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ORIGINAL RESEARCH

The Prognostic Significance of Visceral Adiposity Indices in Conjunction with Plasma Trace Elements in Newly Diagnosed Crohn's Disease

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Purpose: Visceral adipose tissue (VAT) is integral to the pathology of Crohn's disease (CD). While trace element imbalances affect both adipose tissue function and CD progression, their interplay remains poorly characterized. This study aimed to examine whether trace element status affects CD outcomes and whether this relationship is moderated by visceral adiposity.

Patients and Methods: The data were collected retrospectively based on a prospective cohort of 300 patients newly diagnosed with CD from July 2019 to June 2022. Baseline plasma trace element levels were assessed, and VAT was measured via computed tomography (CT) scans at the time of diagnosis. Logistic regression analyses were performed.

Results: Lower zinc and magnesium levels predicted clinical outcomes including intestinal complications and surgery (OR = 0.51, $P = 0.002$; OR = 0.52, $P = 0.001$), and poorer treatment response (OR = 0.39, $P < 0.001$; OR = 0.57, $P = 0.004$). Elevated copper levels were associated with clinical outcomes (OR = 1.68, $P = 0.012$). Notably, stratified analysis revealed that magnesium's protective effect was significant exclusively in patients with visceral-to-subcutaneous adipose tissue ratio (VAT/SAT) ≥ 1, whereas the effect of copper was significant solely in the VAT/SAT < 1 group concerning clinical outcomes.

Conclusion: Dysregulated trace element homeostasis at baseline independently predicts adverse clinical outcomes in CD. The intricate relationship between trace elements and VAT could influence disease progression, suggesting potential targets for personalized treatment.

Keywords: Crohn's disease, clinical outcomes, drug outcomes, visceral adipose tissue, trace elements

Introduction

Crohn's disease (CD) is a subtype of inflammatory bowel disease characterized by transmural involvement of the intestine, episodes of flare-ups and remissions, and irreversible intestinal damage.[1] Recent epidemiological studies indicate rising global incidence rates, particularly in newly industrialized countries.[1,2] The chronic and relapsing nature of CD significantly impacts patients' quality of life and creates substantial socioeconomic burden on healthcare systems worldwide.[3] The pathogenesis of CD is complex, involving interactions among genetic susceptibility, environmental factors, and dysregulated immune responses.[4] In consideration of the severe complications and long-term disease course affecting the life quality of CD patients, early identification and prevention of poor disease outcomes are of great significance.

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Recent evidence suggests that alterations in body composition, particularly an increase in visceral adipose tissue (VAT) may play a crucial role in the pathophysiology and clinical outcomes of CD.[5] VAT functions as a multifunctional metabolic organ, contributing to lipid storage, immune response, and endocrine regulation.[6] CD patients tend to have higher VAT compared to healthy controls (mean difference: 34.5 cm², 95% CI: 18.8–50.1, $P = 0.035$), even in the absence of obesity.[7] Moreover, increased VAT is closely associated with CD severity, disease behavior, complications, surgical risk, and prognosis, and also influences the therapeutic efficacy of anti-TNF medications.[8,9] A recent study indicated a potential association between increased visceral-to-subcutaneous adipose tissue ratio (VAT/SAT) and shorter time to disease flare in CD patients (hazard ratio: 4.8; VAT/SAT ≥1.0 vs <1.0).[10]

Trace element deficiencies contribute to clinical challenges in CD, increasing morbidity and reducing quality of life.[11–13] Essential micronutrients are crucial for immune function, antioxidant defense, and wound healing.[14–17] Some research indicates that CD patients with decreased zinc, calcium, magnesium, and increased copper levels are more likely to experience prolonged hospitalizations, require surgery, and face complications.[12,13,16,18,19] VAT also has a complex interplay with trace elements in the body. Studies have linked serum zinc and magnesium levels to obesity.[17,20] VAT is associated with insulin resistance, and imbalances in trace elements may affect the synthesis and function of insulin.[21] Zinc, copper, and iron play crucial roles in adipogenesis and adipocyte differentiation.[22–24] Magnesium is essential as a cofactor for many enzymes, significantly contributing to the metabolic and endocrine functions of adipose tissue.[25] However, the specific relationships between trace elements and VAT in CD patients remain poorly explored.

To further investigate this issue, we included newly diagnosed CD patients at our IBD center from July 2019 to June 2022, measured their plasma trace element levels at the time of initial diagnosis, and analyzed their VAT area through computed tomography (CT) scans performed within six months of diagnosis.

We aimed to analyze the prevalence of trace element deficiencies at the time of diagnosis, explore how these deficiencies relate to clinical outcomes and responses to medication, and investigate the potential moderating role of visceral adiposity in these associations. Our study seeks to elucidate the impact of trace element levels on the prognosis of CD patients while considering the role of VAT, potentially offering new insights for treatment and management strategies.

Materials and Methods

Study Design and Participants

This research analyzed data from a cohort of newly diagnosed CD patients at the Second Affiliated Hospital of Zhejiang University School of Medicine. Patients first diagnosed with CD at this institution from July 2019 to June 2022 were included. Inclusion criteria required a new diagnosis of active CD. Exclusion criteria were: 1) age under 18 or over 80 years old; 2) pregnancy; 3) taking recent trace element supplements; 4) malignancies; 5) severe psychiatric disorders; 6) infectious diseases; 7) severe comorbidities.

Data Collection

At enrollment, the following data were collected: 1) demographic details (sex, age) 2) disease specifics (diagnosis history, disease location and behavior, surgery history, medication history); 3) laboratory results; 4) examination findings (endoscopic, radiological). Patients were followed up every 3–6 months, with a median follow-up duration of 2.46 years (IQR: 1.94-3.12).

Outcome Definitions

Clinical outcomes included: 1) CD-related complications (intestinal obstruction, fistula, bleeding, *Clostridioides difficile* infection); 2) need for intestinal surgery (excluding perianal procedures). Drug outcomes included: 1) primary or secondary failure of biologics; 2) severe side effects from biologics leading to switch of biological therapy; 3) optimization of biologic therapy (dose escalation or interval reduction not due to weight changes).

