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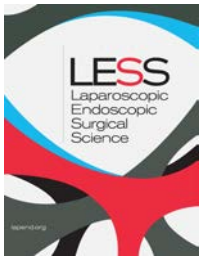

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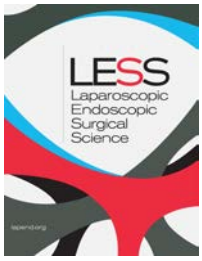

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Laparoscopic Endoscopic Surgical Science (LESS) is a peer-reviewed, independent, international periodical that considers for publication clinical and experimental studies, reviews, case reports, technical contributions, and letters to the editor. Scope of the journal covers the minimally invasive surgical and endoscopic interventions. It is an open access journal and published four times (March, June, September, and December) a year in English. Authors are responsible for the accuracy of data and the journal is in compliance with the uniform requirements for manuscripts submitted to biomedical journals published by the ICMJ (updated in August 2013).

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The diagnostic value of hemogram parameters in gastric cancer and intestinal metaplasia

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ABSTRACT

Introduction: Gastric cancer remains a global health issue with high mortality rates. Early diagnosis can significantly affect disease progression; however, current diagnostic methods are often invasive and costly. In recent years, the diagnostic potential of hematological parameters that reflect systemic inflammation has gained attention. This study aimed to evaluate the role of hemogram markers such as RDW, NLR, and MLR in the diagnosis of gastric cancer and intestinal metaplasia.

Materials and Methods: A total of 155 patients with a diagnosis of gastric cancer, 200 individuals with biopsy-proven intestinal metaplasia, and 353 healthy controls were retrospectively analyzed. Groups were compared in terms of age, sex, and complete blood count parameters. ROC analysis was performed to evaluate diagnostic performance and determine cut-off values.

Results: The mean age was significantly higher in the gastric cancer group ($p<0.001$). Leukocyte count, neutrophils, RDW, NLR, PLR, and MLR were significantly elevated, while hemoglobin and absolute lymphocyte counts were lower ($p<0.001$). RDW demonstrated the highest area under the curve (AUC) in distinguishing gastric cancer patients from healthy individuals (AUC: 0.948, $p<0.001$). In the comparison between intestinal metaplasia and healthy controls, RDW also had the highest AUC value (0.752, $p<0.001$), whereas the diagnostic sensitivity of other hematological parameters was found to be low.

Conclusion: Among hematological parameters, RDW, NLR, and MLR may serve as useful auxiliary biomarkers in the diagnosis of gastric cancer. While RDW holds diagnostic significance in identifying intestinal metaplasia, other parameters had limited value. Given their accessibility and low cost, these parameters may hold a valuable place in clinical practice.

Keywords: Gastric cancer, intestinal metaplasia, hematological parameters, diagnosis, roc analysis

Introduction

Gastric cancer is one of the most frequently diagnosed malignancies worldwide and remains a leading cause of cancer-related mortality.[1] Early diagnosis is critical to improving disease prognosis.[2] Although imaging and endoscopic techniques are commonly employed for diagnostic purposes, the increasing interest in laboratory-based

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markers stems from their non-invasive nature and cost-effectiveness.[3] Complete blood count (CBC) parameters have been studied as biomarkers that reflect systemic inflammation in various cancers.[4] Parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and red cell distribution width (RDW) have shown potential diagnostic value.[5] In this study, we aimed to identify potential hematological biomarkers by comparing CBC parameters among three groups patients with gastric cancer, individuals with intestinal metaplasia, and healthy individuals.

Materials and Methods

This retrospective single-center study was conducted in a tertiary care hospital. Ethical approval was obtained from the Institutional Review Board of Kartal Koşuyolu High Specialization Training and Research Hospital (Date: 18/02/2025, No: 2025/02/1042). This study was conducted in accordance with the principles of the Declaration of Helsinki. A total of 155 patients diagnosed with gastric cancer, 200 individuals diagnosed with intestinal metaplasia by endoscopic biopsy and 353 healthy individuals with normal gastroscopic findings confirmed by gastric biopsy were included in the study. CBC tests were performed within 0–30 days prior to the procedure. Exclusion criteria were active infection, chronic inflammatory disease, liver cirrhosis, hematological and other systemic malignancies, immunosuppressive treatment, use of NSAIDs within 1 week before the procedure, recent surgery or trauma and incomplete data records.

Demographic data including age, sex, and laboratory test results were recorded in a database. Hematological parameters such as hemoglobin (HB), mean corpuscular volume (MCV), red cell distribution width (RDW), platelet count, white blood cell (WBC) count, mean platelet volume (MPV), and absolute neutrophil, lymphocyte, and monocyte counts were measured using the Advia 2120 (Siemens Healthcare Diagnostics). The NLR was calculated by dividing absolute neutrophils by absolute lymphocytes; MLR by dividing absolute monocytes by absolute lymphocytes; PLR by dividing platelet count by absolute lymphocytes. The participants were categorized into three groups: gastric cancer, intestinal metaplasia, and healthy group. These groups were compared based on CBC parameters. ROC analysis was performed to assess diagnostic performance and determine cut-off values.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were presented as median (minimum–maximum). ANOVA or Kruskal-Wallis tests were used for comparisons among groups, and the chi-square test was used for categorical variables. ROC (Receiver Operating Characteristic) analysis was performed to evaluate diagnostic performance between gastric cancer and control groups, as well as intestinal metaplasia and control groups. A p-value <0.05 was considered statistically significant.

Results

A total of 708 individuals were included in the study: 155 (21.9%) had gastric cancer, 200 (28.2%) had intestinal metaplasia, and 353 (49.9%) were healthy group. The gastric cancer group was significantly older (mean age 62.7±11.5 years) and age was significantly higher compared to the control group (p<0.001). Sex distribution also differed among the groups (p<0.001) with a higher proportion of males in the gastric cancer group (Table 1). Significant differences were observed among groups in terms of CBC parameters. WBC, neutrophils, monocytes, RDW, NLR, PLR, and MLR were significantly higher in the gastric cancer group (p<0.001). Hemoglobin and absolute lymphocyte counts were significantly lower in the gastric cancer group (p<0.001). Platelet count did not significantly differ between groups (p=0.136) (Table 2). According to ROC analysis, RDW had the highest diagnostic performance in distinguishing gastric cancer from healthy controls (AUC: 0.948; 91.6% sensitivity, 90.4% specificity; p<0.001) (Fig. 1). Other significant parameters included MLR (AUC: 0.778), NLR (AUC: 0.740), and PLR (AUC: 0.704). Platelet count showed a low AUC and was not statistically significant (AUC: 0.545; p=0.112). In the comparison between intestinal metaplasia and healthy group, RDW again had the highest AUC value (0.752; p<0.001) while other parameters showed low AUC values and limited diagnostic utility (Fig. 2) (Table 3).

Discussion

This study investigated hematological parameters across individuals with gastric cancer, intestinal metaplasia and healthy controls to identify potential non-invasive

Table 1. Comparison of Clinical Characteristics and Laboratory Parameters of Cases

Variable	Gastric cancer group	Intestinal metaplasia group	Healthy group	p
n	155	200	353	
Age (years)	62.7±11.5	58.5±10.8	49.8±13.6	<0.001
Sex (%)				<0.001
Female	61 (39.4)	107 (53.5)	212 (60.1)	
Male	94 (60.6)	93 (46.5)	141 (39.9)	
WBC (10^9 /L)	8.3±2.5	9.6±3.3	7.5±1.5	<0.001
Neutrophil (10^9 /L)	5.3±2.09	6.1±3.05	4.3±1.3	<0.001
Lymphocyte (10^9 /L)	1.9±0.83	2.8±1.6	2.3±0.62	<0.001
Monocyte (10^9 /L	0.72±0.3	0.61±0.23	0.55±0.12	<0.001
Hemoglobin (g/dl)	10.3±1.9	13.4±2.4	14.1±1.08	<0.001
Platelet (10^9 /L)	310.83±130.62	266.7±77.8	265.6±67.2	0.136
RDW				<0.001
NLR	3.53±2.6	2.30±1.5	1.99±0.99	<0.001
PLR	213.5 (151.5-381.8)	129.7 (102.3-377.3)	124.2 (59.8-169.5)	<0.001
MLR	0.4061±0.19106	0.2581±0.13151	0.2473±0.07997	<0.001

Table 2. Diagnostic Performance of Hematological Parameters in Differentiating Gastric Cancer Patients from Healthy Controls Based on ROC Curve Analysis

Variable	Cut Off	AUC	SE	%95 GA	Sensivite	Spesifite	p
RDW	14.2	0.948	0.0127	0.924-0.973	91.61	90.37	<0.001
Platelet (10^9 /L)	289.1	0.545	0.028	0.49-0.599	57.42	63.74	0.112
NLR	2.374	0.740	0.0253	0.691-0.79	74.19	75.64	<0.001
PLR	180.55	0.704	0.0263	0.653-0.756	45.16	99.72	<0.001
MLR	0.394	0.778	0.024	0.731-0.825	55.48	98.87	<0.001

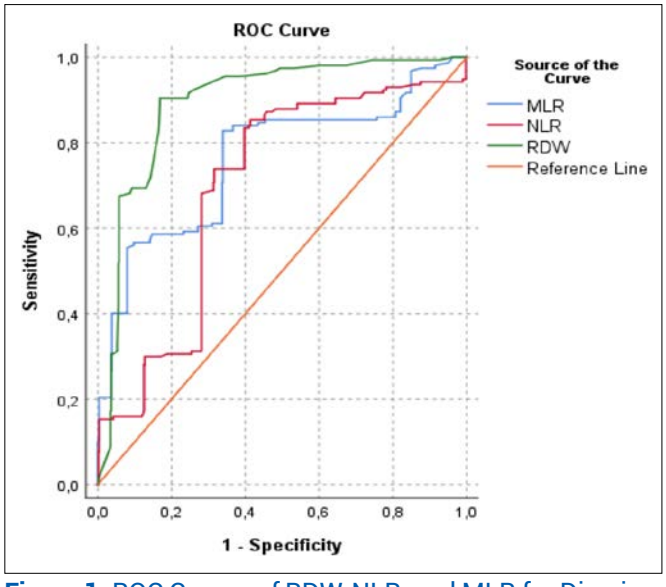

Figure 1. ROC Curves of RDW, NLR, and MLR for Discriminating Gastric Cancer Patients from Healthy Controls.

