

Changes in Serum Mineral and Trace Element Levels Following Laparoscopic Cholecystectomy: A Prospective Pilot Study

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Abstract

Aim: The gallbladder is increasingly recognized as a metabolically active organ that regulates bile acid signaling and systemic metabolic homeostasis. While the metabolic consequences of laparoscopic cholecystectomy (LC) have been extensively studied, its long-term impact on mineral and trace element homeostasis remains unknown. To our knowledge, this is the first prospective study to evaluate the longitudinal changes in multiple serum minerals and trace elements following LC. Therefore, this study aimed to assess changes in serum mineral and trace element levels and body mass index (BMI) at six months after LC in patients with symptomatic gallstone disease.

Materials and Methods: This prospective longitudinal pilot study included 30 patients with symptomatic gallstone disease who underwent LC. Serum samples were collected preoperatively and at six months postoperatively. Serum levels of Cu, Zn, Fe, Mg, Cr, Cd, and Se were measured using inductively coupled plasma mass spectrometry. BMI was calculated by measuring weight before surgery and six months after surgery. Pre- and postoperative measurements and sex-based differences were statistically analyzed, with correction for multiple comparisons by sex.

Results: BMI increased significantly six months after LC, compared with baseline ($p<0.001$). Serum Fe, Zn, Mg, and Cr levels decreased significantly after LC ($p<0.001$), while Cu and Cd levels increased significantly ($p<0.001$). Although a slight decrease in Se levels was observed, it was not statistically significant ($p=0.856$). After correction for multiple comparisons, women had significantly lower preoperative Cr levels and postoperative Fe levels than men.

Conclusion: LC was associated with significant changes in serum mineral and trace element homeostasis and an increase in BMI six months postoperatively. These findings may be related to alterations in BA physiology and enterohepatic circulation following LC; however, the underlying mechanisms remain to be elucidated. Long-term prospective studies integrating BA profiles, gut microbiota, and nutritional biomarkers are required to elucidate the underlying mechanisms of these changes.

Keywords: Laparoscopic cholecystectomy, trace elements, iron, zinc, magnesium, chromium, copper, cadmium, body mass index, bile acids

Introduction

Gallstone disease (GSD) is one of the most common surgical diseases worldwide and, with its increasing incidence over time, represents an important health problem (1). Cholelithiasis, defined as the formation of concentrated bile crystals or stones within the gallbladder (GB), is the most common GB disease. Cholelithiasis is characterized by the formation of crystallized deposits, usually composed of cholesterol or bilirubin, in the GB or bile ducts. Its global prevalence is approximately 6%, and it has been reported to be associated with geographic origin, age,

sex, and metabolic disorders (2). Although patients are generally asymptomatic, invasive treatment modalities, predominantly surgical approaches, are used for patients who are symptomatic (1). Today, laparoscopic cholecystectomy (LC) is accepted as the gold-standard surgical method in the treatment of symptomatic GSD because, owing to its minimally invasive nature, it provides faster recovery, shorter hospital stay, and lower postoperative morbidity compared with open surgery (1,3). Although cholecystectomy has been reported to be a safe procedure in the treatment of patients with gallstones, cholecystectomy has also been associated with metabolic disorders, including type



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2 diabetes mellitus and metabolic dysfunction-associated fatty liver disease. While the GB has traditionally been regarded as a reservoir organ that stores bile, recent evidence has shown that it also has important direct and indirect roles in metabolic regulation (3,4). The primary function of the GB is to store and concentrate bile produced by the liver (5). However, in addition to the well-known roles of bile within the GB in the digestion and absorption of lipids, it also has physiological roles in glucose, lipid, and energy homeostasis (4). Evidence obtained from studies has shown that the elevated cholesterol levels and impaired insulin resistance observed after cholecystectomy indicate that the GB plays a role in metabolic regulation (4,6). Bile acids (BAs) also act as signaling molecules that regulate fundamental metabolic pathways via nuclear receptors such as the farnesoid X receptor (FXR) (6,7). Therefore, unexplained metabolic abnormalities in patients who have undergone cholecystectomy may be related to the different physiological functions of the GB (8,9). As a result of cholecystectomy-related loss of the GB's reservoir and concentrating capacity, various functions, including the regulation of the enterohepatic circulation of concentrated BAs, are altered (10). In this situation, the diluted bile continuously produced by the liver is secreted into the intestine (9). The altered secretion of BAs after cholecystectomy has adverse effects on intestinal functions (11,12).

Minerals and trace elements comprise a heterogeneous group with diverse biological and toxicological roles. While elements such as Fe, Zn, Mg, Cu, and Se contribute to essential physiological processes, Cd is a non-essential toxic element, and the essentiality of Cr in humans remains debated (13). Studies have shown that conjugated bile salts have superior emulsification properties compared with unconjugated ones and facilitate the absorption of lipophilic compounds, including fat-soluble vitamins (14). However, it is thought that changes in BA physiology may alter the intestinal bioavailability and absorption of certain trace elements by affecting micelle stability and the environment of the intestinal lumen (15,16).