Plasma Trace Element Analysis

Peripheral blood samples were collected within 24 hours of patient enrollment. For analysis, 0.50 mL plasma was mixed with 4.50 mL of 1% (v/v) ultrapure nitric acid (65% HNO_3, Merck Suprapur) and allowed to stand for 30 min, resulting in complete digestion and a 10-fold dilution. Trace elements were quantified using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7800, USA) operated at an RF power of 1500 W. The monitored isotopes and linear ranges (μg/L) were: 66Zn 0.5–2000, 63Cu 70–1500, 57Fe 50–2000, 44Ca 60000–120000, and 24Mg 17000–26700. A five-point external calibration curve (PlasmaCal®, SCP Science) was applied, with 89Y (10 μg/L) serving as the internal standard.

Body Composition Measurements

CT data were collected from CD patients at initial diagnosis or within three months prior to diagnosis. Body composition measurements were obtained using specialized software (TomoVision sliceOmatic version 5.0). After selecting the scan slice at the level of the L3 vertebra, muscle and adipose tissues were differentiated and marked based on their anatomical relationships and distinct CT values (Hounsfield units, HU). Muscle tissue was defined as having HU values ranging from −29 to +150. Subcutaneous adipose tissue (SAT) and intermuscular adipose tissue (IMAT) were identified as areas with HU values between −190 and −30, while VAT was defined as areas with HU values between −150 and −50.[10] The software automatically calculated the relevant tissue areas, specifically the visceral adipose tissue area (VATA) and subcutaneous adipose tissue area (SATA).

Based on previous research indicating that total body fat is closely related to height, the obtained areas were divided by the square of height to eliminate height-related influences and accurately reflect tissue content. Thus, the visceral adipose tissue index (VATI) was calculated as VATA (cm^2) / $height^2$ (m^2), and the subcutaneous adipose tissue index (SATI) was derived similarly.[26]

Missing Data

Due to the partial retrieval of clinical data from electronic medical records, not all covariates had complete data. Median imputation was used to address missing variables. The extent of missing data and the imputation process are detailed in Table S1.

Statistical Analysis

Categorical variables were presented as counts and percentages, and continuous variables were described with medians and interquartile ranges (Q1–Q3). Comparisons of categorical variables were performed using the Chi-square test or Fisher's exact test. Spearman's rank correlations were used to analyze the relationships between trace elements, inflammatory markers, and adiposity measures. Logistic regression analyses identified the associations between trace elements and clinical or drug outcomes, with models adjusted for potential confounding factors including age at diagnosis, sex, BMI, FCP, and CRP. To reduce data skewness and heteroscedasticity, and to enhance the robustness of the analysis results in multiple linear regression and logistic regression models, plasma zinc, copper, iron, calcium, magnesium and VATI data were transformed using *Z* scores. All *P*-values were two-sided, with a significance threshold of 0.05.

Ethical Statement

The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (No. 2019–038). Informed consent was obtained from all patients prior to the study in accordance with the Declaration of Helsinki.

Table 1 CD Patients Demographics and Baseline Characteristics

Characteristic	n = 300[1]
Female	76 (25.33%)
Male	224 (74.67%)
Age at diagnosis	27 (21, 34)
Smoke	32 (10.67%)
BMI (kg/m^2)	19.5 (17.9, 22.2)
Family history	10 (3.33%)
Disease location[a]	
L1 (ileal)	118 (39.33%)
L2 (colonic)	18 (6.00%)
L3 (ileocolonic)	161 (53.67%)
L4 (upper GI)	103 (34.33%)
Disease behavior	
B1 (nonstricturing/penetrating)	190 (63.33%)
B2 (stricturing)	72 (24.00%)
B3 (penetrating)	38 (12.67%)
PD (perianal)	210 (70.00%)
Laboratory results	
C-reactive protein (mg/L)	12 (4, 30)
Erythrocyte sediment rate (mm/h)	18 (6, 32)
Fecal calprotectin (μg/g)	1,800 (941, 1,800)
Albumin (g/L)	37.6 ± 5.4
Globulin (g/L)	30.9 ± 5.0
White blood cell count (10^9/L)	6.70 (5.50, 8.35)
Neutrophil count (10^9/L)	4.50 (3.28, 5.85)
Lymphocyte count (10^9/L)	1.46 (1.14, 1.87)
Monocyte count (10^9/L)	0.46 (0.36, 0.58)
Eosinophil count (10^9/L)	0.14 (0.09, 0.22)
Basophil count (10^9/L)	0.03 (0.02, 0.04)
Hemoglobin (g/L)	127 (110, 140)
Mean corpuscular volume (fL)	85 (80, 88)
Mean corpuscular hemoglobin (pg)	27.7 (25.5, 29.1)
Mean corpuscular hemoglobin concentration (g/L)	325 (317, 333)
Platelet count (10^9/L)	301 (236, 376)
CDAI	146 (98, 213)
Zn (μg/L)	779 (656, 1,046)
Cu (μg/L)	1,035 (894, 1,188)
Fe (μg/L)	793 (596, 1,283)
Ca (mg/L)	97 (93, 102)
Mg (mg/L)	21.89 (20.60, 23.22)
Adiposity Measures	**N=269[1]**
IMAT (cm^2)	4.3 (2.4, 7.1)
SAT (cm^2)	83 (41, 130)
VAT (cm^2)	50 (26, 85)
VAT/SAT	0.67 (0.45, 1.02)
SATI (cm^2 /m^2)	29 (14, 47)
VATI (cm^2 /m^2)	17 (9, 30)

Notes: [1]n (%); Median (IQR); Mean ± SD.
Abbreviations: BMI, body mass index; CDAI, Crohn's Disease activity index; Zn, zinc; Cu, copper; Fe, iron; Ca, calcium; Mg, magnesium; IMAT, intra-muscular adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; VAT/SAT, the ratio of visceral adipose tissue to subcutaneous adipose tissue; SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index.

