Zn concentration due to its high analytical reliability. The laboratory reference range for serum Zn is 9 – 18 μmol/L. Serum Zn levels

were classified as "hypozincemia" (< 9 μmol/L), "normozincemia" (within the reference range: 9 – 18 μmol/L), and "hyperzincemia" (> 18 μmol/L).

The study followed the Declaration of Helsinki guidelines (1964), as revised in 2000. The ethics committee institutionally approved it, and all participants signed informed consent.

Descriptive statistics were conducted to analyze our data. Variables were tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. Categorical variables were presented as numbers and percentages. Continuous data were presented as mean and standard deviation or as the median and interquartile range (IQR). Comparisons between groups for categorical variables were made using the Chi-square ($\chi 2$) test or Fisher`s exact test. The Mann-Whitney U test was used for comparisons of non-normally distributed continuous variables. Spearman's rank correlation and Pearson's correlation test were used to assess the association between serum Zn level and various clinical parameters. Kendall's Tau was applied to study associations between serum Zn level expressed as an ordinal variable and disease severity. A p-value < 0.05 was considered statistically significant. All statistical analyzes were performed using SPSS, version 19.

RESULTS

The study population included 80 adults aged 18 to 66 years. The average age of the studied HS patients (n = 40) was 39.5 ± 12.2 years (median 39.5; IQR 28.2 – 50.0), while the average age of the controls (n = 40) was 40.3 ± 12.6 (median 40.5; IQR 29.0 – 51.0). The sex distribution in both groups showed that 10% (4/40) were females and 90% (36/40) were males.

Serum Zn concentration displayed a significant difference (p = 0.006) in patients (mean rank 47.64) and controls (mean rank 33.36). Among all participants, those with hypozincemia were 16.3% (13/80), with normozincemia 75.0% (60/80) and with hyperzincemia 8.7% (7/80) of the subjects **(Table 1).** Hypozincemia was found more commonly (p = 0.02) in patients with HS (84.6%) than in controls (15.4%). In the group of HS patients, hypozincemia was found in 24.5% (11/40), normozincemia in 67.5% (27/40), and hyperzincemia in 5.0% (2/40).

Table 1. *Serum Zn levels (zincemia) in study participants*

Variable	Study subjects (n = 80)	HS patients (n = 40)	Controls (n = 40)	P
Zincemia				
• Hypozincemia (< 9 μmol/L)	16.3% (13/80)	24.5% (11/40)	5% (2/40)	0.02
• Normozincemia (9 μmol/L-18 μmol/L)	75.0% (60/80)	67 % (27/40)	80% (32/40)	
• Hyperzincemia (>18 μmol/L)	8.7% (7/80)	5% (2/40)	15% (6/40)	

Data on patients' demographics, smoking, family HS history, disease duration, clinical HS assessment (severity and phenotype) and CDs are summarized in **Table 2**. The average HS onset was 30.98 ± 10.13 years with a disease duration median of 6 (IQR 4-10). Comorbidities were registered in 60% of HS patients and there were polymorbid patients with two or more CDs. The most common CDs were diseases of the circulatory system (I00 – I99) – in 14/40 of patients (35%), followed by endocrine, nutritional and metabolic diseases (E00 – E90) – in 8/40 patients (20%) and diseases of the digestive system (K00 – K93) – in 6/40 of patients (15%).

No significant associations were found between serum Zn concentration and categorical variables such as sex (p = 0.46), smoking (p = 1.0), HS family history (p = 0.23), HS duration (p = 1.0), and CDs (p = 0.23). A negative correlation with no statistical significance between Zn concentration and age of HS onset (r = -0.238, p = 0.139) and no correlation with HS disease duration (r_s = 0.062, p = 0.704) were established.

Serum Zn concentration in patients with Hurley stage II (mean rank 26.34) differed significantly (p = 0.002) from Zn concentration in patients with Hurley stage III (mean rank 15.21). Similar findings were detected using the IHS4 scale - serum Zn concentration in patients with moderate HS (mean rank 27.15) was higher (p = 0.012) than Zn concentration in patients with severe HS (mean rank 17.3).