Although there is growing evidence that cholecystectomy may affect metabolic homeostasis through changes in BA physiology, its long-term effects on serum mineral and trace element homeostasis have not yet been fully elucidated. Accordingly, the present pilot study included both nutritionally relevant elements (Fe, Zn, Mg, Cu, and Se) and elements of toxicological relevance or of uncertain biological relevance (Cd and Cr) to explore whether LC is associated with broader changes in the serum elemental profile. In this study, we aimed to evaluate changes in preoperative and 6-month postoperative serum levels of Cu, Zn, Fe, Mg, Cr, Cd, and Se in patients who underwent LC.

Materials and Methods

Study Groups

This study included 30 patients with symptomatic cholelithiasis who underwent LC at the General Surgery Clinic of Private Niğde Hayat Hospital. A diagnosis of symptomatic cholelithiasis was made by abdominal ultrasonography in patients presenting with symptoms such as postprandial abdominal pain, abdominal distension, and pain radiating to the right shoulder (17). Patients with acute cholecystitis, choledocholithiasis, diabetes, hypertension, nephrotic syndrome, pancreatitis, anaemia, familial hyperlipidaemia, hyperthyroidism or hypothyroidism, coronary artery disease, other metabolic diseases, morbid obesity (body mass index, BMI ≥ 40 , pregnancy, those using lipid-lowering therapy, those with hormonal disorders, and patients who had undergone any small intestine surgery were not included in the study. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (approval no: 2025/70, date: 29.07.2025), and patients who voluntarily agreed to participate were enrolled in the study. Written informed consent was obtained from all participants prior to enrollment in the study. All study procedures were carried out in accordance with the ethical principles of the Declaration of Helsinki.

Collection of Blood Samples

For each participant, 5 mL of blood was drawn into two sterile tubes containing gel. Similarly, when the patients attended the general surgery clinic for follow-up, blood samples were collected 6 months after LC. Based on data from previous studies, it has been shown that lipid levels are affected by the time elapsed after cholecystectomy, with the most pronounced changes observed at six months after surgery (18). Therefore, therefore, in our study, it was preferred to collect blood samples 6 months after LC. Blood samples collected in gel-containing tubes before and after LC were allowed to clot at room temperature, and then the clotted samples were centrifuged at $3000 \times g$ for 10 minutes to separate the serum phase. Serum samples were stored at -80°C until mineral and trace-element levels were analyzed.

Determination of BMI

The body weights and heights of participants in the study group were measured before and after LC surgery. BMI values were calculated by dividing body weight in kilograms by the square of height in metres (kg/m^2). According to the World Health Organization's diagnostic criteria for obesity, individuals with a BMI $\geq 30 \text{ kg}/\text{m}^2$ are considered obese (19).

Measurement of Mineral and Trace Element Levels

Serum mineral and trace element levels (Cu, Cr, Cd, Mg, Fe, Zn, and Se) were determined using inductively coupled plasma mass spectrometry (ICP-MS; Thermo Scientific iCAP RQ, Bremen, Germany), which is widely accepted as the reference analytical technique for multi-element determination in biological samples because of its excellent analytical accuracy, a wide linear dynamic range, and the ability to measure multiple elements simultaneously at trace levels. Prior to ICP-MS analysis, samples were subjected to microwave-assisted digestion (MARS 6, CEM Corporation, Matthews, NC, USA). Calibration curves were constructed using multi-element standard solutions with terbium (Tb) as the internal standard. The calibration curves showed good linearity ($R^2 > 0.99$) for all elements. The limits of detection for the analysed elements were in the ppb range and were determined from calibration curves generated by the ICP-MS system. Throughout the analysis, quality control measures such as blanks and standard evaluations were applied. Each sample was analysed in triplicate and findings were recorded in ppb or $\mu\text{g/L}$.

Statistical Analysis

Numerical variables were summarized as mean $\pm$ standard deviation (SD) and minimum-maximum values. Normality was assessed using the Shapiro-Wilk test and Q-Q plots. Preoperative and postoperative measurements were compared using paired-samples t-tests or Wilcoxon signed-rank tests, as appropriate. Effect sizes were reported as Cohen's d_z for paired t-tests and matched-pairs rank-biserial correlation (r_{rb}) for Wilcoxon tests. Sex-based comparisons were performed using Welch's independent-samples t-test, with Hedges' g reported as the effect size. Bonferroni correction was applied to the 16 sex-based comparisons, yielding an adjusted significance threshold of $p < 0.003$. Statistical analyses were performed using IBM SPSS

version 26 (SPSS, Inc., Chicago, IL, USA). A two-sided p -value < 0.05 was considered statistically significant, except for Bonferroni-adjusted comparisons.