Results

Baseline Characteristics of Crohn's Disease Patients

A total of 300 newly diagnosed CD patients were enrolled, with their baseline clinical characteristics shown in Table 1. The male-to-female ratio was approximately 3:1, with 224 males (74.67%) and 76 females (25.33%). The typical age at diagnosis was 27 years. Smokers made up 10.67% (32/300) of the patients, with a median BMI of 19.5 kg/m². A family history of CD was reported in 3.33% of patients.

According to the Montreal classification, the disease locations at diagnosis were L1 in 118 patients (39.33%), L2 in 18 patients (6.00%), L3 in 161 patients (53.67%), and L4 in 103 patients (34.33%). In terms of disease behavior, B1 was the most common (190/300, 63.33%), followed by B2 (72/300, 24.00%) and B3 (38/300, 12.67%). Additionally, perianal disease was present in 210 patients (70.00%).

Of the 300 patients initially diagnosed with CD, 269 underwent CT imaging assessment for body composition analysis at baseline. IMAT measurements revealed a median area of 4.3 cm². The median VAT area was 50 cm², while the median SAT area was 83 cm². The ratio of visceral adipose tissue to subcutaneous adipose tissue (VAT/SAT), indicative of adipose tissue distribution, had a median of 0.67. When adjusted for height, the median VATI was 17 cm²/m², and the SATI was 29 cm²/m².

Trace Elements Deficiency in CD Patients

Table 2 shows the prevalence of plasma trace elements deficiencies in the CD initial diagnosis cohort (n = 300). Iron deficiency was the most common, affecting 25.67% (77/300) of patients, followed by zinc deficiency at 3.67% (11/300). Deficiencies in calcium and magnesium were less common, observed in 1.00% (3/300) and 0.36% (1/300) of patients, respectively, with copper deficiency occurring in 0.67% (2/300).

Correlation Analysis of Trace Elements with Inflammatory Markers, and Adiposity Measures in CD Patients

Correlation analysis of trace elements with inflammatory markers, and adiposity measures in CD Patients is shown in Figure 1. Plasma zinc and iron levels showed positive correlations with BMI, but negatively associated with inflammatory markers fecal calprotectin (FCP), C-reactive protein (CRP), platelet count (PLT), and erythrocyte sediment rate (ESR). In contrast, copper levels demonstrated positive correlations with FCP, CRP, ESR, and PLT. Calcium levels, like zinc and iron, positively correlated with BMI, but negatively correlated with FCP, CRP, and the VAT/SAT ratio. Notably, magnesium levels exhibited negative correlations specifically with VATI and the VAT/SAT ratio, suggesting a unique relationship with visceral adiposity measures.

Trace Elements and Clinical Outcomes: Stratified Analysis by VAT/SAT

Of the 300 initially enrolled CD patients, 3 had severe mental illnesses, 2 had prior bowel surgery, 9 were previously treated with biologics for other conditions, and 17 were lost to follow-up. Consequently, 269 patients were included in

Table 2 Plasma Micronutrient Deficiency in CD Patients

Characteristic	n = 300
Zn	11 (3.67%)
Cu	2 (0.67%)
Fe	77 (25.67%)
Ca	3 (1.00%)
Mg	1 (0.36%)
n (%)	

Abbreviations: Zn, zinc; Cu, copper; Fe, iron; Ca, calcium; Mg, magnesium.

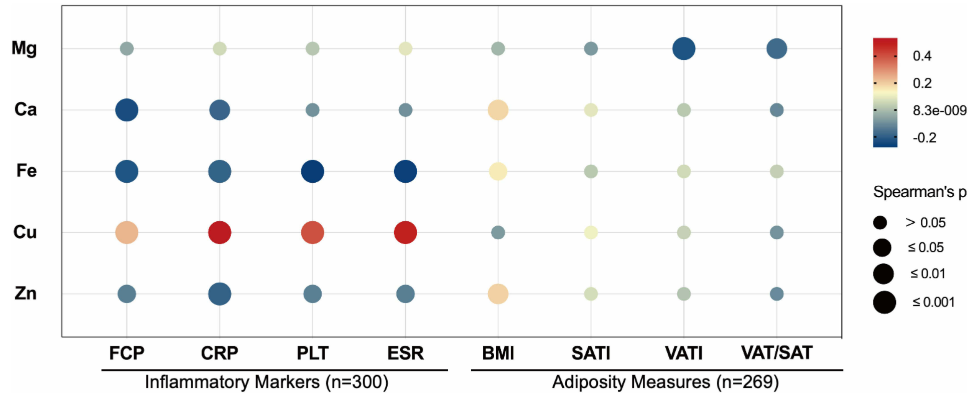

Figure 1 Correlation heatmap of trace elements with inflammatory markers and adiposity measures in Crohn's disease patients.

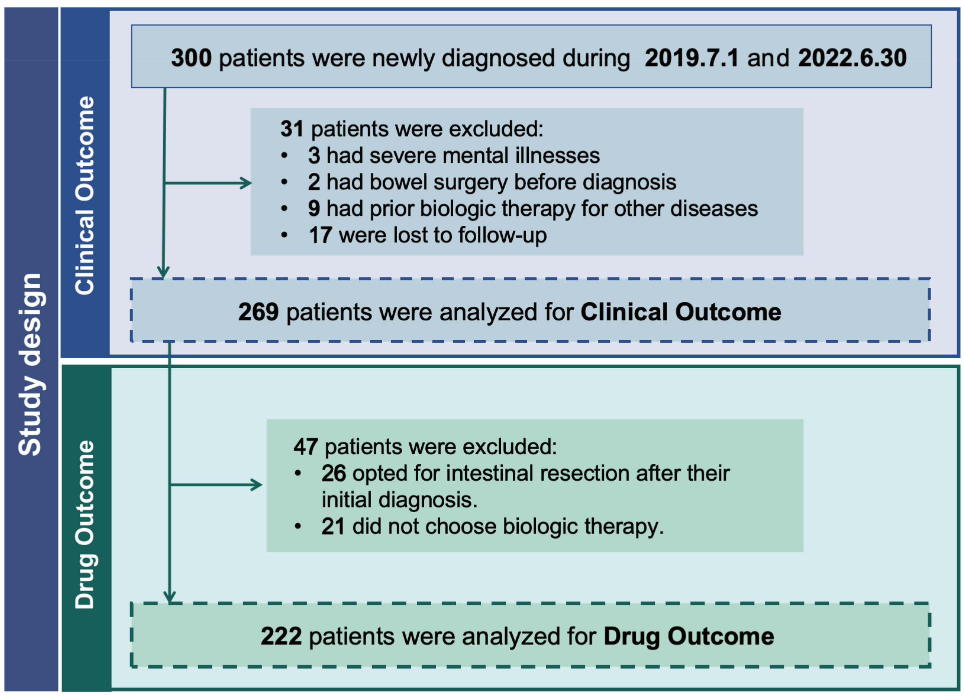

Figure 2 Summary of the study patients flow.