In Hurley Stage II, 10.5% of patients had hypozincemia, compared to 42.9% in Hurley Stage III **(Figure 1)**. Hypozincemia was detected in 7.7% of patients with moderate HS and in 37% with severe HS according to the IHS4 scale **(Figure 2).** We found a significant negative correlation between hypozincemia and HS severity assessed by Hurley Stage (τ_c= -0.383, p = 0.014) and IHS4 (τ_c = -0.343, *p* = 0.022).

Table 2. *Demographics, history of smoking, familial HS, disease duration, clinical evaluation and comorbidities of HS patients*

Variable	Category	HS patients, n = 40 % (n)
Sex	Male	97.5% (35)
	Female	12.5% (5)
Smoking	Yes	77.5% (31)
	No	22.5% (9)
Family history of HS	Yes	17.5% (7)
	No	82.5% (33)
Disease duration	≤ 5 years	32.5% (13)
	> 5 years	67.7% (27)
Hurley Stage	I	0
	II	47.5% (19)
	II	52.5% (21)
IHS4	Mild	0
	Moderate	32.5% (13)
	Severe	67.5 (27)
HS-PGA	Clear	0
	Minimal	0
	Mild	5.0% (2)
	Moderate	35.0% (14)
	Severe	40.0% (16)
	Very severe	20.0% (8)
HS phenotype	Regular	55.0% (22)
	Follicular-furunculous	0
	Anogenital/sacrogluteal	2.5% (1)
	Conglobate	0
	Elephantiasis nostras-like	0
	Pyoderma gangrenosum-like	0
	Cutis verticis gyrata-like	2.5% (1)
	Syndromic	0
	Mixed	40.0% (16)
Comorbidities	Yes	60% (24)
	No	40% (16)