Results

The mean age of the patients with symptomatic gallstones included in the study was 44.73 years (range 31-67). Of these, 63.33% were female ($n=19$) and 36.66% were male ($n=11$). A statistically significant increase was observed in BMI from $28.4 \pm 3.10 \text{ kg/m}^2$ before LC to $29.8 \pm 3.97 \text{ kg/m}^2$ six months after LC (Table 1; $p < 0.001$). The proportion of patients with BMI $\geq 30 \text{ kg/m}^2$ increased from 33.3% (10/30) before LC to 46.7% (14/30) six months after LC. Mineral and trace element levels in serum samples collected from patients before LC and 6 months after LC were compared. Cr, Fe, Zn, and Mg levels decreased after LC (Table 1; $p < 0.001$), whereas Cu and Cd levels increased (Table 1; $p < 0.001$). Although serum Se levels were lower after LC compared with pre-LC values, this decrease was not statistically significant (Table 1; $p = 0.856$). After Bonferroni correction for multiple comparisons (adjusted significance threshold, $p < 0.003$), women had significantly lower preoperative Cr levels and lower postoperative Fe levels than men. No other sex-based comparisons met the Bonferroni-adjusted significance threshold (Table 2).

Discussion

Increasing evidence suggests that the GB is not merely a passive bile reservoir but an active regulator of systemic metabolic homeostasis (6,7,20-25). While the metabolic consequences of cholecystectomy on glucose and lipid metabolism and on fatty liver disease have been extensively investigated, its potential impact on mineral and trace element homeostasis remains almost entirely unexplored. To our knowledge, this is the first

Table 1. Comparison of BMI and mineral and trace element levels before and after LC operation

	Before LC Mean $\pm$ SD (min-max)	After LC Mean $\pm$ SD (min-max)	p	Effect size
BMI	28.4 ± 3.10 (22.8-34.4)	29.8 ± 3.97 (22.5-39.8)	r_{rb}	r_{rb}
Cr	4.09 ± 0.691 (3.01-5.55)	3.62 ± 0.640 (2.83-5.18)	$< 0.001^a$	$r_{rb} = -1.00$
Cu	848 ± 221 (506-1361)	1270 ± 458 (591-2200)	$< 0.001^a$	$r_{rb} = 1.00$
Fe	1178 ± 130 (836-1372)	970 ± 127 (757-1257)	$< 0.001^b$	$d_z = -1.48$
Zn	691 ± 127 (404-892)	574 ± 113 (387-796)	$< 0.001^b$	$d_z = -1.01$
Mg	7920 ± 853 (6371-9734)	6610 ± 694 (5310-7960)	$< 0.001^b$	$d_z = -2.12$
Se	66.0 ± 5.32 (54.4-77.4)	65.9 ± 5.54 (53.6-76.3)	0.856 ^b	$d_z = -0.03$
Cd	31.1 ± 2.16 (23.1-36.5)	38.0 ± 3.40 (29.5-43.9)	$< 0.001^b$	$d_z = 2.45$

^aWilcoxon signed-rank test, ^bpaired-samples t-test. Effect sizes are reported as matched-pairs rank-biserial correlation (r_{rb}) for Wilcoxon signed-rank tests and Cohen's d_z for paired-samples t-tests

BMI: Body mass index, SD: Standard deviation, Min-max: Minimum-maximum

prospective study to demonstrate that LC is associated with persistent changes in several circulating minerals and trace elements six months postoperatively.

It is increasingly accepted that changes in intestinal physiology, nutrient absorption, and enterohepatic circulation following LC may have long-term effects on metabolic homeostasis. Given that these changes may also affect the intestinal absorption and metabolism of trace elements, this study evaluated changes in serum trace element levels before LC and six months postoperatively. Among the symptomatic patients with gallstones who participated in the study, 63.33% were female and 36.66% were male; the average age was 44.7 years. The higher number of female patients in our study group is consistent with the higher prevalence of GSD in women reported in the literature (2,26-28).

Although trace elements constitute only a small part of the diet, they play important roles in physiological and biochemical processes (29). Adequate intake of trace elements is essential for maintaining human metabolic homeostasis, and imbalances can lead to the development of cardiovascular, digestive, endocrine, blood, and other diseases (20). Although LC is considered a safe and effective treatment method for symptomatic GSD, there is increasing evidence that changes in intestinal physiology and nutrient absorption following surgery can affect metabolic homeostasis (3,7). The effects of these changes on serum trace element homeostasis remain unclear.

In our study, six months after LC, serum Fe, Zn, Cr, and Mg levels decreased, whereas Cd and Cu levels increased (all $p < 0.001$). Fe and Zn are absorbed primarily in the proximal small intestine, and their intestinal bioavailability is influenced by luminal conditions and interactions with other minerals (30,31). Therefore, maintaining their solubility in the lumen is critical for efficient absorption. Bile salts play an important role in the physicochemical environment of the intestinal lumen and facilitate the micellar solubilization and absorption of lipids and fat-soluble compounds (14,32).