the clinical outcome analysis (Figure 2). Over the two-year follow-up period, 21.19% (57/269) of the patients experienced at least one adverse clinical outcome. Complications were observed as follows: intestinal obstruction in 15.24% (41/269) of patients, intestinal fistula in 4.46% (12/269), gastrointestinal bleeding in 0.74% (2/269), and *Clostridioides difficile* infection in 0.74% (2/269). Additionally, 15.61% (42/269) of patients required bowel surgery, with 11.90% (32/269) undergoing partial small bowel resection and 3.72% (10/269) undergoing partial colectomy.

Multivariate logistic regression analysis, adjusted for age at diagnosis, sex, BMI, FCP, and CRP, revealed that decreases in plasma zinc (OR = 0.51, 95% CI: 0.34–0.77, P = 0.002) and magnesium levels (OR = 0.52, 95% CI: 0.35–0.77, P = 0.001) were significant predictors of adverse clinical outcomes in CD patients. Conversely, copper levels showed a significant positive association with adverse event risk (OR = 1.68, 95% CI: 1.12–2.51, P = 0.012). Plasma iron and calcium levels did not show significant predictive value after adjustment (Figure 3).

Prior research indicated a correlation between increased VAT/SAT and stricturing behavior in CD.[27] A higher VAT/SAT ratio (≥1.0) was associated with a reduced time to IBD flare (hazard ratio: 4.8; VAT/SAT ≥1.0 vs <1.0).[10] Based on

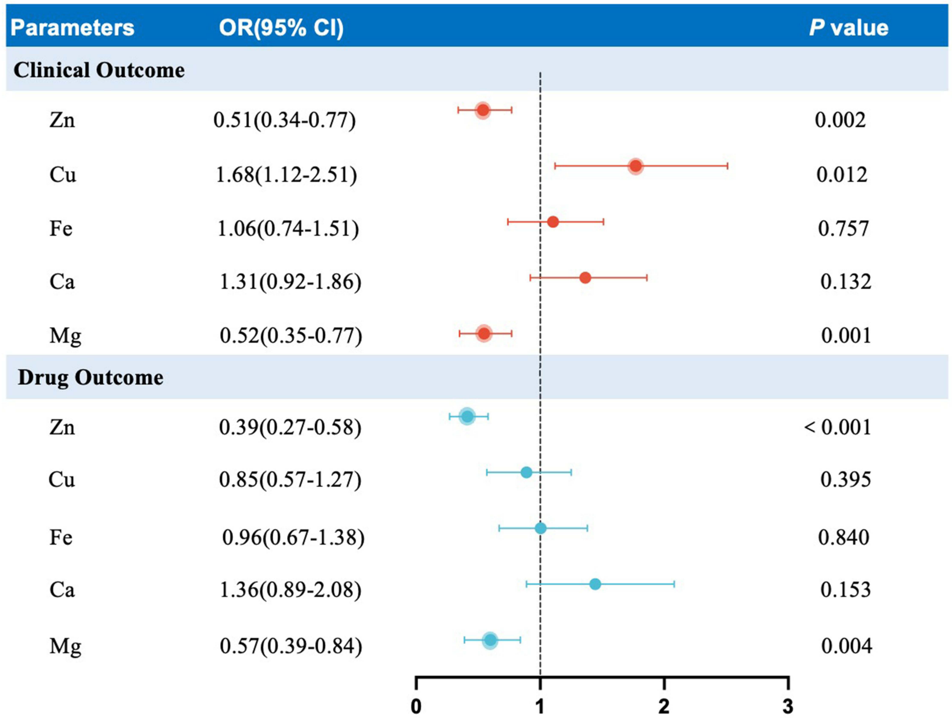

Figure 3 Multivariate logistic regression analysis of trace elements and adverse outcomes in Crohn's disease patients.

prior findings on VAT, we stratified 269 CD patients into VAT/SAT ≥ 1 (n = 69) and VAT/SAT < 1 (n = 200) groups for logistic regression analysis.[28] The results revealed that plasma magnesium levels significantly predicted adverse clinical outcomes only in the VAT/SAT ≥ 1 group (OR = 0.22, 95% CI: 0.08–0.56, P = 0.002), but not in the VAT/SAT < 1 group (OR = 0.96, 95% CI: 0.56–1.64, P = 0.888) (P for interaction = 0.013). Conversely, plasma copper levels demonstrated significant predictive capacity for adverse clinical outcomes exclusively in the VAT/SAT < 1 group (OR = 2.19, 95% CI: 1.24–3.87, P = 0.007), while no significant predictive effect was observed in the VAT/SAT ≥ 1 group (OR = 1.36, 95% CI: 0.57–1.61, P = 0.499) (P for interaction = 0.187) (Figure 4).

Trace Elements and Drug Outcomes: Stratified Analysis by VAT/SAT

Following the clinical outcome analysis, we assessed drug outcomes in a subset of our study cohort. Initially, 269 patients were included in the study. However, 47 were excluded: 26 due to intestinal resection post-initial diagnosis, and 21 who did not opt for biologic therapy. This left 222 patients for the analysis of specific drug-related outcomes (Figure 2).

In the multivariable logistic regression analysis, zinc levels were significantly associated with a reduced likelihood of the drug outcome (OR = 0.39, 95% CI: 0.27–0.58, P < 0.001). Similarly, magnesium showed a protective effect (OR = 0.57, 95% CI: 0.39–0.84, P = 0.004). Other trace elements, including copper, iron, and calcium, did not demonstrate significant associations with the outcome (Figure 3).