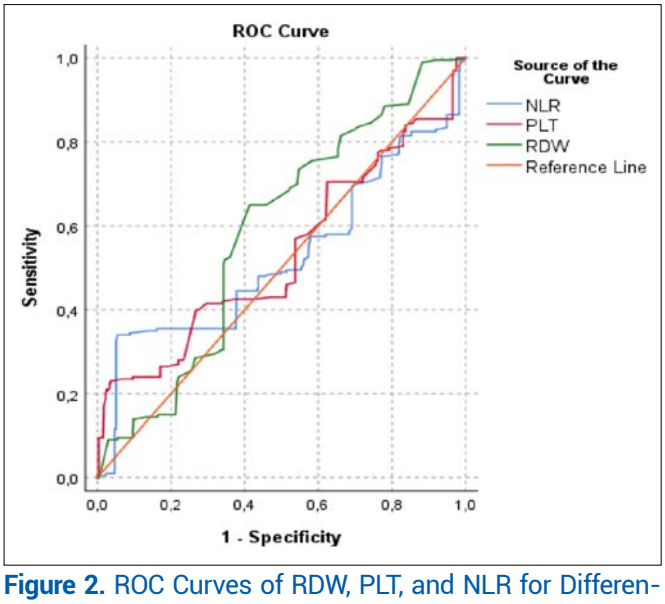

Figure 2. ROC Curves of RDW, PLT, and NLR for Differentiating Patients with Intestinal Metaplasia from Healthy Controls.

Table 3. Diagnostic Performance of Hematological Parameters in Differentiating Patients with Intestinal Metaplasia from Healthy Controls Based on ROC Curve Analysis

Variable	Cut Off	AUC	SE	%95 GA	Sensivite	Spesifite	p
RDW	14.0	0.752	0.0225	0.708-0.796	65	82.44	<0.001
Platelet (10^9 /L)	342.1	0.542	0.0257	0.492-0.592	23	97.45	0.101
NLR	3.748	0.586	0.0255	0.536-0.636	34.5	99.43	<0.001
PLR	172.27	0.513	0.0256	0.463-0.563	22	99.72	0.619
MLR	0.401	0.487	0.0255	0.437-0.537	20.5	98.87	0.613

diagnostic biomarkers. Our findings indicate that RDW, NLR, and MLR are significantly associated with gastric cancer, whereas only RDW demonstrated limited but statistically significant diagnostic value in intestinal metaplasia.

Gastric cancer remains a highly lethal disease, and early detection is essential to improving outcomes.[6] The risk of progression from intestinal metaplasia to gastric cancer can increase by up to 30-fold.[7] Prior studies have explored inflammatory markers such as NLR, PLR, MPV, and platelet count in patients with gastric cancer, but few studies have compared these parameters across gastric cancer, intestinal metaplasia, and healthy individuals.[8] Inflammatory markers such as RDW, NLR, and MLR were significantly elevated in the gastric cancer group, while hemoglobin and absolute lymphocyte counts were decreased. These findings align with existing literature indicating systemic inflammation and hematological dysregulation in malignancy.[9] RDW had the highest diagnostic power (AUC: 0.948) supporting previous findings that associate RDW with cellular irregularities and inflammation.[10] Elevated NLR and MLR levels may reflect neutrophilia and suppressed immune response during cancer progression, a phenomenon linked to poor prognosis in many solid tumors.[11]

In the intestinal metaplasia group, hematological changes were less pronounced. RDW alone showed significant diagnostic value (AUC: 0.752), suggesting that even premalignant lesions may exhibit systemic hematological changes. However, the lack of significance in other inflammatory markers implies that intestinal metaplasia may not elicit a strong systemic inflammatory response. A strength of this study lies in its evaluation of both malignant and premalignant conditions, demonstrating how hematological parameters vary across the disease spectrum.[12-14] The consistent performance of RDW highlights its potential as an early, accessible diagnostic tool, particularly in patients where invasive diagnostic procedures are not feasible or in population screening efforts.

Conclusion

RDW, NLR, and MLR may serve as practical, non-invasive, and low-cost biomarkers in the diagnosis of gastric cancer. RDW may also have value in detecting intestinal metaplasia, a premalignant condition. These findings underscore the clinical utility of hematological markers in early detection and suggest the need for prospective studies to validate their use in routine screening.

Limitations of the Study

This study has several limitations. Its retrospective design prevents the establishment of causal relationships. Additionally, some confounding factors that may influence hematological parameters such as subclinical inflammation or unreported medication use could not be fully excluded. Prospective studies are needed to validate these findings in broader populations.

Disclosures

Ethics Committee Approval: Ethical approval was obtained from the Institutional Review Board of Kartal Koşuyolu High Specialization Training and Research Hospital (Date: 18/02/2025, No: 2025/02/1042).

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Original Article

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The role of Alvarado and Ohmann scoring systems in diagnosing appendicitis and assessing disease severity

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ABSTRACT

Introduction: Acute appendicitis is among the most common causes of acute abdomen. While diagnosis is generally straightforward, it may be challenging to differentiate from other conditions, particularly in pregnant women and the elderly. Currently, several scoring systems have been developed to aid in diagnosis. This study aims to evaluate the significance of these scoring systems in diagnosing appendicitis and assessing the severity of inflammation.

Materials and Methods: A total of 210 patients hospitalized between 01/01/2016 and 01/06/2019 at the General Surgery Clinic of the Republic of Türkiye S.B.U Van Training and Research Hospital for acute appendicitis were examined retrospectively. Appendectomy was performed following ultrasonography for patients evaluated using the Alvarado and Ohmann scoring systems, and these scores were compared with intraoperative severity scores. The predictive value of the Alvarado and Ohmann scoring systems in diagnosing acute appendicitis was analysed.

Results: A moderate positive correlation was identified between the Alvarado and Ohmann scores (r=0.508; p<0.001). The Alvarado score demonstrated a statistically significant accuracy in predicting acute appendicitis diagnosis based on histopathological findings (p=0.027), whereas the Ohmann score did not show statistical significance (p=0.807). Although both scores correlated weakly with intraoperative inflammation grading, a significant association was found between the Alvarado scoring system and intraoperative severity grading (r=0.30; p=0.002). No significant correlation was observed between the Ohmann score and intraoperative severity grading (r=0.09; p=0.384).

Conclusion: The Alvarado scoring system proved valuable in predicting appendicitis, while the Ohmann scoring system was more useful in suggesting the exclusion of appendicitis.

Keywords: Alvarado, appendicitis, inflammation, Ohmann

Introduction

Acute appendicitis is one of the most frequent causes of acute abdomen. With timely and accurate diagnosis, acute appendicitis (AA) generally has low mortality and morbidity. However, delayed intervention can lead to progression from simple appendicitis to perforation. Historically, AA diagnoses based solely on physical examination and symptoms have led to perforation rates of around 20%

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and negative appendectomy (NA) rates ranging from 2% to 30%, both of which are relatively high. Extending the preoperative observation period can potentially reduce negative laparotomy rates; however, prolonged waiting also risks perforation, thereby increasing morbidity and mortality.[1,2] In recent years, various scoring systems have been implemented in clinical practice to support the early diagnosis and treatment of acute appendicitis. Among the most commonly utilized systems in daily practice are the Alvarado, Ohmann, Eskelinen, and Lintula scores. The application of these scoring systems helps reduce negative laparotomy rates and the risk of increased perforation rates associated with prolonged observation and hospital stay in patients without acute appendicitis.[3-5] Among these, the scoring system developed by Alvarado is the most widely recognized and utilized.[6,7] This system relies on symptoms, clinical findings, and laboratory results to guide surgical decision-making. The Alvarado scoring system, specifically developed for diagnosing acute appendicitis, is based on clinical indicators and leukocyte count, with a maximum score of 10 (Table 1). The Ohmann score is another scoring system that can be easily applied to diagnose appendicitis in patients presenting with abdominal pain (Table 2).[8] This study aims to evaluate the effectiveness of these two scoring systems in patients diagnosed with acute appendicitis and to provide a cost-effective diagnostic tool, particularly for physicians in peripheral healthcare settings.