Cholecystectomy alters the pattern of BA delivery to the intestine and may modify enterohepatic circulation and the intestinal microenvironment (33,34). In this context, the decreases in serum Fe and Zn observed in our study may partly reflect changes in their intestinal bioavailability associated with altered bile flow and changes in the intestinal environment after cholecystectomy. However, as intestinal absorption and BA profiles were not directly assessed in the present study, this proposed mechanism remains speculative.

Naik et al. (35) reported a high prevalence of iron deficiency among symptomatic patients with gallstones, suggesting that iron metabolism may be closely related to GSD. However, this study only evaluated the preoperative period and did not examine changes in Fe homeostasis after cholecystectomy. In our study, significantly lower serum Fe levels observed six months after LC

Table 2. Comparison of demographic characteristics and serum mineral and trace element levels according to sex

		Female (n=19) Mean $\pm$ SD (Min-max)	Male (n=11) Mean $\pm$ SD (Min-max)	p	Hedges' g
Age (year)		44.16 $\pm$ 9.82 (31.00-67.00)	45.73 $\pm$ 7.71 (37.00-61.00)	0.632	-0.17
BMI		29.20 $\pm$ 3.32 (23.53-34.38)	27.13 $\pm$ 2.25 (22.84-30.42)	0.053	0.67
Cr	Before LC	3.80 $\pm$ 0.60 (3.01-5.12)	4.58 $\pm$ 0.56 (3.70-5.55)	0.001*	-1.31
	After LC	3.41 $\pm$ 0.50 (2.83-4.69)	3.99 $\pm$ 0.71 (2.83-5.18)	0.028	-0.98
Cu	Before LC	884,19 $\pm$ 242,97 (506,20-1361,21)	784,42 $\pm$ 168,06 (525,02-1029,39)	0.196	0.44
	After LC	1300,25 $\pm$ 505,66 (591,19-2157,04)	1230,30 $\pm$ 381,34 (822,38-2200,20)	0.658	0.15
Fe	Before LC	1148,80 $\pm$ 134,88 (836,05-1336,60)	1232,63 $\pm$ 105,27 (1077,14-1372,02)	0.064	-0.67
	After LC	914,35 $\pm$ 95,27 (756,63-1117,68)	1067,08 $\pm$ 119,28 (878,10-1257,05)	0.002*	-1.42
Zn	Before LC	679,45 $\pm$ 124,71 (403,80-891,60)	709,71 $\pm$ 135,88 (472,90-891,60)	0.552	-0.23
	After LC	569,07 $\pm$ 110,95 (407,10-796,00)	581,37 $\pm$ 119,91 (387,30-782,60)	0.786	-0.10
Mg	Before LC	7773,25 $\pm$ 801,13 (6371,40-9206,50)	8172,48 $\pm$ 918,21 (6372,20-9734,00)	0.245	-0.46
	After LC	6470,24 $\pm$ 574,92 (5309,90-7825,90)	6861,29 $\pm$ 833,58 (5704,80-7960,30)	0.188	-0.56
Se	Before LC	66,54 $\pm$ 5,53 (59.72-77.40)	65.19 $\pm$ 5.06 (54.38-70.85)	0.505	0.24
	After LC	66.17 $\pm$ 5.65 (54.37-76.30)	65.31 $\pm$ 5.55 (53.64-73.03)	0.687	0.15
Cd	Before LC	30.83 $\pm$ 2.17 (23.09-33.96)	31.63 $\pm$ 2.15 (29.31-36.45)	0.336	-0.36
	After LC	37.74 $\pm$ 3.48 (29.51-43.96)	38.36 $\pm$ 3.38 (32.13-43.51)	0.634	-0.18

Data are presented as mean $\pm$ SD. *Welch's independent-samples t-test. Effect sizes are reported as Hedges' g. Bonferroni correction was applied for 16 comparisons, resulting in an adjusted significance threshold of $p < 0.003(0.05/16)$. LC: Laparoscopic cholecystectomy, BMI: Body mass index; SD: standard deviation

suggest that alterations in Fe status may persist after surgery or be associated with postoperative changes in biliary physiology. However, given the prospective pre-post observational design of our study, a causal relationship cannot be established, and this hypothesis requires confirmation in larger, long-term prospective studies. A notable decrease in serum Fe concentrations and a significant increase in serum Cd concentrations were observed six months after LC. Fe and Cd can share intestinal metal transport pathways, and experimental studies suggest that alterations in Fe status may influence intestinal Cd uptake (36-38). Consequently, the decrease in serum Fe observed in our study may have contributed to the increase in Cd concentrations through shared metal transport pathways. However, because metal transporter expression and intestinal Cd absorption were not directly assessed, this interpretation should be regarded as a plausible mechanistic hypothesis rather than evidence of a causal relationship. Furthermore, serum Cd concentrations may be influenced by environmental exposure, dietary factors, and other physiological factors that were not comprehensively assessed in the present study (38).