Patients were divided into two groups according to their VAT/SAT. Among patients with VAT/SAT ≥1 (n = 47), magnesium exhibited a pronounced protective effect against adverse outcomes (OR = 0.06, 95% CI: 0.01–0.51, P = 0.010). In contrast, within the VAT/SAT <1 group (n = 175), magnesium showed no significant association with outcomes (OR = 0.79, 95% CI: 0.50–1.25, P = 0.319) (P for interaction = 0.017) (Figure 4). Other trace elements, including zinc, copper, iron, and calcium, demonstrated no significant differences in stratified analyses.

Discussion

Trace element deficiencies and VAT accumulation are prevalent in CD patients, yet their underlying mechanisms and potential interrelations remain elusive. Our study revealed significant associations between trace elements, VAT, and

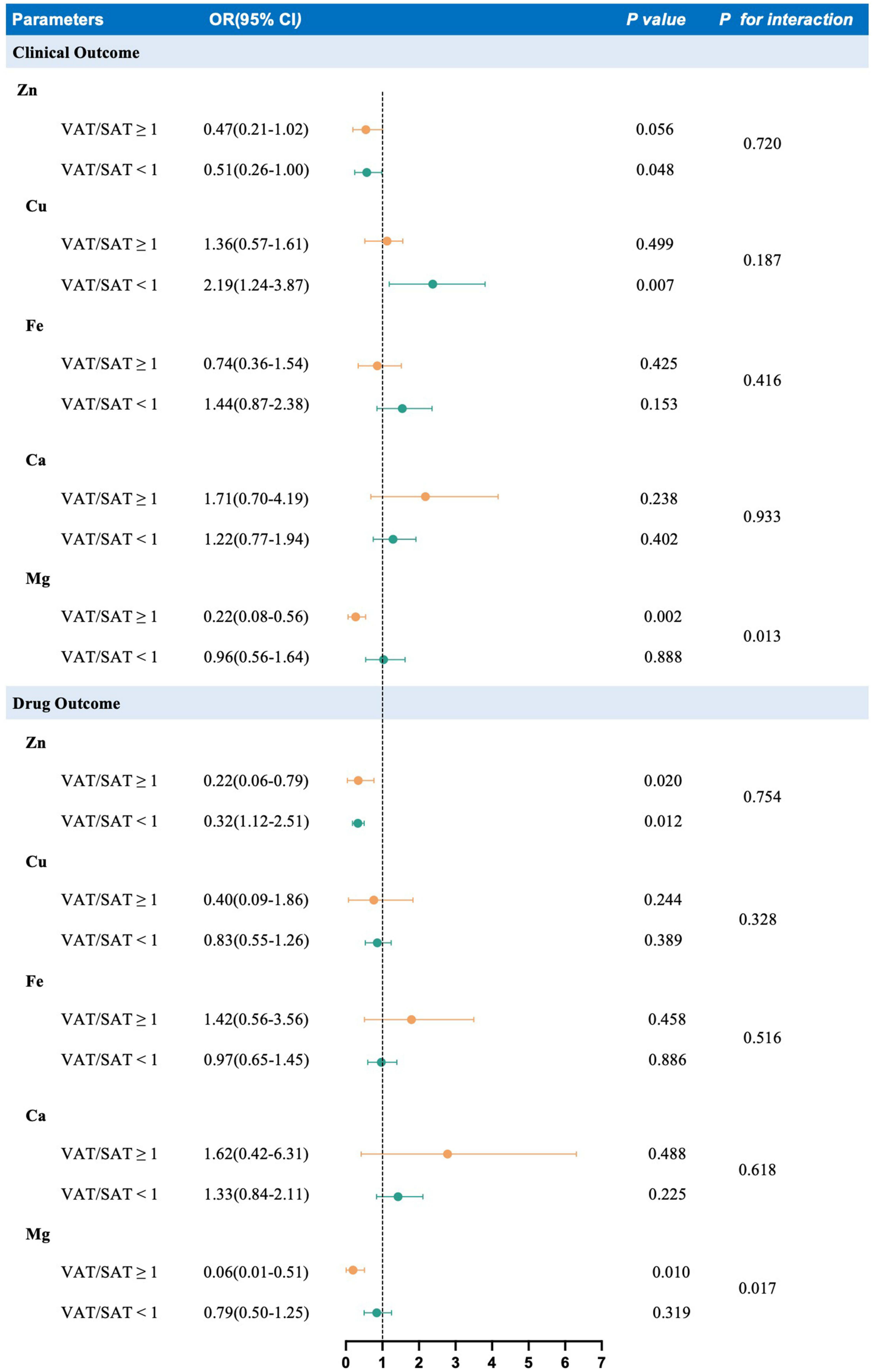

Figure 4 Stratified analysis of trace elements and adverse outcomes in Crohn's disease patients based on visceral-to-subcutaneous adipose tissue ratio.

disease outcomes in newly diagnosed CD patients. Notably, magnesium levels inversely correlated with VATI. Lower levels of zinc and magnesium were associated with adverse clinical outcomes, whereas elevated copper levels predicted poor clinical outcomes. Importantly, the protective effect of magnesium against adverse clinical outcomes was observed exclusively in patients with high VAT (VAT/SAT ≥1), while copper's detrimental effect was seen only in the low VAT group (VAT/SAT <1). In terms of drug outcomes, reduced zinc levels were predictive of unfavorable responses across all patients, while magnesium's protective effect was significant only in those with high VAT (VAT/SAT ≥1). These findings suggested a complex interplay between trace elements and VAT in CD, potentially influencing disease progression and treatment response.