Materials and Methods

This retrospective study examined 210 patients who were hospitalized with acute appendicitis between 01/01/2016 and 01/06/2019 at the General Surgery Clinic of the Republic of Türkiye S.B.U Van Training and Research Hospital. Ethical approval for the study was granted by the Ethics Committee of the same institution (Consent No. 2019/16) on 22/08/2019. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Alvarado and Ohmann scores were calculated for all patients presenting with abdominal pain who subsequently underwent appendectomy at the clinic (Tables 1 and 2). All patients underwent physical examination, laboratory testing, and radiological imaging (USG and CT). Informed consent for surgery was obtained from each patient. Pathology results from all operated patients were analyzed to assess the accuracy of the scoring systems. Patients with an Ohmann score between 6.5 and 12 and an Alvarado score below 7 were placed under clinical observation and were given medical treatment. Patients who declined surgery, had an inconclusive diagnosis of acute appendicitis, or whose symptoms regressed with medical management alone were excluded from the study. The Ohmann scoring system comprises a total of 8 parameters. Patients with a cumulative score of 12 or above are considered to have a high likelihood of acute appendicitis, and surgical intervention is recommended. Scores between 6.5 and 12 place patients in a 'suspicious' category, for which clinical follow-up is advised. For those scoring 6.5 or below, an acute appendicitis diagnosis is generally ruled out.[5] The Alvarado scoring system, which consists of 8 parameters, has a confidence interval of 78-82%.[6,9] Surgical intervention is recommended for patients with an Alvarado score of 7 or higher, while clinical follow-up is advised for those with a score below 7.[10] In this study, the Mann-

Table 1. Alvarado scoring

Feature	Score when present
Migration of pain	1
Anorexia	1
Nausea	1
Tenderness in right lower quadrant	2
Rebound pain	1
Elevated temperature	1
Leukocytosis	2
Shift of white blood cell count to left	1
Total (maximum)	10

Table 2. Ohman scoring

Parameter	Result
Tenderness in right lower quadrant	4.5 points
Rebound tenderness, contralateral	2.5 points
Dysuria	2.0 points
Constant pain	2.0 points
White blood cell >10,000/mL	1.5 points
Patient aged >50 years	1.5 points
Local guarding	1.0 point
Shifting pain	1.0 point
Total <6.5	Acute appendicitis unlikely

Table 3. Intraoperative severity scoring

Major finding	Points
Negative appendectomy	0
Increased vascularity	1
Perforated appendix	2
Perforated appendix + phlegmonous appendicitis	3

heim Peritonitis Index (MPI) was used intraoperatively to assess the severity of peritonitis (Table 3). While the MPI is not specific to acute appendicitis, it is a widely used scoring system for evaluating peritonitis severity.[11] In the intraoperative peritonitis scoring system, findings such as negative laparotomy, increased vascularity, perforation, and phlegmonous appendicitis were evaluated macroscopically. This study aims to diagnose acute appendicitis using the Mannheim scoring intraoperatively and to determine the degree of correlation between inflammation severity and the Alvarado and Ohmann scoring systems.

Statistical Analysis

Continuous and categorical data were analyzed using SPSS software (Version 20.0, IBM, Armonk, NY, USA). Descriptive statistics for categorical data are presented as frequencies and percentages, while continuous data are expressed as mean±standard deviation, minimum-maximum, and median values according to their distribution. Since the Alvarado and Ohmann scores were not normally distributed (Kolmogorov-Smirnov test), these variables, along with ordered variables from the intraoperative severity scoring, were compared using the Kruskal-Wallis test. Potential predictors identified in previous analyses were included in the multivariate analysis, and logistic regression was performed to determine independent predictors based on pathology results. Agreement between pathology and USG results was assessed using Kappa statistics. A Type I error rate of less than 5% was considered statistically significant.

Results

The study included a total of 210 patients, with 50.48% (n=106) being female and 49.52% (n=104) male. Standard laparoscopic appendectomy was performed in 128 patients (60.9%), while open appendectomy via McBurney's incision was performed in 82 patients (39.1%). The overall mean age of patients was 33 years, with a mean age of 30 years for female patients and 36 years for male patients.

A statistically significant correlation was observed between the Alvarado and Ohmann scores (r=0.508; p<0.001). Based on histopathological results, the Alvarado scoring system was statistically significant for patients diagnosed with appendicitis (p=0.027), whereas the Ohmann scoring system did not show statistical significance (p=0.807).

When white blood cell (WBC) counts were evaluated based on scoring system results, a statistically significant difference was observed for the Alvarado score (p=0.004), whereas the Ohmann score did not show statistical significance (p=0.834) (Fig. 1 and 2).

Intraoperative Peritonitis Severity Scoring

In examining the correlation between the Alvarado and Ohmann scoring systems and intraoperative peritonitis severity, a statistically significant correlation was found with the Alvarado score (p=0.002), while no significant correlation was observed with the Ohmann score

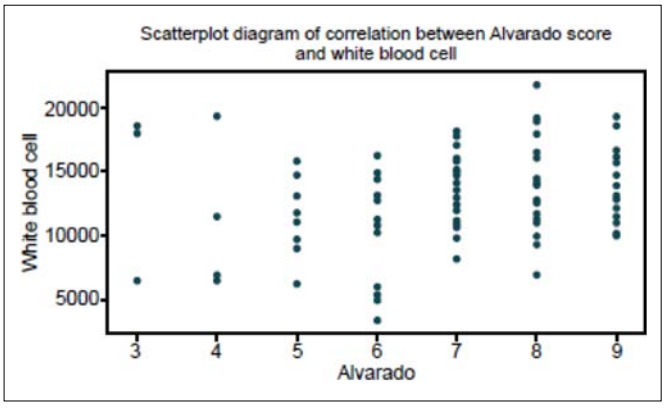

Figure 1. Relationship between Alvarado score and white blood cell count.

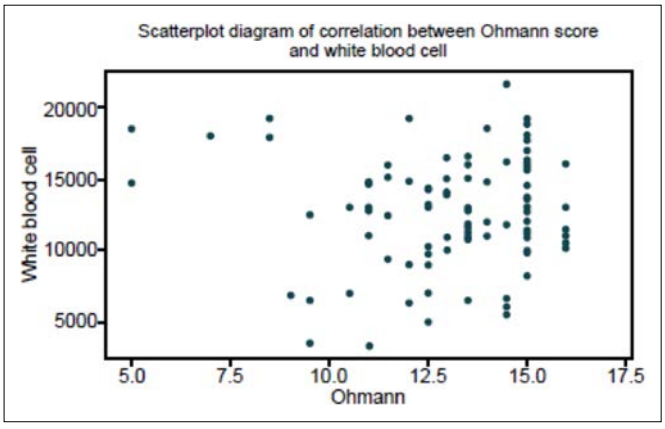

Figure 2. Relationship between Ohmann score and white blood cell count.

(p=0.384). When patients were grouped by intraoperative peritonitis scores, those with scores of 0–3 showed a statistically significant association with the Alvarado score (p=0.016). The Alvarado score was 7 for patients with intraoperative peritonitis scores of 0, 1, or 2, and also 7 for those with a score of 3. In contrast, no statistically significant association was found between the Ohmann score and these four peritonitis severity groups (p=0.547).

Reliability of Ultrasonography

Ultrasonography (USG) demonstrated a specificity of 92.86% and a sensitivity of 80.22% in relation to histopathology results. The consistency of USG with final histopathology findings was 48.3%.

Discussion

Acute appendicitis is one of the leading causes of acute abdominal pain. Preoperative diagnosis is particularly challenging in premenopausal and elderly female patients, as gynecological and genitourinary pathologies often present with similar clinical symptoms, leading to potential confusion with appendicitis.[12,13] Delayed diagnosis may lead to perforation and sepsis, increasing both mortality and morbidity. Additionally, the literature reports negative laparotomy rates ranging from 10% to 40%.[14,15] Despite the availability of advanced imaging methods like USG and CT, scoring systems such as Alvarado and Ohmann have been developed to help reduce negative laparotomy rates. This study examines the correlation between intraoperative peritonitis severity scoring and the Alvarado and Ohmann scoring systems.

The Alvarado scoring system has demonstrated high specificity and sensitivity, establishing it as a straightforward and effective diagnostic tool.[9,16] Numerous studies have been conducted to improve the accuracy of acute appendicitis diagnosis.[17] Clinical scoring systems have been developed to reduce the number of patients requiring surgical intervention and to distinguish between delayed and uncomplicated appendicitis.[6] In their study, Kariman et al. demonstrated that inflammation severity increases in parallel with higher Alvarado scores.[18] Among patients presenting to the clinic with acute abdominal pain, the rate of acute appendicitis diagnosis was 93% for those with an Alvarado score of 7 or higher, compared to 26% for those with a score below 7. Our findings align with the literature, showing that the Alvarado score is statistically significant in diagnosing acute appendicitis (p=0.027). The Mannheim Peritonitis Index, as it is not specific to appendicitis, was not utilized in this study.[11] In this study, a simple intraoperative peritonitis severity scoring method was employed to macroscopically assess the intensity of inflammation. This scoring system categorizes peritonitis severity into four groups: minimal changes, limited necrosis without perforation, peritonitis with perforation, and limited peritonitis.[12] Dumlu et al. reported that, despite achieving statistical significance, no strong correlation was found with the peritonitis severity score.[17] In our study, patients were assigned scores of 0, 1, 2, or 3 based on laparotomy findings. A score of 0 was given to patients without appendicitis, 1 to those with increased vascularity, 2 to those with perforation, and 3 to those with phlegmonous findings. These scores were found to be statistically significant when compared with the Alvarado score.

The Ohmann scoring system is a straightforward tool used in diagnosing acute appendicitis. In a study conducted by Zielke et al., the Ohmann scoring system was shown to be effective in supporting the diagnosis of acute appendicitis.[19] In our study, a statistically significant difference was observed when comparing the Alvarado and Ohmann scores. However, when evaluated against histopathological data, the Ohmann score did not reach statistical significance (p=0.807). In another study, the Ohmann score was found to be more effective in excluding the diagnosis of appendicitis.[20] In our study, no statistically significant correlation was observed between the intraoperative severity score and WBC count (p=0.384). We suggest that a low Ohmann score may help exclude the diagnosis of appendicitis, whereas a high Ohmann score may indicate the need for further diagnostic evaluation.