Magnesium absorption in the intestine occurs through both passive paracellular diffusion and active transcellular transport involving the transient receptor potential melastatin channels TRPM6 and TRPM7 (39). Magnesium absorption efficiency is influenced by luminal factors, including pH, mineral solubility, food matrix composition, and intestinal transit time (39,40). In our study, serum Mg levels decreased significantly six months after LC. Changes in BA dynamics and the intestinal environment following cholecystectomy may influence intestinal mineral absorption and could therefore contribute to the observed change in serum Mg (34). However, intestinal Mg absorption, BA profiles, and related transport mechanisms were not directly assessed in the present study; therefore, this interpretation remains hypothesis-generating. Additionally, in patients experiencing BA diarrhea post-cholecystectomy, accelerated intestinal transit and increased gastrointestinal losses may further diminish magnesium absorption (41).

Supporting our findings, a previous study noted reduced serum and erythrocyte magnesium concentrations in patients with post-cholecystectomy syndrome and reported symptomatic improvement with magnesium supplementation. However, the lack of a control group and the selective patient population limit the causal interpretation of the association between magnesium status and post-cholecystectomy syndrome (42). Interactions between divalent minerals, fatty acids, and other lipophilic components during intestinal digestion may influence their physicochemical behavior and bioavailability (16). Such nutrient-mineral interactions could represent a mechanism

contributing to the postoperative change in serum Mg observed in our study. However, because fat digestion, intestinal free fatty acid concentrations, and Mg absorption were not directly assessed, this possibility remains speculative. Rather than indicating that cholecystectomy directly causes magnesium deficiency, our findings suggest that altered BA dynamics, changes in the intestinal environment, and potential nutrient-mineral interactions may collectively contribute to the observed postoperative decrease in serum Mg.

In our study, serum Cu levels increased significantly six months after LC compared with preoperative levels. Copper homeostasis is regulated through coordinated intestinal absorption. Fraser et al. (43) reported early postoperative changes in serum Fe and Zn concentrations following cholecystectomy and cardiac surgery, whereas serum Cu remained relatively stable during the early postoperative period. These findings highlight the influence of the acute surgical response on circulating trace element concentrations. In contrast, our study assessed serum Cu levels over a longer period by comparing preoperative values with those obtained six months after surgery. Therefore, the observed increase in serum Cu is less likely to reflect solely a transient acute-phase response to surgical trauma. Postoperative changes in hepatobiliary physiology and intestinal homeostasis may contribute to the observed increase in serum Cu; however, because copper absorption, biliary excretion, and related regulatory mechanisms were not directly assessed, this interpretation remains hypothesis-generating.

Six months after LC, serum Se levels did not change significantly compared with preoperative levels, whereas serum Cr levels decreased significantly. These findings suggest that the postoperative changes observed in our study were not uniform across all trace elements, potentially reflecting differences in their absorption, transport, and homeostatic regulation. Selenium is generally well absorbed, although its bioavailability varies according to its chemical form, dietary composition, and interactions with the gut microbiota (44-46). These characteristics may partly explain the relative stability of serum Se levels observed in our study. In contrast, the intestinal absorption and bioavailability of Cr are relatively low and may be influenced by dietary and gastrointestinal factors (47). Therefore, changes in the intestinal environment following cholecystectomy could contribute to the observed decrease in serum Cr. Because dietary intake, intestinal absorption, gut microbiota, and element-specific transport mechanisms were not directly assessed, these interpretations are hypothesis-generating and do not provide evidence of a causal relationship.

In this study, BMI values recorded prior to surgery and six months after LC showed a significant postoperative increase.

This finding aligns with previous research, which has also documented an increase in BMI following cholecystectomy (21,22,33,48). In a cross-sectional study, Cao et al. (21) reported that cholecystectomy was independently associated with higher BMI, with a more pronounced association among younger adults. These findings suggest that the metabolic changes associated with cholecystectomy may extend beyond its effects on bile storage and digestion, potentially involving broader alterations in metabolic homeostasis. Although postoperative dietary changes may also contribute to weight gain, dietary intake was not monitored in our study; therefore, the relative contribution of dietary and metabolic factors to the observed increase in BMI could not be determined.

Recent research suggests that the GB functions not only as a passive bile reservoir but also as an active participant in the regulation of systemic metabolic homeostasis (6,7,20,25). Following cholecystectomy, the physiological meal-dependent pattern of BA delivery to the intestine becomes less pronounced, with bile entering the duodenum in a more continuous manner. This change may alter enterohepatic circulation and the BA pool composition, thereby affecting metabolic signaling pathways mediated by the FXR, Takeda G protein-coupled receptor 5, and fibroblast growth factor 19. Given that these pathways are involved in the regulation of glucose metabolism, energy expenditure, lipid homeostasis, and insulin sensitivity, alterations in BA signaling have been proposed as a potential mechanism contributing to long-term weight gain and metabolic disturbances following cholecystectomy (6,7,21,22,24,34,49,50). These physiological changes may affect both systemic energy metabolism and intestinal absorption processes. Consequently, the simultaneous increase in BMI and changes in serum mineral and trace element levels observed in our study may reflect overlapping mechanisms involving post-cholecystectomy remodeling of the BA-gut microbiota-metabolic axis. Assessing changes in BMI alongside mineral and trace element levels is therefore an important aspect of this study. Although increased body weight is known to affect mineral and trace element metabolism, the distinct directional changes in individual analytes suggest that factors beyond weight change may also be involved; this possibility, however, could not be directly tested in the present study. Specifically, post-cholecystectomy systemic metabolic remodeling and element-specific intestinal transport mechanisms may contribute to the observed changes in mineral and trace element levels. However, given the limited number of studies on this topic, the proposed mechanisms should be considered hypothesis-generating rather than as evidence of a causal relationship.