Our study corroborated and expanded upon existing research regarding the relationships between trace elements and inflammatory markers in CD patients. A study reported significant negative correlations between plasma zinc levels and CRP and FCP, while showing a positive correlation with albumin. The positive correlations we found between copper levels and inflammatory markers (FCP, CRP, ESR, and PLT) also corroborated previous findings. Similarly, we found negative correlations between plasma iron and inflammatory markers, consistent with previous studies showing lower plasma iron levels in moderate to severe CD.[29] This inverse relationship may be mediated by inflammatory cytokines, particularly Interleukin-6, which affects iron homeostasis through hepcidin regulation.[30] Regarding magnesium, our study found no significant correlations with inflammatory markers, consistent with some previous research.[31] In contrast, a clinical study found significant negative correlations between serum magnesium levels and both CDAI scores ($P < 0.001$) and CRP ($P = 0.001$).[32]

Our analysis revealed that among the deficient elements, only baseline magnesium levels showed a significant association with VATI. This finding aligns with existing literature documenting the relationship between magnesium deficiency and altered body fat distribution. A cross-sectional study involving 130 healthy adults found significant negative correlations between serum total magnesium levels and body weight ($P = 0.003$) as well as waist circumference ($P = 0.03$).[33] A 30-year prospective cohort study of 5115 young adults found an inverse relationship between magnesium intake and obesity incidence, further supporting this connection.[34]

Given the established relationship between VAT and clinical prognosis in CD, as well as the association between baseline specific trace elements and VATI, we investigated the prognostic value of trace elements in predicting adverse outcomes in CD patients. Our multivariate logistic regression analysis revealed that baseline low plasma magnesium and zinc levels, along with high plasma copper levels were associated with poor clinical outcomes. Notably, our stratified analysis based on VAT/SAT demonstrated differential prognostic values of trace elements. In patients with VAT/SAT ≥ 1, low plasma magnesium levels predicted both adverse clinical and drug-related outcomes, while this effect was not observed in patients with VAT/SAT < 1. Conversely, high plasma copper levels were associated with poor clinical prognosis only in patients with VAT/SAT < 1.

Zinc deficiency has been consistently associated with adverse events in CD patients, including increased hospitalizations and complications.[31] A study of CD patients undergoing anti-TNF-α treatment found that those with persistent active disease tended to have lower zinc intake compared to patients achieving remission, highlighting a potential connection between zinc status and treatment response.[35] Additionally, recent study demonstrated that zinc supplementation improves intestinal barrier function in CD patients.[36] Further clinical investigation revealed that normalization of serum zinc levels correlated with reduced hospitalization rates, decreased surgical interventions, and lower complication risks in these patients.[37]

Our study demonstrates a significant interaction between plasma magnesium levels and VAT in predicting CD prognosis (P for interaction < 0.05). This finding aligns with potential associations between magnesium and visceral adiposity revealed in previous research. Studies have found that fatty acids can bind to magnesium, reducing free magnesium levels.[38] The CARDIA study, which followed 5,115 young adults for 30 years, demonstrated that dietary magnesium intake inversely associated with obesity risk.[34] In both schizophrenia patients and healthy controls, dietary magnesium intake negatively correlated with VAT in females ($r = -0.60$, $P = 0.011$ and $r = -0.47$, $P = 0.041$, respectively).[39] Research has shown that magnesium influences key enzymes in lipid metabolism, including lipoprotein lipase, HMG-CoA reductase, and lecithin-cholesterol acyltransferase, which may be an important mechanism for the interaction between magnesium and adipose tissue.[25] Additionally, one study found that magnesium filaments implanted in mouse white adipose tissue significantly reduced white fat accumulation. Further investigation revealed that magnesium binds to the DFG motif in mTOR, promoting mTORC2 activation and M2 polarization in macrophages, thereby reducing fat accumulation.[40]

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In our stratified analysis of this interaction, we found that plasma magnesium levels significantly predicted CD prognosis only in patients with high VAT, while this predictive effect was not observed in the low VAT group. This finding may reflect the unique physiological environment in patients with high VAT. In high VAT states, increased secretion of proinflammatory cytokines from VAT creates a more pronounced inflammatory microenvironment, in which variations in magnesium levels may have more critical effects on immune regulation and inflammation control.[41] Moreover, patients with high VAT often experience metabolic dysregulation, and magnesium, as a cofactor for numerous metabolic enzymes, may have more significant impacts on disease progression in this population when its levels fluctuate.[42] However, the precise mechanisms underlying the interaction between magnesium levels and VAT in affecting clinical outcomes in CD patients, as well as the causal relationship between magnesium and visceral adiposity, warrant further investigation.

Regarding the association between elevated copper levels and adverse clinical outcomes, recent research provides new insights. Studies have shown significantly higher plasma copper concentrations in active CD patients ($P < 0.01$).[43] A study identified several differentially expressed cuproptosis-related genes (CuDEGs) in CD samples which were found to be associated with immune cell infiltration and metabolic pathway activation, suggesting a potential role of copper-related cellular processes in CD pathogenesis.[44] Recent research has shown that copper sequestration by the ATP7A transporter is essential for normal adipocyte differentiation.[23] Additionally, copper acts as an endogenous regulator of lipolysis by modulating PDE3B activity.[45] These findings highlight the intricate balance between copper levels and adipose tissue function, which may underlie the differential prognostic value observed in our study.

Despite showing potential benefits, trace element supplementation for CD patients currently lacks unified guidelines.[17,46,47] Zinc supplementation may reduce inflammation, enhance intestinal barrier function, and maintain CD remission, yet standardized protocols remain absent.[36] Although studies have indicated that magnesium supplementation can improve CD patient outcomes, traditional formulations may paradoxically worsen diarrhea, causing further magnesium depletion.[17,48] These research findings demonstrate that further investigation into trace element applications for IBD treatment is necessary, highlighting the urgent need for large-scale randomized controlled trials to develop more targeted formulations with fewer side effects, establish scientific supplementation protocols, and ultimately optimize personalized treatment strategies for CD patients.

Our study has many strengths. First, this novel approach, combining trace element analysis with visceral adiposity assessment in newly diagnosed CD patients, has the potential to provide valuable insights into disease mechanisms and prognostic factors. Second, our cohort possessed relatively comprehensive baseline clinical and imaging data, as well as a biobank, allowing for a multi-dimensional assessment of disease risk stratification and prognosis. This study also has several limitations. Our retrospective design prevented us from establishing causal relationships between plasma magnesium levels and VAT accumulation. Moreover, the single-center nature of our study may have led to potential selection bias. Additionally, we were unable to obtain information on dietary habits and intake, which could potentially influence trace element levels in our study, although we recorded medication and health-supplement use. Prospective, multi-center studies are warranted to longitudinally monitor trace elements and visceral adiposity in CD patients, while elucidating the underlying biological mechanisms by which trace elements modulate VAT accumulation. Such investigations would provide critical insights into disease pathogenesis and enhance our understanding of the prognostic implications for clinical outcomes.