WBC counts were evaluated in relation to the scoring systems, a statistically significant association was observed with the Alvarado score, whereas no significant association was found with the Ohmann score. These findings are consistent with those reported in the literature.[6,19]

Yılmaz et al., aimed to evaluate 2 of the current scoring systems with respect to accurate diagnosis of the disease and indication of inflammation severity. A total of 105 patients diagnosed with acute appendicitis were included in the study. Subsequent to Alvarado and Ohmann scoring, ultrasonography image was obtained and appendectomy was performed. A unique intraoperative severity scoring system was used to measure severity of inflammation and to compare Alvarado and Ohmann scoring system results to assess accuracy of predictive value for acute appendici-

tis. Moderate positive correlation was found between Alvarado score and Ohmann score (r=0.508; p<0.001). Rate of Alvarado score successfully predicting diagnosis of acute appendicitis based on histopathological results was statistically significant (p=0.027), while rate of Ohmann score was not statistically significant (p=0.807). Correlation between both scores and grading of inflammation performed during the operation was weak, but statistical significance was observed between Alvarado scoring system and intraoperative severity scoring (r=0.30; p=0.002). No statistical difference was observed between Ohmann scoring and intraoperative severity scoring (r=0.09; p=0.384). In conclusion, Alvarado score is better able to predict acute appendicitis and provide an idea of severity of inflammation. Ohmann score is more useful to provide guidance and eliminate acute appendicitis from consideration when conditions are more uncertain and obscured.[21,22]

In our study, ultrasonography (USG) demonstrated a specificity of 92.86% and a sensitivity of 80.22% when compared to histopathology results. The concordance of USG with final histopathological findings was found to be 48.3%. This may be attributed to the subjective nature of both ultrasonographic and pathological evaluations. Our findings are consistent with the data reported in the literature.[23]

We also believe that there is no significant correlation between the Ohmann score and the severity of inflammation. In cases where appendicitis cannot be definitively diagnosed, additional scoring systems may aid in clarifying the diagnosis. The Alvarado scoring system is a reliable tool for appendicitis, as it provides information on the severity of inflammation and is simple and easy to apply. Numerous studies have shown that the Ohmann scoring system is more effective for excluding acute appendicitis than for confirming the diagnosis.[19] As our study is a single-center study, we believe that further multi-center, prospective studies with larger patient populations are needed.

Disclosures

Ethics Committee Approval: Ethical approval for the study was granted by the Ethics Committee of the S.B.U Van Training and Research Hospital (No. 2019/16, Date: 22/08/2019).

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The relationship between gastric wall thickness and age, gender, body mass index in patients undergoing laparoscopic sleeve gastrectomy

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ABSTRACT

Introduction: The most feared complication of sleeve gastrectomy is the development of leakage from the gastrectomy line. The aim of this study is to determine the range of gastric wall thickness in the fundus, corpus and antrum and to provide ideas that may help minimize complications that may occur after laparoscopic sleeve gastrectomy.

Materials and Methods: 101 consecutive patients who underwent sleeve gastrectomy surgery for obesity and severe obesity between 2017 and 2018 in this study were analyzed. Sleeve gastrectomy specimens were fixed in 10% formol solution. Sections were taken from the antrum, corpus and fundus and stained with hematoxylin and eosin. Measurements were made between the serosa and mucosa pili at five different points of each preparation. Results from these five different sites were averaged and recorded.

Results: Our study was conducted on a total of 101 cases, 79 (78.2%) women and 22 (21.8%) men. Mean age is 38.79±10.34 (61-19) years. Body mass index (BMI) ranged between 36.4kg/m2 and 64.9kg/m2 with a mean of 46.07±5.55kg/m^2. While 76 (75.2%) of the patients had a BMI level below 50kg/m^2, 25 (24.8%) had a BMI level of 50kg/m^2 and above. Gastric wall thicknesses of 101 patients who underwent sleeve gastrectomy were measured at antrum, corpus and fundus localizations and classified according to gender, age, and BMI. As a result of the statistical analysis, results obtained between the groups according to gastric wall measurements were not statistically significant ($p>0.05$). In our study, no statistical differences were found between gastric wall thickness and age, gender, and BMI.

Conclusion: Accurate determination of stomach wall thickness will help prevent complications that may result in death.

Keywords: Sleeve gastrectomy, gastric wall thickness, obesity

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Introduction

In the treatment of obesity, surgical treatments are used when the effectiveness of medical treatments is limited.[1,2] Today, laparoscopic sleeve gastrectomy (LSG) is frequently preferred in bariatric surgery.[2] Although at first glance LSG may give the impression of a deceptively simple surgical procedure, it is a surgical method that is open to significant complications that may have serious negative consequences for the patient when they occur during and after surgery. One of the most important of these complications is stapler line leakage.[3] There are many reasons for stapler line leakage after LSG. Further studies are needed to determine these reasons and find solutions.[4,5] Some of the reasons for stapler line leakage are stapler selection that is not compatible with the thickness of the stomach wall, insufficient duration of tissue compression, or inappropriate stapler pressure. The leakage and bleeding rates reported after bariatric procedures performed using stapler devices range from 0.4% to 4%.[1] The objectivity of stapler selection has not yet been fully established. This is because there is no available method for objective measurement of tissue thickness before cartridge selection. The aim of this study is to determine the range of gastric wall thickness in the fundus, corpus and antrum and to provide ideas that may help minimize complications that may occur after LSG.

Materials and Methods

Ethics committee approval was received for the study from the local clinical research ethics committee with decision number HNEAH KAEK 2019/KK/15. Informed consent was obtained from all individual participants included in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

G Power 3.1 program was used to calculate the number of samples and perform power analysis. Data from Huang R and Gagner M's study titled 'A thickness calibration device is needed to determine staple height and avoid leaks in laparoscopic sleeve gastrectomy' were used as reference. Mean and standard deviation values were given for stomach wall thickness in female and male patients who underwent LSG. The effect size of stomach wall thickness was calculated as (d:0.5). It was determined that at least 46 samples should be studied with 80% power and 20% alpha error in the analysis.

We included 101 patients who underwent consecutive sleeve gastrectomy surgery for obesity and between 2017 and 2018 in our clinic. Resected gastric antrum, corpus and fundus gastric wall thicknesses were measured under microscope and recorded. Pathology preparations were analyzed.

It was decided that the patients required surgery according to the criteria specified in the Medical Procedures Directive of the Ministry of Health. After the preoperative blood tests and radiological imaging were completed, internal medicine, pulmonology, endocrinology, cardiology, psychiatry and anesthesia consultations were routinely performed. Gastroscopic examinations were performed routinely. Patients who did not have mass lesions, ulcers or gastritis at the end of gastroscopic examination were included. Patients with gastritis and ulcer problems were included in the study if they had normal gastric mucosa during the control gastroscopic examination performed after medical treatment. Preoperative breathing exercises and prophylactic thromboembolism treatment were performed.

All operations were performed by surgeons with experience in bariatric surgery working in our clinic. The procedure was performed in the French position with the patients in reverse Trendelenburg position and using the five trocar method. Starting from the prepyloric area of approximately 3-4 cm, the stomach was mobilized by cutting the gastrocolic and gastrosplenic ligaments with 5 mm ligasure. A 38 Fr orogastric tube was placed. After the resection was completed, the specimen was removed and sent to the pathology laboratory.

Sleeve gastrectomy specimens were fixed in 10% formol solution overnight and subjected to routine tissue follow-up in the pathology laboratory. A 0.5 cm wide, 2 cm long piece sampling of the gastric wall layers was taken from the antrum, corpus, and fundus at 1 cm from the gastric staple line. After tissue tracing, the sections were embedded in paraffin blocks and 7 micron sections were taken. The sections were stained with hematoxylin and eosin, and serosa and mucosa borders were determined under a microscope by a single pathologist. The same pathologist made measurements full thickness specimen between serosa and mucosa pili at five different points in each preparation (Fig. 1). Due to the variable pili folds of the mucosa, the results obtained from five different regions were averaged and recorded.

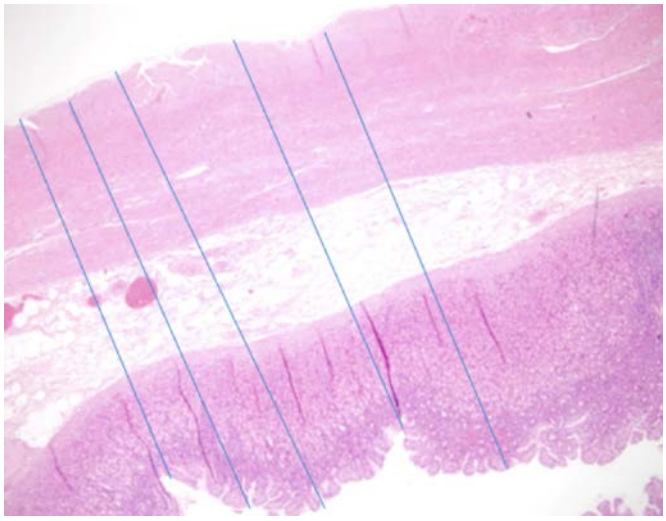

Figure 1. Measuring the full thickness of the gastric antrum wall of a male patient with a body mass index of 42kg/m^2.