Our findings expand the current understanding of cholecystectomy beyond its effects on BA physiology and lipid metabolism. The persistent changes in multiple serum mineral and trace element levels observed six months after cholecystectomy are consistent with broader metabolic remodeling. These results further support the emerging view that the GB serves not only as a passive reservoir for bile but also as an integral component of systemic metabolic regulation. Future large-scale mechanistic studies integrating BA profiling, gut microbiota characterization, intestinal mineral transport pathways, and metabolic biomarkers are needed to elucidate the biological mechanisms underlying these observations and to assess their potential clinical implications.

Study Limitations

This pilot study represents, to our knowledge, the first prospective longitudinal investigation of changes in serum mineral and trace element levels following LC. However, several limitations should be considered. First, the study included only 30 participants, which limits the precision and generalizability of the findings, particularly for sex-based subgroup comparisons. Second, the study used a pre-post observational design without a healthy or non-surgical control group. Therefore, the preoperative measurements should not be considered healthy baseline values because all participants had symptomatic GSD, and the observed longitudinal changes cannot be attributed solely to LC. In addition, disease-related gastrointestinal symptoms, dietary changes, medication use, and perioperative supportive interventions were not systematically quantified; therefore, their potential influence on preoperative serum mineral and trace element concentrations could not be evaluated. Furthermore, method-specific clinical reference intervals were not established in the study population. Therefore, the absolute serum concentrations should not be interpreted as evidence of element deficiency or toxicity. The present findings primarily reflect longitudinal within-patient changes. Third, individual BA profiles, gut microbiota, and relevant nutritional biomarkers were not assessed, limiting our ability to directly examine the proposed mechanisms linking postoperative changes in and intestinal physiology to mineral and trace element homeostasis. Furthermore, serum mineral and trace element levels were assessed at only two time points, immediately before LC and six months after surgery; therefore, early and intermediate postoperative changes could not be characterized. Urinary excretion of minerals and trace elements was also not assessed. An additional limitation is the lack of dietary monitoring throughout the study. Dietary assessment would have facilitated evaluation of the potential effects of habitual dietary intake

and postoperative dietary changes on serum mineral and trace element levels and BMI.

Conclusion

In this prospective pilot study, LC was associated with a significant increase in BMI and a distinct shift in the serum elemental profile six months after surgery, characterized by decreased Fe, Zn, Mg, and Cr levels and increased Cu and Cd levels, while Se levels remained unchanged. These findings suggest that the gallbladder may play a role in maintaining mineral and trace element homeostasis beyond its classical function in bile storage. Monitoring body weight and selected mineral and trace element levels may therefore be considered during the postoperative follow-up of patients undergoing LC, pending confirmation of these preliminary findings in larger controlled studies.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (approval no: 2025/70, date: 29.07.2025), and patients who voluntarily agreed to participate were enrolled in the study.