Conclusion

In conclusion, our study offers novel insights into the intricate connections between plasma trace element status, VAT, and clinical outcomes in newly diagnosed CD patients. The differential prognostic value of trace elements based on visceral adiposity underscores the importance of considering both nutritional status and body composition in the management of CD. Routine assessment of trace element status and visceral adiposity in clinical practice could enhance risk stratification and personalization of treatment approaches for these patients. Future research should aim to clarify the mechanisms behind these associations and investigate therapeutic strategies that target trace element status and adiposity in CD patients.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Dolinger M, Torres J, Vermeire S. Crohn's disease. *Lancet Lond Engl*. 2024;403(10432):1177–1191. doi:10.1016/S0140-6736(23)02586-2
2. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet Lond Engl*. 2017;390(10114):2769–2778. doi:10.1016/S0140-6736(17)32448-0
3. Roda G, Chien Ng S, Kotze PG, et al. Crohn's disease. *Nat Rev Dis Primer*. 2020;6(1):1–19. doi:10.1038/s41572-020-0156-2
4. Torres J, Mehandru S, Colombel JF, et al. Crohn's disease. *Lancet Lond Engl*. 2017;389(10080):1741–1755. doi:10.1016/S0140-6736(16)31711-1
5. Bilski J, Mazur-Bialy A, Wojcik D, et al. Role of obesity, mesenteric adipose tissue, and adipokines in inflammatory bowel diseases. *Biomolecules*. 2019;9(12):780. doi:10.3390/biom9120780
6. Karaskova E, Velganova-Veghova M, Geryk M, et al. Role of adipose tissue in inflammatory bowel disease. *Int J Mol Sci*. 2021;22(8):4226. doi:10.3390/ijms22084226
7. Barroso T, Conway F, Emel S, et al. Patients with inflammatory bowel disease have higher abdominal adiposity and less skeletal mass than healthy controls. *Ann Gastroenterol*. 2018;31(5):566–571. doi:10.20524/aog.2018.0280
8. Gu P, Chhabra A, Chittajallu P, et al. Visceral Adipose Tissue Volumetrics Inform Odds of Treatment Response and Risk of Subsequent Surgery in IBD Patients Starting Antitumor Necrosis Factor Therapy. *Inflamm Bowel Dis*. 2022;28(5):657–666. doi:10.1093/ibd/izab167
9. Yarur AJ, Bruss A, Moosreiner A, et al. Higher intra-abdominal visceral adipose tissue mass is associated with lower rates of clinical and endoscopic remission in patients with inflammatory bowel diseases initiating biologic therapy: results of the constellation study. *Gastroenterology*. 2023;165(4):963–975.e5. doi:10.1053/j.gastro.2023.06.036
10. Sehgal P, Su S, Zech J, et al. Visceral adiposity independently predicts time to flare in inflammatory bowel disease but body mass index does not. *Inflamm Bowel Dis*. 2023;30(4):594–601. doi:10.1093/ibd/izad111
11. Ghishan FK, Kiela PR. Vitamins and minerals in inflammatory bowel disease. *Gastroenterol Clin North Am*. 2017;46(4):797–808. doi:10.1016/j.gtc.2017.08.011
12. Weisshof R, Chermesh I. Micronutrient deficiencies in inflammatory bowel disease. *Curr Opin Clin Nutr Metab Care*. 2015;18(6):576–581. doi:10.1097/MCO.0000000000000226
13. Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. *Inflamm Bowel Dis*. 2012;18(10):1961–1981. doi:10.1002/ibd.22906
14. Ulmer DD. Trace elements. *N Engl J Med*. 1977;297(6):318–321. doi:10.1056/NEJM197708112970607
15. Mertz W. The essential trace elements. *Science*. 1981;213(4514):1332–1338. doi:10.1126/science.7022654
16. Yu Z, Song W, Ren X, et al. Calcium deficiency is associated with malnutrition risk in patients with inflammatory bowel disease. *Postgrad Med*. 2024;136(4):456–467. doi:10.1080/00325481.2024.2359895
17. Touyz RM, de Baaij JHF, Hoenderop JGJ. Magnesium disorders. *N Engl J Med*. 2024;390(21):1998–2009. doi:10.1056/NEJMra1510603
18. Vaghari-Tabari M, Jafari-Gharabaghlou D, Sadeghsoltani F, et al. Zinc and selenium in inflammatory bowel disease: trace elements with key roles? *Biol Trace Elem Res*. 2021;199(9):3190–3204. doi:10.1007/s12011-020-02444-w
19. Zhang L, Shao F, Li L. Association of copper and zinc Intake with inflammatory bowel disease and fecal incontinence symptoms: evidence from the National Health and Nutrition Examination Survey. *Biol Trace Elem Res*. 2021;199(7):2543–2551. doi:10.1007/s12011-020-02390-7
20. Severo JS, Morais JBS, Beserra JB, et al. Role of Zinc in Zinc-α2-glycoprotein metabolism in obesity: a review of literature. *Biol Trace Elem Res*. 2020;193(1):81–88. doi:10.1007/s12011-019-01702-w
21. Guerrero-Romero F, Rodríguez-Morán M. Low serum magnesium levels and metabolic syndrome. *Acta Diabetol*. 2002;39(4):209–213. doi:10.1007/s005920200036
22. Suzuki T, Komatsu T, Shibata H, et al. Crucial role of iron in epigenetic rewriting during adipocyte differentiation mediated by JMJD1A and TET2 activity. *Nucleic Acids Res*. 2023;51(12):6120–6142. doi:10.1093/nar/gkad342