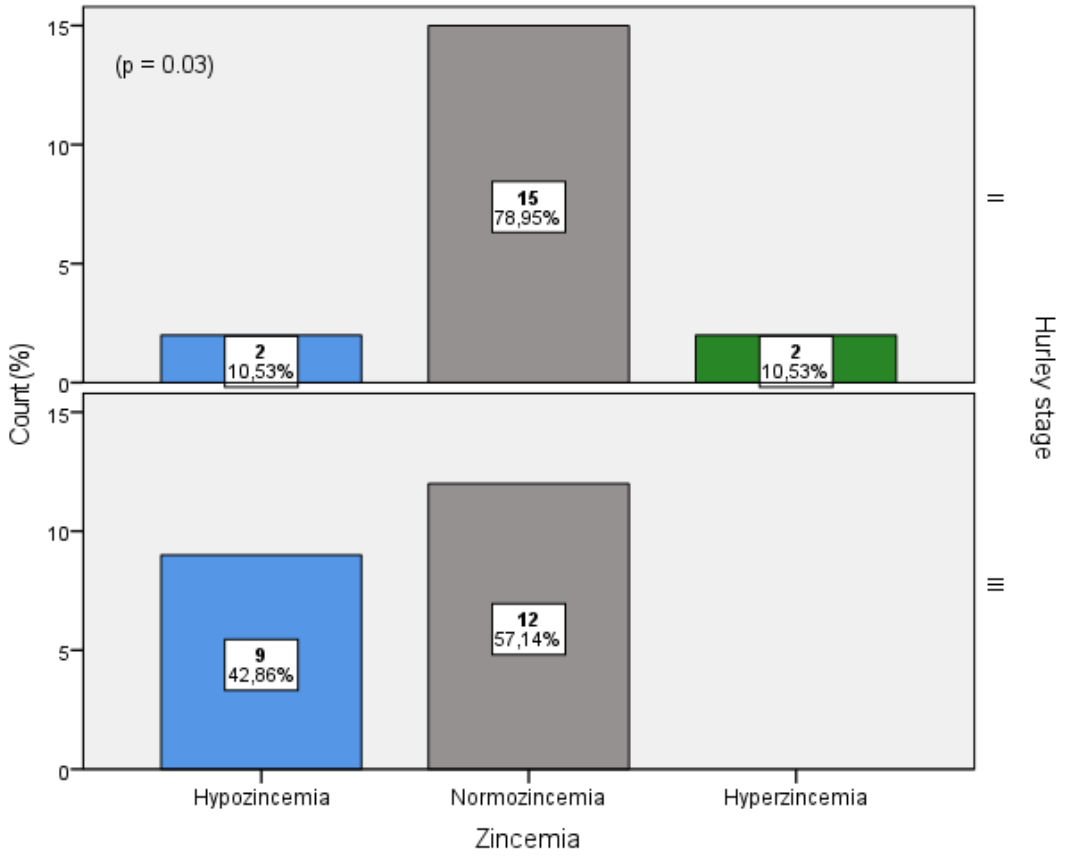

Figure 1. Distribution of HS patients according to Hurley stage and Zn level

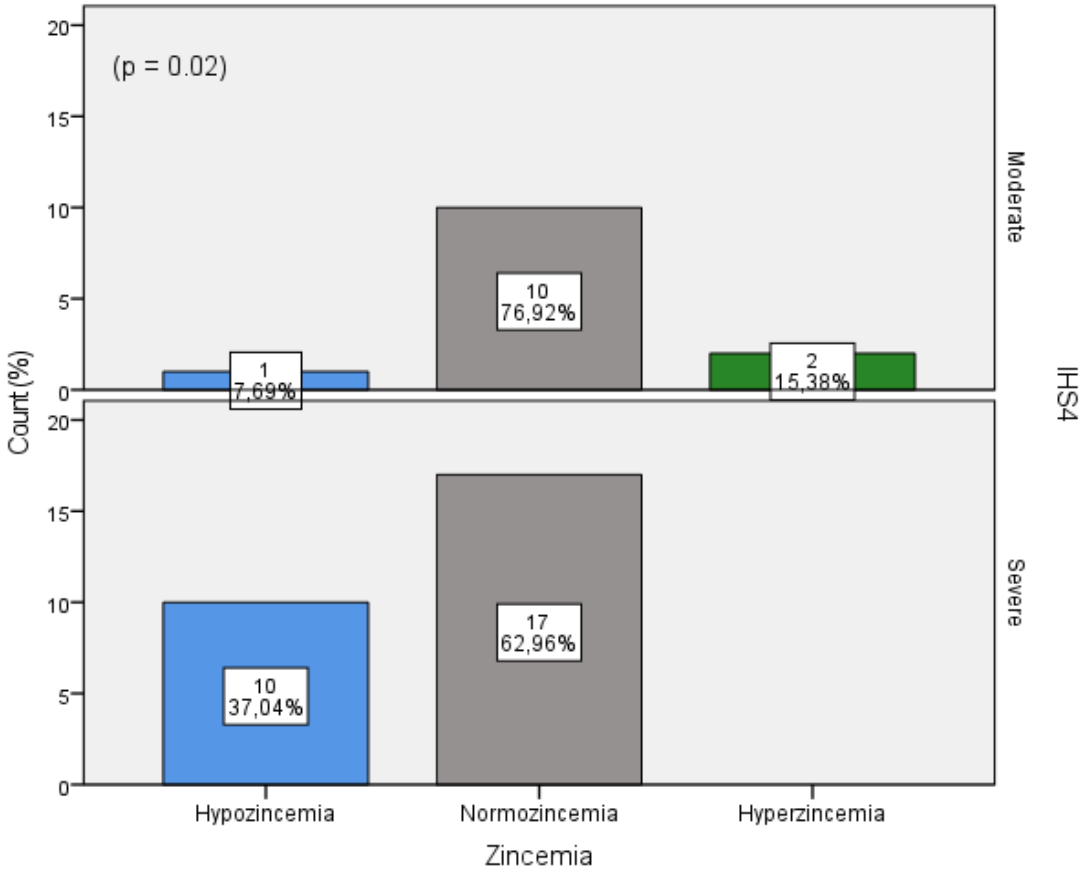

Figure 2. Distribution of HS patients according to IHS4 score and Zn level (zincemia)

Limitations. The study's limitations include its single-center design and small sample size. As a result, analyses to assess associations between zinc levels and HS variables with more than three categories (such as HS-PGA scoring and HS phenotypes) were not performed.

DISCUSSION

Zinc is one of the five minerals and vitamins (zinc, iron, vitamin D, vitamin A and vitamin B12) most commonly found to have a beneficial role as a supplement therapy for HS patients (43). In general, Zn deficiency can be inherited or acquired (due to decreased intake, inability to absorb, increased metabolic demand, or excessive excretion (44). The exact cause of zinc deficiency in patients with HS is still unknown.