Informed Consent: Written informed consent was obtained from all participants prior to enrollment in the study. All study procedures were carried out in accordance with the ethical principles of the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.B., Concept: S.E., Design: S.E., Data Collection or Processing: H.B., S.E., Analysis or Interpretation: H.B., S.E., Literature Search: H.B., S.E., Writing: H.B., S.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Wang K, Liu Z, Tang R, Sha Y, Wang Z, Chen Y, et al. Gallstones in the era of metabolic syndrome: pathophysiology, risk prediction, and management. *Cureus*. 2025;17:e80541.
2. Wang X, Yu W, Jiang G, Li H, Li S, Xie L, et al. Global epidemiology of gallstones in the 21st century: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2024;22:1586-95.
3. Zhang Y, Dai X, Duan R, Wei L. Research progress in the treatment of gallstones with laparoscopic and endoscopic surgery: a narrative review. *BMC Surg*. 2025;25:238.
4. Arrese M, Cortés V, Barrera F, Nervi F. Nonalcoholic fatty liver disease, cholesterol gallstones, and cholecystectomy: new insights on a complex relationship. *Curr Opin Gastroenterol*. 2018;34:90-6.
5. Jones MW, Weir CB, Marietta M. Gallstones (Cholelithiasis). 2026 Jun 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.
6. Cortés VA, Barrera F, Nervi F. Pathophysiological connections between gallstone disease, insulin resistance, and obesity. *Obes Rev*. 2020;21:e12983.
7. Ciaula AD, Garruti G, Wang DQH, Portincasa P. Cholecystectomy and risk of metabolic syndrome. *Eur J Intern Med*. 2018;53:3-11.
8. Chavez-Tapia NC, Kinney-Novelo IM, Sifuentes-Rentería SE, Torres-Zavala M, Castro-Gastelum G, Sánchez-Lara K, et al. Association between cholecystectomy for gallstone disease and risk factors for cardiovascular disease. *Ann Hepatol*. 2012;11:85-9.
9. Sonne DP, Hare KJ, Martens P, Rehfeld JF, Holst JJ, Vilsbøll T, et al. Postprandial gut hormone responses and glucose metabolism in cholecystectomized patients. *Am J Physiol-Gastrointest Liver Physiol*. 2013;304:G413-9.
10. Yun S, Choi D, Lee KG, Kim HJ, Kang BK, Kim H, et al. Cholecystectomy causes ultrasound evidence of increased hepatic steatosis. *World J Surg*. 2016;40:1412-21.
11. Fort JM, Azpiroz F, Casellas F, Andreu J, Malagelada JR. Bowel habit after cholecystectomy: physiological changes and clinical implications. *Gastroenterology*. 1996;111:617-22.
12. O'Donnell LJ. Post-cholecystectomy diarrhoea: a running commentary. *Gut*. 1999;45:796-7.
13. Rolić T, Yazdani M, Mandić S, Distant S. Iron metabolism, calcium, magnesium and trace elements: a review. *Biol Trace Elem Res*. 2025;203:2216-25.
14. Moghimipour E, Ameri A, Handali S. Absorption-enhancing effects of bile salts. *Molecules*. 2015;20:14451-73.
15. Zuvarox T, Goosenberg E, Belletieri C. Malabsorption syndromes. 2025 Jul 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
16. Corte-Real J, Bohn T. Interaction of divalent minerals with liposoluble nutrients and phytochemicals during digestion and influences on their bioavailability – a review. *Food Chem*. 2018;252:285-93.
17. Calvo MM, Bujanda L, Heras I, Calderon A, Cabriada JL, Orive V, et al. Magnetic resonance cholangiography versus ultrasound in the evaluation of the gallbladder. *J Clin Gastroenterol*. 2002;34:233-6.
18. Malik AA, Wani ML, Tak SI, Irshad I, Ul-Hassan N. Association of dyslipidaemia with cholelithiasis and effect of cholecystectomy on the same. *Int J Surg*. 2011;9:641-2.
19. World Health Organization. Obesity and overweight [Internet]. Geneva: World Health Organization; Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
20. Shi Y, Zou Y, Shen Z, Xiong Y, Zhang W, Liu C, et al. Trace Elements, PPARs, and metabolic syndrome. *Int J Mol Sci*. 2020;21:2612.
21. Cao J, Mao W, Jiang Q, Huang X, Tan Y, Zuo F, et al. Hepatic steatosis mediates the relationship between cholecystectomy and BMI increase: a population-based study. *Front Med (Lausanne)*. 2025;12:1620036.
22. Huh JH, Lee KJ, Cho YK, Moon S, Kim YJ, Han KD, et al. Cholecystectomy increases the risk of metabolic syndrome in the Korean population: a longitudinal cohort study. *Hepatobiliary Surg Nutr*. 2023;12:523-33.
23. Chen Y, Wu S, Tian Y. Cholecystectomy as a risk factor of metabolic syndrome: from epidemiologic clues to biochemical mechanisms. *Lab Invest*. 2018;98:7-14.
24. Bahri MH, Navabian S, Akbari H, Bagherpour JZ, Bozorgmehr R, Mohammaditabar M. Impact of cholecystectomy on metabolic dysfunction-associated steatotic liver disease and metabolic syndrome: a 6-month prospective cohort study. *BMC Gastroenterol*. 2025;25:671.