23. Yang H, Kabin E, Dong Y, et al. ATP7A-dependent copper sequestration contributes to termination of β-CATENIN signaling during early adipogenesis. *Mol Metab*. 2024:80101872. doi:10.1016/j.molmet.2024.101872
24. Chen CW, Chen LK, Huang TY, et al. Nitric oxide mobilizes intracellular Zn2+ via the GC/cGMP/PKG signaling pathway and stimulates adipocyte differentiation. *Int J Mol Sci*. 2022;23(10):5488. doi:10.3390/ijms23105488
25. Pelczyńska M, Moszak M, Bogdański P. The role of magnesium in the pathogenesis of metabolic disorders. *Nutrients*. 2022;14(9):1714. doi:10.3390/nu14091714
26. Zhu M, Li H, Yin Y, et al. U-shaped relationship between subcutaneous adipose tissue index and mortality in liver cirrhosis. *J Cachexia Sarcopenia Muscle*. 2022;14(1):508–516. doi:10.1002/jcsm.13154
27. Bryant RV, Schultz CG, Ooi S, et al. Visceral adipose tissue is associated with stricturing Crohn's disease behavior, fecal calprotectin, and quality of life. *Inflamm Bowel Dis*. 2019;25(3):592–600. doi:10.1093/ibd/izy278
28. El-Serag HB, Hashmi A, Garcia J, et al. Visceral abdominal obesity measured by CT scan is associated with an increased risk of Barrett's oesophagus: a case-control study. *Gut*. 2014;63(2):220–229. doi:10.1136/gutjnl-2012-304189
29. Su J, Ren Y, Liu L, et al. Decreased serum iron concentration and total iron binding capacity are associated with serious Crohn's disease. *Sci Rep*. 2022;12(1):3923. doi:10.1038/s41598-022-07948-0
30. Camaschella C, Nai A, Silvestri L. Iron metabolism and iron disorders revisited in the hepcidin era. *Haematologica*. 2020;105(2):260–272. doi:10.3324/haematol.2019.232124
31. Brownson E, Saunders J, Jatkowska A, et al. Micronutrient status and prediction of disease outcome in adults with inflammatory bowel disease receiving biologic therapy. *Inflamm Bowel Dis*. 2023:izad174. doi:10.1093/ibd/izad174
32. Rosanoff A, Seelig MS. Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals. *J Am Coll Nutr*. 2004;23 (5):501S–505S. doi:10.1080/07315724.2004.10719389
33. Shamnani G, Rukadikar C, Gupta V, et al. Serum magnesium in relation with obesity. *Natl J Physiol Pharm Pharmacol*. 2018;1. doi:10.5455/njppp.2018.8.0104016022018
34. Lu L, Chen C, Yang K, et al. Magnesium intake is inversely associated with risk of obesity in a 30-year prospective follow-up study among American young adults. *Eur J Nutr*. 2020;59(8):3745–3753. doi:10.1007/s00394-020-02206-3
35. Rizzello F, Saracino IM, Gionchetti P, et al. Nutritional biomarkers for the prediction of response to anti-TNF-α therapy in Crohn's disease: new tools for new approaches. *Nutrients*. 2024;16(2):280. doi:10.3390/nu16020280
36. Sturniolo GC, Di Leo V, Ferronato A, et al. Zinc supplementation tightens "leaky gut" in Crohn's disease. *Inflamm Bowel Dis*. 2001;7(2):94–98. doi:10.1097/00054725-200105000-00003
37. Peng X, Yang Y, Zhong R, et al. Zinc and inflammatory bowel disease: from clinical study to animal experiment. *Biol Trace Elem Res*. 2025;203 (2):624–634. doi:10.1007/s12011-024-04193-6
38. Kurstjens S, de Baaij JHF, Overmars-Bos C, et al. Increased NEFA levels reduce blood Mg2+ in hypertriacylglycerolaemic states via direct binding of NEFA to Mg2. *Diabetologia*. 2019;62(2):311–321. doi:10.1007/s00125-018-4771-3
39. Konarzewska B, Stefańska E, Wendołowicz A, et al. Visceral obesity in normal-weight patients suffering from chronic schizophrenia. *BMC Psychiatry*. 2014:1435. doi:10.1186/1471-244X-14-35
40. Zhang A, Jiang J, Zhang C, et al. Thermogenic adipocytes promote M2 macrophage polarization through CNNM4-mediated Mg secretion. *Adv Sci Weinh Baden-Wurtt Ger*. 2024;11(47):e2401140. doi:10.1002/advs.202401140
41. Man K, Kallies A, Vasanthakumar A. Resident and migratory adipose immune cells control systemic metabolism and thermogenesis. *Cell Mol Immunol*. 2022;19(3):421–431. doi:10.1038/s41423-021-00804-7
42. Karlsson T, Rask-Andersen M, Pan G, et al. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. *Nat Med*. 2019;25(9):1390–1395. doi:10.1038/s41591-019-0563-7
43. Ringstad J, Kildebo S, Thomassen Y. Serum selenium, copper, and zinc concentrations in Crohn's disease and ulcerative colitis. *Scand J Gastroenterol*. 1993;28(7):605–608. doi:10.3109/00365529309096096
44. Yuan Y, Fu M, Li N, et al. Identification of immune infiltration and cuproptosis-related subgroups in Crohn's disease. *Front Immunol*. 2022:131074271. doi:10.3389/fimmu.2022.1074271
45. Krishnamoorthy L, Cotruvo JA, Chan J, et al. Copper regulates cyclic-AMP-dependent lipolysis. *Nat Chem Biol*. 2016;12(8):586–592. doi:10.1038/nchembio.2098
46. Chao HC. Zinc deficiency and therapeutic value of zinc supplementation in pediatric gastrointestinal diseases. *Nutrients*. 2023;15(19):4093. doi:10.3390/nu15194093
47. Forbes A, Escher J, Hébuterne X, et al. ESPEN guideline: clinical nutrition in inflammatory bowel disease. *Clin Nutr*. 2017;36(2):321–347. doi:10.1016/j.clnu.2016.12.027
48. Reif S, Klein I, Lubin F, et al. Pre-illness dietary factors in inflammatory bowel disease. *Gut*. 1997;40(6):754–760. doi:10.1136/gut.40.6.754