Statistical Analysis

IBM SPSS Statistics 22 (IBM SPSS, Türkiye) program was used for statistical analyses while evaluating the findings obtained in the study. The suitability of the parameters to normal distribution was evaluated by Shapiro Wilks test and it was determined that the parameters were suitable for normal distribution. In addition to descriptive statistical methods (mean, standard deviation, frequency), Student's t test was used for comparisons of parameters showing normal distribution according to gender in the comparison of quantitative data. Continuity (Yates) Correction was used for comparison of qualitative data. Significance was evaluated at p<0.05 level.

Results

The study was conducted on a total of 101 patients, 79 (78.2%) women and 22 (21.8%) men. Mean age is 38.79±10.34 (18-61) years. BMI levels ranged between 36.4kg/m^2 and 64.9kg/m^2 with a mean of 46.07±5.55kg/m^2. While 75.2% of the patients had a BMI level below 50kg/m^2, 24.8% had a BMI level of 50kg/m^2 and above (p<0.05).

The distribution of BMI and age groups by gender is given in Table 1. Accordingly, 40.9% of men had a BMI level of 50kg/m^2 and above, which was higher than that of women (20.3%) but not statistically significant (p>0.05). The proportion of men over 40 years of age (63.6%) was statistically significantly higher than women (35.4%) (p:0.033).

Fundus, corpus, and antrum thicknesses according to gender and BMI are given in Table 2. There was no statistically significant difference between the fundus, corpus, and antrum thicknesses in both male and female patient groups, in those with a BMI below 50kg/m^2 and in those with a BMI of 50kg/m^2 and above (p>0.05).

Table 1. Assessment of body mass index and age by gender

	Woman, n (%)	Man, n (%)	p
BMI (kg/m^2)			
<50	63 (79.7)	13 (59.1)	0.088
≥50	16 (20.3)	9 (40.9)	
Age (years)			
≤40	51 (64.6)	8 (36.4)	0.033*
>40	28 (35.4)	14 (63.6)	

Continuity (yates) correction; *p<0.05; BMI: Body mass index.

Table 2. Evaluation of fundus, corpus, and antrum thicknesses according to gender and body mass index

Thickness (mm)	BMI<50 kg/m^2 Mean±SD	BMI≥50 kg/m^2 Mean±SD	p
Woman			
Fundus	5.54±1.57	6.16±1.24	0.144
Corpus	6.4±1.34	6.84±1.27	0.238
Antrum	6.09±1.54	6.78±1.51	0.115
Man			
Fundus	5.82±0.71	5.91±1.55	0.847
Corpus	6.46±1.62	6.42±1.46	0.954
Antrum	6.4±1.53	6.22±0.79	0.753

Student t test; BMI: Body mass index; SD: Standard Deviation.

Both male and female patients were divided into age groups as below 40 years and above 40 years. The results of gastric fundus, corpus, and antrum measurements of female and male patients according to age groups are given in Table 3. There was no statistically significant difference in fundus, corpus, and antrum thicknesses between age groups in both men and women (p>0.05).

Both male and female patients were separately divided into two groups as BMI>50kg/m^2 and BMI≥50kg/m^2 and gastric fundus, corpus and antrum thicknesses were measured (Table 4). No statistically significant difference was found between the fundus, corpus and antrum thicknesses of women and men in both groups of patients with BMI levels below and above 50kg/m^2 (p>0.05).

Table 3. Evaluation of fundus, corpus, and antrum thicknesses in sexes according to age groups separately

Thickness (mm)	Age ≤40 years Mean±SD	Age >40 years Mean±SD	p
Woman			
Fundus	5.63±1.44	5.73±1.69	0.784
Corpus	6.57±1.26	6.33±1.46	0.443
Antrum	6.29±1.61	6.11±1.46	0.612
Man			
Fundus	5.77±0.80	5.90±1.27	0.805
Corpus	6.0±1.31	6.7±1.61	0.310
Antrum	6.4±1.1	6.28±1.37	0.843

Student t test; SD: Standard Deviation.

There were no significant statistical differences between the fundus-corpus, corpus-antrum, and fundus-antrum wall thicknesses of 101 patients that underwent sleeve gastrectomy whose mean gastric wall thicknesses were calculated (p=0.7 p=0.3 p=0.5, respectively) (Fig. 2).

Discussion

Today, despite the increasing experience in LSG applications in bariatric surgery, the number of complications including staple line leaks remains constant and solutions are still being sought to prevent such complications.[4] There is still limited data on the optimal size of linear staples to be selected according to gastric wall thickness in LSG.[6] In terms of staple and bariatric procedures, Hazem

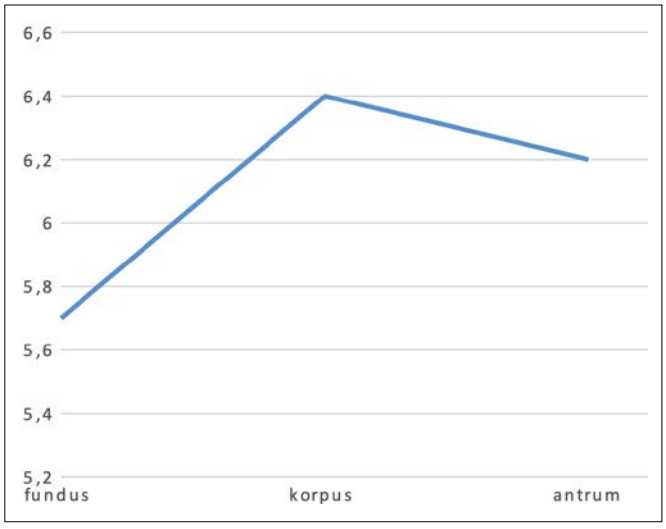

Figure 2. Graphic of mean gastric fundus, corpus and antrum wall thickness.

Table 4. Evaluation of fundus, corpus, and antrum thicknesses in body mass index groups separately according to gender

BMI (kg/m²) Thickness (mm)	Woman Mean±SD	Man Mean±SD	p
<50			
Fundus	5.54±1.57	5.82±0.71	0.328
Corpus	6.4±1.34	6.46±1.62	0.876
Aantrum	6.09±1.54	6.4±1.53	0.510
≥50			
Fundus	6.16±1.24	5.91±1.55	0.661
Corpus	6.84±1.27	6.42±1.46	0.464
Antrum	6.78±1.51	6.22±0.79	0.243

Student t test; BMI: Body mass index; SD: Standard Deviation.

Elariny was the first to measure gastric wall thickness at three different points in patients who were operated on. He demonstrated that the gastric tissue was thickest in the pyloric region and thinnest in the fundus.[7]

Rawlins et al. measured the wall thickness of resected sleeve gastrectomy specimens and showed that gastric wall thickness was significantly different in the antrum, corpus, and fundus. They found that the gastric wall in the antrum was statistically thicker in men than in women. They observed that BMI affected the antrum wall thickness only in those with a BMI above 50kg/m². In the light of these data, they concluded that a thicker staple cartridge should be used in the antrum.[8] In our study, no significant statistical difference was found in the gastric antrum corpus and fundus region according to gender and BMI.

Van Rutte et al. measured the wall thickness of resected sleeve gastrectomy specimens at 5 different points along the main line in 33 patients with a mean age of 42 years. Their measurements were based on the pressure after flattening the gastric folds with finger pressure and subtracting the weight pressure of the gastric specimen. The mean compression pressure was 2.80g/m², 2.5 times lower than previous studies. The gastric antrum was thicker than the fundus and there was a significant difference in gastric wall thickness. As a result, it was reported that the use of a purple cartridge in the gastric antrum and corpus and a gold cartridge in the fundus may be appropriate.[9]

Huang et al.[10] found that the gastric antrum was the thickest and the gastric fundus was the thinnest in both sexes. When evaluated in terms of gastric wall thickness and

appropriate staple use, 16.55% of female patients were found to be suitable for black cartridge use in the gastric antrum region. They emphasized that there is no standard method for measuring gastric wall thickness today.[7] For this reason, in our study, we planned to measure gastric wall thickness under a microscope, which we think is a more sensitive measurement method.

According to some studies, gender is a factor affecting gastric wall thickness.[7,8,10] In Rawlins' study, gastric antrum wall thickness was found to be statistically thicker in male patients than in female patients. In addition, it was shown that gastric wall thickness was increased in patients with BMI≥ 50kg/m^2.[8] In some other studies, a significant relationship between BMI and gastric wall thickness could not be demonstrated.[7,9,10]

Complete knowledge of stomach wall thickness enables better stapler use. Thus, it is one of the factors that can reduce the staple line leakage rate. There are also studies on preoperative measurement of gastric wall thickness by ultrasonography (USG) and computed tomography (CT).[11,12] In a study by Yazar et al. using preoperative USG and pathologic measurements of postoperative gastric specimens, it was concluded that gastric antrum wall thickness was not related with gender or BMI, but gastric wall thickness increased in patients with gastritis.[11] Unlike our study, only antrum wall thickness was measured in this study.[11] The part of the study in which pathologic measurements were performed used the same method technically as our study. However, the study did not mention how gastric mucosa folds were standardized. Since we realized that the most variable gastric wall layer in our study was the mucosa, we measured the mucosa layer from 5 different points and averaged it in the histopathological examination. Similarly, no relationship was found between gender, BMI, and stomach wall thickness. Pickhardt and Asher found no significant relationship between antral thickness and gender in their study in which gastric wall thickness was measured in the portal venous phase, axial sections and using an electronic ruler to obtain the actual wall thickness size with oral and intravenous contrast-enhanced CT.[12] Similar to this study, there was no statistical relationship between antrum wall thickness and gender in our study.