25. Tinkov AA, Korobeinikova TV, Morozova GD, Aschner M, Mak DV, Santamaria A, et al. Association between serum trace element, mineral, and amino acid levels with non-alcoholic fatty liver disease (NAFLD) in adult women. *J Trace Elem Med Biol.* 2024;83:127397.
26. Wang S, Wang Y, Xu J, Chen Y. Is the oral contraceptive or hormone replacement therapy a risk factor for cholelithiasis: a systematic review and meta-analysis. *Medicine (Baltimore).* 2017;96:e6556.
27. Grundy K, Nelson A. Gallbladder disease. *InnovAiT.* 2025;18:24-30.
28. Ning Q, Liu F, Fang Y, Zhu X, Liu J, Li Z. Estimating global prevalence of gallbladder stones in general population from 2000 to 2024: systematic review and meta-analysis. *Ann Med.* 2025;57:2570795.
29. Yan S, Yu L, Fang S, Gu C. The association between intakes of dietary trace minerals and gallstone disease: a cross-sectional study from National Health and Nutrition Examination Survey 2017 to 2018. *Medicine (Baltimore).* 2024;103:e37741.
30. Nishito Y, Kambe T. Absorption mechanisms of iron, copper, and zinc: an overview. *J Nutr Sci Vitaminol (Tokyo).* 2018;64:1-7.
31. Einhorn V, Haase H, Maeres M. Interaction and competition for intestinal absorption by zinc, iron, copper, and manganese at the intestinal mucus layer. *J Trace Elem Med Biol.* 2024;84:127459.
32. Stojančević M, Pavlović N, Goločorbin-Kon S, Mikov M. Application of bile acids in drug formulation and delivery. *Front Life Sci.* 2013;7:112-22.
33. Amaral Raposo M, Sousa Oliveira E, Dos Santos A, Guadagnini D, El Mourabit H, Housset C, et al. Impact of cholecystectomy on the gut-liver axis and metabolic disorders. *Clin Res Hepatol Gastroenterol.* 2024;48:102370.
34. Ahmed M. Functional, diagnostic and therapeutic aspects of bile. *Clin Exp Gastroenterol.* 2022;15:105-20.
35. Naik S, Abuji K, Dahiya D, Sharma P, Das R, Behera A, et al. Prevalence of iron deficiency anaemia in patients of cholelithiasis undergoing laparoscopic cholecystectomy. *Int Surg J.* 2022;9:1335-9.
36. Giosek Ž, Kot K, Rotter I. Iron, zinc, copper, cadmium, mercury, and bone tissue. *Int J Environ Res Public Health.* 2023;20:2197.
37. Bárány E, Bergdahl IA, Bratteby LE, Lundh T, Samuelson G, Skerfving S, et al. Iron status influences trace element levels in human blood and serum. *Environ Res.* 2005;98:215-23.
38. Fujiwara Y, Lee JY, Banno H, Imai S, Tokumoto M, Hasegawa T, et al. Cadmium induces iron deficiency anemia through the suppression of iron transport in the duodenum. *Toxicol Lett.* 2020;332:130-9.
39. Schuchardt JP, Hahn A. Intestinal absorption and factors influencing bioavailability of magnesium-an update. *Curr Nutr Food Sci.* 2017;13:260-78.
40. Kiela PR, Ghishan FK. Physiology of intestinal absorption and secretion. *Best Pract Res Clin Gastroenterol.* 2016;30:145-59.
41. Vijayvargiya P, Camilleri M, Carlson P, Nair A, Nord SL, Ryks M, et al. Effects of colessevelam on bowel symptoms, biomarkers, and colonic mucosal gene expression in patients with bile acid diarrhea in a randomized trial. *Clin Gastroenterol Hepatol.* 2020;18:2962-70.e6.
42. Porr PJ, Szántay J, Rusu M. Post-cholecystectomy syndrome and magnesium deficiency. *J Am Coll Nutr.* 2004;23:745S-7S.
43. Fraser WD, Taggart DP, Fell GS, Lyon TD, Wheatley D, Garden OJ, et al. Changes in iron, zinc, and copper concentrations in serum and in their binding to transport proteins after cholecystectomy and cardiac surgery. *Clin Chem.* 1989;35:2243-7.
44. Wang X, Zhong Y, Zhu Z, Zhang N, Chen X, Wang F, et al. Gut microbiota: a new perspective for bioavailability of selenium and human health. *Npj Sci Food.* 2025;9:228.
45. Ferreira RLU, Sena-Evangelista KCM, de Azevedo EP, Pinheiro FI, Cobucci RN, Pedrosa LFC. Selenium in human health and gut microflora: bioavailability of selenocompounds and relationship with diseases. *Front Nutr.* 2021;8:685317.
46. Ha HY, Alfulaij N, Berry MJ, Seale LA. From selenium absorption to selenoprotein degradation. *Biol Trace Elem Res.* 2019;192:26-37.
47. Garc a E, Cabrera C, Lorenzo ML, L pez MC, S nchez J. Estimation of chromium bioavailability from the diet by an in vitro method. *Food Addit Contam.* 2001;18:601-6.
48. Sarı İ, Bolat H,  zmen E, K se B, Ayan D. Effect of laparoscopic cholecystectomy on plasma levels of EETs, arachidonic acids derived lipid mediators. *Postgrad Med J.* 2025;101:828-35.
49. T cho AL, Malhotra P, Dudeja PK, Gill RK, Alrefai WA. Intestinal absorption of bile acids in health and disease. *Compr Physiol.* 2019;10:21-56.
50. Rodr guez-Antonio I, L pez-S nchez GN, Garrido-Camacho VY, Uribe M, Ch vez-Tapia NC, Nu o-L ambarri N. Cholecystectomy as a risk factor for non-alcoholic fatty liver disease development. *HPB.* 2020;22:1513-20.