The first study measuring serum Zn level in HS patients was conducted in 2018 by Poveda et al. in Spain (24). It was a multicentral case-control study with 122 participants. To our knowledge, this is the only study of serum Zn levels in patients with HS to date. This pilot study showed that HS cases were significantly more likely than controls ($p < 0.001$) to have serum Zn levels below the 25th percentile (83.3 μg/dL), with defined normal values of more than 60 μg/dL and less than 150 μg/dL Our results revealed that serum Zn concentration significantly differed in patients and controls. When normal serum Zn concentration, was considered as defined by the laboratory (reference range: 9 – 18 μmol/L), our study additionally showed that hypozincemia was significantly more common ($p = 0.02$) in HS patients than in controls.

Data on HS patients involved in the study such as the age of HS onset, smoking status, family history and comorbidities were similar to those previously reported in the literature (41, 45). HS has been reported to be more common in women. In contrast, our study revealed male prevalence (male to female ratio = 9:1). Male prevalence (male to female ratio = 1.7:1) was also registered in a previous study of the demography of 344 HS patients in our Expert Centre (41, 46). Additionally, some Asian studies noted this reverse sex ratio as well (47, 48).

The median duration of HS symptoms was 6 years (IQR 4-10), which may explain the absence of patients in Hurley stage I, as well as those with mild disease according to the IHS4 assessment and those in the clear to minimal severity categories based on the HS-PGA score. Considering HS patients our study found no significant correlations between serum Zn concentration and the age of HS onset and HS disease duration, and no significant associations between serum Zn concentration and variables such as sex, smoking, HS family history, HS duration subgroups, and CDs. The variables selected for analysis of associations with lower zinc levels in the pilot study by Poveda do not completely overlap with ours. The pilot showed no association between lower serum and age at onset, family history, pain and pruritus.

Serum Zn concentration in our group of HS patients with Hurley stage II, and moderate HS (using the IHS4 scale) differed significantly from Zn concentration in patients with Hurley stage III and severe HS. In the pilot Spanish study (24), lower serum zinc levels (below 25th percentile) were significantly associated with Hurley III, Dermatology Life Quality Index ≥ 9, number of affected sites ≥ 3, genital location, and perineal location. We found a significant negative correlation between Zn deficiency (hypozincemia) and HS severity assessed by Hurley Stage and IHS4 score. Therefore, Zn deficiency is not only associated with HS but might also be a marker of disease severity. These results are consistent with the conclusions in previous trials, which showed positive clinical responses after Zn supplementation therapy in HS patients (25-27). Zn cannot be stored in significant amounts and requires regular intake through food or supplementation. Long-term Zn supplementation therapy for HS patients is recommended in international HS guidelines and the Bulgarian HS consensus. The initial dosage of 90 mg of oral zinc gluconate per day may be reduced based on treatment outcomes and any gastrointestinal side effects, such as gastric irritation, nausea, vomiting, or gastric bleeding (6, 49). This therapy appears to be suppressive, not curative (25). Patients taking high-dose Zn long-term should be monitored for signs and symptoms of Zn excess and copper deficiency (49). Zn deficiency is well documented and analyzed in patients with some inflammatory dermatoses (50), metabolic syndrome (51), diabetes (52), inflammatory bowel disease (53), depression (54) etc. In our study, HS comorbidities were registered in 60% of HS patients. The most common CDs were diseases of the circulatory system (35%), followed by endocrine, nutritional and metabolic diseases (20%) and diseases of the

digestive system (15%). We share the theoretical proposal by Poveda et al. (24) that Zn supplementation may be beneficial in HS patients – as treatment of HS and as prevention or control of HS comorbidities and their complications.

CONCLUSION

Our case-control study revealed that HS patients have significant differences in the serum Zn concentrations compared to controls. HS was significantly associated with hypozincemia. A significant negative correlation between HS severity and hypozincemia was also established.

Evaluating serum Zn concentrations in HS patients before starting zinc gluconate supplementation, along with monitoring zinc levels during treatment, may be important for determining whether adequate zinc levels are reached and, additionally, for preventing chronic zinc excess. It also may contribute to a better understanding of the cause-and-effect relationship between HS and Zn status.

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