According to the results of the study conducted by Booker et al., gastric fundus wall thickness was found to be significantly thicker in men than in women, but no significant difference was found between the groups in terms of age and BMI.[13] In our study, when men and women were evaluated in terms of gastric fundus wall thickness, no statistically significant difference was found, although technical measurements were similar to Booker et al.[13] In the study by Larsen, gastric wall thickness measured by endoscopic ultrasound was not correlated with BMI. In addition, no difference was observed between antrum, corpus, and fundus. In addition, the thickest measured gastric localization in patients with obesity was recorded as fundus and the thinnest measured as corpus.[14] In our study, no significant results were found in terms of BMI and age and gastric wall thickness.

The limitation of our study is the stomach wall thickness was measured as full thickness. Gastric mucosa thickness fluctuates due to gastric folds. For this reason, we made measurements from five different regions. It may also be an option to take measurements between the muscularis propria and serosa, where more stable measurements can be made from the stomach wall layers. We think that similar studies need to be conducted in larger patient groups.

Conclusion

Acurate determination of the gastric wall thickness will help to avoid complications that may result in mortality. In our study, no statistically significant difference was found in antrum, corpus and fundus wall thickness measurements according to gender, age and BMI. Further studies on gastric wall thickness are needed. We think that this study may contribute to the relationship between staplers, which are frequently used in bariatric surgery, and stomach wall thickness.

Disclosures

Ethics Committee Approval: Ethics committee approval was received for the study from the Haydarpasa Numune Training and Research Hospital Ethics Committee with decision number HNEAH KAEK 2019/KK/15 (Date: 19/02/2019).

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Original Article

Weight loss outcomes of gastric balloon placement vs. intragastric botulinum toxin-a injection: A retrospective analysis

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ABSTRACT

Introduction: This study investigates the effectiveness of intragastric balloon placement (IGBP) and intragastric botulinum toxin-A injection (IGBTI) on weight-loss parameters in overweight and obese patients.

Materials and Methods: The study included 165 overweight and obese patients (matched for age and gender) treated with IGBTI (n=123) or IGBP (n=42). The patients' anthropometric data, such as total weight loss (TWL) and body mass index loss (BMIL), were evaluated and compared retrospectively in the first, third, sixth, and twelfth months after the intervention.

Results: Mean age, TWL, and BMIL values at all follow-up points in patients with IGBP were significantly higher than in patients with IGBTI (p<0.001). Similarly, the BMIL of patients who underwent IGBP at the end of the first, third, sixth, and twelfth months was significantly higher than the BMIL of patients who underwent IGBTI (2.54±0.20 vs. 1.80±0.13, p=0.002; 3.8±0.24 vs. 2.41±0.18, p<0.001; 4.19±0.45 vs. 2.38± 0.21, p<0.001; 4.19± 0.45 vs. 1.27±0.21, p<0.001; respectively). At the end of twelve months, 97 (68%) patients with IGBTI lost weight, while weight loss was observed in 35 (81.5%) patients with IGBP.

Conclusion: Significant decreases in weight and BMI were observed in patients after both IGBP and IGBTI. Based on TWL and BMIL values, we conclude that IGBP is superior to IGBTI.

Keywords: Intragastric balloon placement, intragastric botulinum toxin-a injection, endoscopic weight loss treatment, obesity

Introduction

Obesity is a global public health problem that causes an increase in the prevalence of some diseases, such as type 2 diabetes, coronary heart disease, sleep apnea, and stroke.[1] As per the 2023 World Obesity Atlas report, 38% of the world's population presently falls into the categories of overweight or obese, exhibiting a body mass index (BMI) exceeding 25 kg/m^2.[2] Projections indicate that by 2035, the global prevalence of overweight and obesity is expected to climb to 51%, showing the trajectory of the obesity epidemic. The economic impact of obesity and related disorders on the global economy was 1.96 trillion US dollars, which contributed to 2.4% of the total gross domestic product (GDP) in 2020. These numbers are estimated to double by 2035 with an economic impact of 4.32 trillion US dollars, contributing to 2.9% of total GDP.[2]

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Even a 5-10% reduction in body weight is significant for treating obesity and related diseases.[1] The treatment options are lifestyle modifications, pharmacological treatments, and bariatric surgery to reduce the excess weight of individuals with obesity.[3] However, permanent weight loss is often tricky with lifestyle changes and pharmacological treatment alone. Therefore, invasive weight loss treatments have become the primary method of treatment for severe obesity.[4] The most effective weight loss intervention for obesity is bariatric surgery.[5] Bariatric surgery achieves better long-term weight loss and reduction of comorbidities[6] and is mainly indicated for patients with a Body Mass Index (BMI) over 35 kg/m^2. Bariatric surgery is more costly and more invasive and, therefore, might be less preferable for some groups of patients.[7] For an intermediate group of patients who do not respond to medical treatment and are not suitable for or do not want to have a bariatric procedure; new endoscopic techniques have emerged in recent years that offer less invasive and more cost-effective options. These methods include intragastric balloon placement (IGBP), intragastric botulinum toxin-A injection (IGBTI), transpyloric shuttle, transoral gastroplasty, transoral endoscopic restrictive implant system, duodenal-jejunal bypass liner, and gastric electrical stimulation.[8-10]

IGBP is a safe option for class I obesity and is also used as a bridging procedure for patients with severe obesity before bariatric surgery.[11] The gastric balloon causes satiety by reducing stomach capacity and slowing gastric emptying due to its space-occupying effect. A systematic review of IGBP reported that patients treated with IGBP lost 13.16% of their total body weight (TBWL) in 6 months.[12] In another review, TBWL was 9.7% in the first six months, and the effectiveness of IGBP decreased after six months.[11] However, the primary limitation of IGBP therapy is the common occurrence of weight gain, which is thought to result from the necessary removal of the balloon.[13,14] The most common side effects associated with IGBP range from simple reactions such as nausea, vomiting, and abdominal pain to more severe pancreatitis and stomach perforation.[15,16]

Botulinum toxin A (BTxA) is a neurotoxin produced by the bacterium Clostridium botulinum that decreases smooth and striated muscle contractions by preventing the release of the neurotransmitter acetylcholine from the axon terminals of the neuromuscular junctions by blocking synaptic vesicles. It is applied in a wide variety of different medical situations, such as strabismus, cervical dystonia, achalasia, anal fissure, and hyperhidrosis.[17] The application of BTxA in treating obesity is rooted in its potential to affect the functioning of the stomach muscles. BTxA injections reduce gastric emptying, trigger an extended fullness, and decrease the appetite by hindering the muscles' contractions in the stomach's antrum and corpus. However, given conflicting research results on IGBTI, it remains a controversial approach to weight loss.[18]

Few studies have performed comparative analyses of IGBP and IGBTI. Therefore, in this article, we investigate the effectiveness of IGBP and IGBTI in individuals with overweight and obesity during the 12-month post-intervention period. By understanding the potential benefits and drawbacks of these endoscopic treatments, we aim to contribute valuable insights into the evolving landscape of obesity management, offering patients and healthcare providers a nuanced perspective on the available options.

Materials and Methods

The patients who had intragastric balloon placement (IGBP) or intragastric botulinum toxin-A injection (IGBTI) for treatment of overweight and obesity who were prospectively followed up for at least 12 months between January 2018 and October 2022 were analyzed retrospectively for this study. A cohort of 123 patients had IGBTI, and 42 had IGBP. This study was conducted per the tenets of the Declaration of Helsinki, and written informed consent was obtained from all subjects and approved by the local ethics committee (TUTF-GOBAEK 2024/219).

Endoscopic weight loss treatments were not applied to patients under the age of eighteen, elderly patients aged 65 and above, female patients who were pregnant or lactating, patients with myopathy or neuromuscular disorders, patients with a history of hypersensitivity to BTxA, patients with cardiovascular disease, and those with psychiatric disorders. Further, IGBTI or IGBP were not performed if gastric ulcers, tumors, erosive gastritis/esophagitis, hiatal hernia, or food residues were found during endoscopy. Patients were not under any anticoagulant or antiaggregant treatments. Retrospective data were retrieved from the patients' files, including sociodemographic, anthropometric, procedural details, and weight loss parameters. Patients lacking follow-up data were excluded from the study.

The indication criteria for both procedures were the same: age between 18 and 65 years and body mass index (BMI)>25 kg/ m^2. Body weight and height were measured, and BMI was calculated before the procedures [body weight (kg)/ height (m^2)]. Body weight and BMI were measured in the first, third, sixth, and twelfth months. Patients' complaints related to the procedures were collected during the follow-ups.

IGBTI Procedure

After 8–12 hours of fasting, the patients underwent upper GI endoscopy under sedation. As mentioned above, the first step was to evaluate endoscopic findings that might complicate further BTxA injection or IGB placement. AbobotulinumtoxinA (Dysport® 500 IU Ipsen Pharmaceuticals, France) was injected in two different doses, 250 IU and 500 IU. Each BTxA flacon was diluted with 20 ml of 0.9% saline and 0.1 ml of blue dye. Injections were administered at 10 points in the gastric antrum and 5 points in the corpus and the fundus, each containing 1 ml of prepared solution using a sclerotherapy needle.

IGBP Procedure

The patients fasted 8-12 hours before the procedure and received sedation for upper GI endoscopy. The primary step was to ensure that no anatomical or endoscopic pathology would prevent placing a space-occupying device in the stomach. The endoscope was removed to advance the balloon introducer manually to the stomach and reintroduced to inflate the balloon under direct vision of the scope. Two types of intragastric space-occupying devices were used: MedSil® and Spatz®. The balloon was inflated with 550 ml saline and 5 ml of blue dye for both devices. After the inflation was completed, the adapter was removed, and the stomach was evaluated for any leak of blue dye or bleeding. No adjustments were made to any patient who underwent Spatz®.

Patients were observed in the endoscopy unit before discharge for 30 to 60 minutes after they emerged from sedation after the procedure for both procedures. Patients were referred to a dietitian immediately after the endoscopic procedure. At discharge, a proton pump inhibitor (PPI), an anti-emetic, and antispasmodic pills were prescribed. The first week's nutrition mainly consisted of a liquid diet, which was later followed by a reduced-calorie diet supported by a high-protein, low-carbohydrate, and low-fat supplement advised by the dietician (1100–1250 kcal/ day). The patients were advised to exercise daily for 30 to 45 minutes. The patients were reviewed in the bariatric outpatient clinic every month to assess their progress, including weight loss and any adverse side effects, for six months.

Statistical Analysis

Statistical evaluation was performed using SPSS 20 statistical software. The Kolmogorov-Smirnov test was used to assess the normality of continuous data. Descriptive statistics are presented as mean, standard error, minimum and maximum values for continuous variables, and frequency (n) and percentage (%) for categorical variables. Fisher's Exact test was used to compare categorical data, and the Mann-Whitney U test and independent samples t-test were used for comparisons of continuous variables between groups, based on distribution characteristics.

To assess the changes in weight-related parameters (TWL, %TWL, BMIL, %EWL) over time and between treatment groups, a mixed-design ANOVA (also known as split-plot ANOVA) was applied. This approach allowed us to evaluate both within-subject effects (changes over time within the same group) and between-subject effects (differences between the IGBTI and IGBP groups). Where appropriate, post-hoc pairwise comparisons were conducted with Bonferroni correction. Statistical significance was set at $p<0.05$.

Results

Patient Demographics

The average age was 36.39±0.89 years (range: 18–61) for the IGBTI group and 38.42±1.65 years (range: 18–62) for the IGBP group. Of the 165 patients, 90.2% (n=111/123) in the IGBTI group and 86% (n=36/42) in the IGBP group were female. Baseline mean weight, BMI, excess BMI, and excess weight were significantly higher in IGBP patients compared to IGBTI patients ($p<0.001$). The average balloon placement duration in the IGBP group was 9.54±3.14 months. Demographic characteristics are summarized in Table 1.

Overall Weight Loss Outcomes

In both groups, weight, BMI, excess BMI, and excess weight showed significant reductions from baseline at all follow-up intervals ($p<0.001$). Compared to the IGBTI group, IGBP patients had significantly greater reductions

Table 1. Distribution of demographic and anthropometric data of patients

	IGBTI (n=123) Mean±S.E (Min-Max)	IGBP (n=42) Mean±S.E (Min-Max)	p
Gender			
Female, n (%)	111 (90.2%)	36 (86%)	0.446¥
Male, n (%)	12 (9.8%)	6 (14%)	
Age (years)	36.39±0.89 (18-61)	38.42±1.65 (18-62)	0.177*
Height	164.78±0.62 (152-189)	166.52±0.62 (152-189)	0.097£
Body Weight	86.29±1.21 (65-136)	100.28±4.61 (72-270)	<0.001£
BMI	31.71±0.36 (24-48)	36.07±1.39 (29-88)	<0.001£

Normally distributed numerical data are presented as mean±standard deviation with range values, categorical data are presented as number (percentage) values. IGBP: Intragastric Balloon Placement; IGBTI: Intragastric Botulinum Toxin-A Injection; BMI: Body Mass Index. *Independent sample t test, ¥Fisher's Exact test, £ Mann-Whitney U test.

in weight and BMI, and higher BMIL and %TWL values across most follow-up points (p=0.003 for weight, p=0.006 for BMI, p<0.001 for BMIL, p<0.001 for %TWL). Exceptions included BMIL between 3 and 6 months (p=0.313) and %TWL in the first month (p=0.051), which did not differ significantly.

At 12-month follow-up, 37.3% (n=46/123) of IGBTI patients had not lost any weight, compared to only 19% (n=8/42) in the IGBP group.

The %EWL values also differed significantly between groups at the 1st, 3rd, and 6th months (p=0.002 for each interval), but not at the 12th month (p=0.088). Additionally, there was no significant difference in %EWL change between groups over time (p=0.987). Full details of the weight-related parameters are provided in Table 2.

Subgroup Analysis by Balloon Type

Among patients treated with IGBP, MedSil® remained in the stomach for an average of 5.94±1.43 months, while Spatz® remained in place for 12 months (p<0.001, Table 3). At the 6-month follow-up, there were no significant differences between the two balloon types in TWL, %TWL, %EWL, or BMIL. However, by the 12th month, Spatz® significantly outperformed MedSil® in all these parameters (TWL: p<0.001, %TWL: p<0.001, %EWL: p=0.002, BMIL: p<0.001). Patients with MedSil® also showed significant decreases in all weight-related parameters between months 6 and 12 (p<0.001), indicating weight regain following removal.

Correlation Analyses

There was a weak positive correlation between patients' initial weight, excess weight, and BMI and their weight loss outcomes. In contrast, a strong positive correlation was observed between weight loss and the duration of IGB placement. A moderate positive correlation was also found between %EWL and balloon duration (Table 4).

In the IGBTI group, almost no correlation was found between the amount of BTxA administered and most weight loss parameters, except for TWL and BMIL at the 6-month interval, where significance was observed (p=0.002 for both). However, the percentage of BMI loss (%BMIL) did not differ significantly between the 250 IU and 500 IU dosing groups at any time point (Table 5).

Discussion

This study is one of the few studies comparing IGBTI and IGBP for weight loss. IGBP was superior to IGBTI in the amount and duration of weight loss, but IGBTI was also effective for weight control in different degrees of obesity. However, almost 40 % of the patients did not lose weight after IGBTI. Another interesting finding was the absence of a consistent correlation between the amount of BTxA applied and the weight loss outcomes in different intervals.

The frequency of proceeding to further obesity treatments, such as bariatric surgery, after failed lifestyle interventions and pharmacological therapy is low, with only 1% of these individuals undergoing weight-loss surgery.[19] Therefore, there is a significant unresolved problem for

Table 2. Comparison of weight parameters in consequent follow-up intervals of IGBTI and IGBP groups. Data are given as Mean±S.E (Min-Max)

	IGBTI		IGBP		p£		IGBTI		IGBP		p£
Weight						BMI					
0	86.29±1.21	(65-136)	100.28±4.61	(72-270)	p<0.001	0	31.71±0.36	(24-48)	36.07±1.39	(29-88)	p<0.001
1 m	81.35±1.14[a]	(59-128)	93,14±4,59[a]	(65-263)		1 m	29.92±0.36[a]	(23-44.6)	33.41±1.42[a]	(25.4-85.9)	
3 m	79.66±11.11[a,b]	(56-122)	89.28±4.54[a,b]	(63-257)		3 m	29.31±0.35[a,b]	(21.9-40.6)	32.02±1.40 [a,b]	(24.6-83.9)	
6 m	79.69±1.08[a,b]	(58-121)	87.09±4.49[a,b]	(60-252)		6 m	29.32±0.35[a,b]	(23-42.5)	31.21±1.37 [a,b]	(23.4-82.3)	
12 m	82.76±1.18[a,c,d]	(59-128)	88.73±4.35[a,b]	(57-244)		12 m	30.43±0.36[a,c,d]	(23-42.5)	31.79±1.33 [a,b]	(22.3-79.7)	
p*	p<0.001		p<0.001			p*	p<0.001		p<0.001		
TWL						%TWL					
1 m	4.93±0.35	(0-20)	6.97±0.62	(0-22)	p<0.001	1 m	5.65±0.40	(0-25)	7.30±0.64	(0-18)	p<0.001
3 m	6.62±0.49[b]	(-4-20)	10.74±0.77[b]	(0-27)		3 m	7.51±0.54[b]	(-5-25)	11.28±0.77 [b]	(0-23)	
6 m	6.59±0.59[b]	(-8-28)	12.88±0.95[b,c]	(0-27)		6 m	7.30±0.63[b]	(-9-25)	13.45±0.90 [b]	(0-25)	
12 m	3.52±0.56[c,d]	(-1.-40)	11.27±1.23[b,c]	(-2-26)		12 m	3.89±0.59[b,c,d]	(-11-33)	11.61±1.22 [b]	(-2-27)	
p*	p<0.001		p<0.001			p*	p<0.001		p<0.001		
BMIL						%EBMIL					
1 m	1,80±0,13	(0-8)	2.48±1.35	(0-6)	p<0.001	1 m	45.82±4,41	(0-400)	50.30±3,62	(0-93)	p<0.001
3 m	2,41±0,18[b]	(-2-8)	3.88±1.70[b]	(0-8)		3 m	60.43±5,95[b]	(-27-500)	63.45±4,40 [b]	(0-107)	
6 m	2,38±0,21[b]	(-3-11)	4.09±2.97[b]	(-1-9)		6 m	56.43±6,31[b]	(-54-454)	60.16±5,74	(-5-178)	
12 m	1,27±0,21[c,d]	(-4-16)	4.17± 2.93[b]	(-1-9)		12 m	75,94±9,64	(-100-500)	97.45±22,23 [b,c,d]	(-36-404)	
p*	p<0.001		p<0.001			p*	p<0.001		p<0.001		

The parameters were analyzed within each group over time (comparing different follow-up points) and between the two groups at the same follow-up time points [m - months]. The p* value compares the same group's follow-up periods . The p£ value represents the comparison between the two groups at the exact follow-up times. IGBP: Intragastric Balloon Placement; IGBTI: Intragastric Botulinum Toxin-A Injection; BMI: Body Mass Index, TWL: Total Weight Loss; %TWL: Percentage Total Weight Loss, BMIL: Body Mass Index Loss; %BMIL: Percentage Body Mass Index Loss. Mixed Design ANOVA. Letters represent p values of different time intervals' comparisons within each other. a) p<0.05 compared to baseline, (b) p<0.05 compared to first month, (c) p<0.05 compared to third month, (d) p<0.05 compared to sixth month.

Table 3. Comparison of patients in terms of devices that occupy space in the stomach. Data are given as Mean±S.E (Min-Max)

	TWL		%TWL		%EWL		BMIL		%EBMIL	
6th Month										
Spatz®	14.00±4.34	(0-23)	14.00±4.56	(0-25)	53.24±29.76	(0-144)	5.20±0.32	(0.1-8.60)	55.27±7.17	(9-140)
Medsil®	11.33±8.05	(0-27)	11.94±7.81	(0-23)	51.83±33.87	(0-93)	4.10±0.64	[(-0.2) - 9.20]	51.47±6.17	[(-3.33) - 108]
p	0.169*	0.284*	0.886*	0.105*	0.690*					
12th Month										
Spatz®	15.84±6.65	(0-26)	15.72±6.54	(0-27)	59.36±36.80	(0-144)	5.86±0.47	(0.1-9.20)	56.05±9.50	[(-2) - 168]
Medsil®	4.94±5.22	[(-2) - 13]	5.27±5.56	[(-2) - 16]	24.44±28.96	(0-93)	1.82±0.42	[(-0.5) - 5.20]	36.68±6.34	[(-10) - 115]
p	<0.001£	<0.001£	0.002*	<0.001*	0.085*					
IGB duration (months)										
Spatz®	12.00±0.00	(12-12)								
Medsil®	5.94±1.43	(3-8)								
p	<0.001£									

%EWL: Percent Excess Weight Loss; TWL: Total Weight Loss; %TWL: Percent Total Weight Loss; IGBP: Intragastric Balloon Placement; IGBTI: Intragastric Botulinum Toxin-A Injection; BMIL: Body Mass Index Loss. *Independent samples t-test; £ Mann-Whitney U test.

this large group of patients who cannot lose weight with conservative methods. Offered as an outpatient endoscopic procedure, IGBs are intended to fill this gap effectively and safely.[20] IGBs increase satiety by affecting both stomach capacity and stretch receptors and are, therefore, a non-surgical procedure to treat obesity. IGB may be attractive to patients compared to surgical treatment because it is less invasive, repeatable, and reversible. Additionally, IGBP is a temporary method, as the prosthesis remains in the stomach cavity for a limited time.[21]

In our study, two different balloon brands —MedSil® and Spatz®—were used, and the anthropometric data of the patients were evaluated in the first, third, sixth, and twelfth at 1-, 3-, 6- and 12-months post-procedure. The corresponding TWLs were 7.14 (7.30%), 11.00 (11.28%), 13.19 (13.45%), and 11.54 (11.61%) kg, while BMILs were 2.54, 3.80, 4.19, and 4.19 kg/m^2, respectively. Although initial weight loss efficacy did not differ between the two brands, patients in the MedSil® group began to regain weight after balloon removal around 6 months, whereas those with Spatz® maintained weight loss for up to 12 months—the duration of balloon implantation. This outcome was expected, as weight regain is common once the device is removed, particularly in patients who fail to adopt lasting lifestyle changes.

Several studies have reported comparable results following IGB placement. Ribeiro da Silva et al.[21] reported a TWL of 11.94 kg and %EWL of 42.16% at 6 months. Fuller et al.[22] reported a TWL of 9.4 kg, Gaur et al.[23] and Sallet et al.[24] found a TWLs of 18.3 kg and 17.4 kg, respectively. Doğan et al.[25] documented an average TWL of 9.5 kg at the balloon removal, and 7.6 kg one-year post-removal. Similarly, Lee et al.[26] observed a mean TWL of 9.95 kg (10.76%), BMIL of 3.72 kg/m^2, and %EWL of 43.67% with a mean implantation time of 251.4 days. The 13.45% TWL observed in our IGBP group at 6 months is with the 13.16% TWL reported in the meta-analysis by Dayyeh et al.[12] According to established standards, a ≥10% reduction in total body weight maintained for one year is considered a successful outcome.[27] By the end of our study, %TWL was 15.72 in the Spatz® group and 5.27 in the MedSil® group, supporting the notion that Spatz® IGBP offers superior long-term control due to its extended residence time in the stomach.

IGBTI has also emerged as a minimally invasive endoscopic option for obesity treatment. Originally used for motility disorders such as oropharyngeal dysphagia, achalasia, esophageal spasms, anismus, rectocele, and anal fissure.

Table 4. Correlation of weight loss with some parameters

	TWL		%EWL	
	r	p	r	p
Baseline Weight	0.268	<0.001	-0.127	0.104
Excess Weight	0.206	0.008	-0.141	0.070
Baseline BMI	0.188	0.016	-0.141	0.070
Amount of BTxA	-0.034	0.706	-0.170	0.061
Age	0.002	0.976	-0.085	0.276
IGB placement duration	0.681	<0.001	0.450	0.003

(r) Pearson correlation coefficient, %EWL: Percent Excess Weight Loss; TWL: Total Weight Loss; BMI: Body Mass Index; IGB: Intragastric Balloon; BTxA: Botulinum Toxin A.

[28,29] BTxA was later applied intragastrically to target the body, fundus, and antrum, which play key roles in mechanical digestion, satiety signaling, and gastric emptying.[30,31] By impairing these functions via IGBTI, recent studies aimed to promote early satiety and delayed gastric emptying, resulting in weight loss.[32] Gui et al.[33] reported a 37.8% reduction in food intake and a 14% weight loss in rats following BTxA injection into the antrum. The first human case of IGBTI was published by Rollnik et al.[34] who observed an 8.9% weight reduction and 6.5% BMI decrease at 4 weeks post-injection Sánchez et al.[35] reported an average weight loss of 4.6 kg after 24 weeks in 52 obese patients treated with IGBTI. Similarly Albani et al.[36] found that patients lost about 4 kg at one month after receiving 500 IU of BTxA. A meta-analysis of seven studies administering 100–500 IU of BTxA found weight loss ranging from 4.9% to 9.0% over 5 to 24 weeks.[18] However, not all studies support its efficacy. Bustamante et al.[37] in a meta-analysis of four randomized controlled trials, found BTxA was not superior to placebo. Similarly, de Moura et al.[38] concluded that IGBTI was ineffective for preoperative weight loss in patients with super-obesity.

In our study, IGBTI was applied to 123 patients. The dose started at 250 IU and was later increased to 500 IU. TWL at 1, 3, 6, and 12 months was 4.93 (5.65%), 6.62 (7.51%), 6.59 (7.30%), and 3.52 (3.89%) kg, respectively. Corresponding BMIL values were 1.79 (5.64%) kg/m^2, 2.4 (7.56%) kg/m^2, 2.39 (7.53%) kg/m^2, and 1.28 (4.03%) kg/m^2, respectively. Altunel et al.[39] reported higher TWL values—7.6 kg at 3 months and 9.8 kg at 6 months—after 500 IU of BTxA, likely due to higher baseline BMI in their cohort.

BTxA is often preferred for its technical simplicity and minimal side effects,[40] though its effect typically diminishes within 3–6 months without causing permanent damage.[41] In our cohort a substantial proportion of IGBTI patients failed to respond. Specifically, 17% (n=21) did not lose weight in the first month, 23.6% (n=29) in the third month (including 5 who gained weight), and 31.7% (n=39) in the sixth month (8 of whom gained weight). By the end of the 12-month follow-up, 37.3% (n=46) of patients in the IGBTI group had not lost weight. This lack of response was not statistically associated with BTxA dose. In contrast, only one in five IGBP patients failed to lose weight, suggesting that IGBTI may carry a significantly higher risk of treatment failure. These findings highlight the critical limitation of IGBTI's clinical efficacy, especially in light of its nearly 40% non-responder rate. This underscores the need for improved patient selection and further investigation into predictors of treatment success.

Many studies have attempted to determine the superiority of different obesity treatment methods; however, few directly compare IGBTI and IGBP. Tayyem et al.[42] found that initial weight, excess weight, and BMI were higher in the IGBP than the IGBTI group. After 6 months, TWL was 9.6kg in the IGBTI group and 15.6 in the IGBP group. BMIL was 5.6 kg/m² for IGBP versus 3.2 kg/m² for IGBTI. Interestingly, %EWL was higher in the IGBTI group (59.1%) compared to IGBP (42.2%).[42] In another study, Kanlioz et al.[43] reported BMILs of 3.95 kg/m² and 1.6 kg/m² at six months for IGBP and IGBTI, respectively. Al et al.[44], showed similar trends: patients in the IGBP group lost 9.0 kg (5.0–12.0) in the first month and 19 kg (13.0–30.0) by month six, while the IGBTI group lost 6.0 kg (2.0–8.0) and 13 kg (1.0–19.0), respectively (p<0.001).

Consistent with these findings, our study demonstrated that initial weight, excess weight, and BMI were signif-

Table 5. Comparison of weight parameters of patients who had BTxA dose of 250 IU and 500 IU. Data are given as mean±S.E (Min-Max)

	250 IU		500 IU		p		250 IU		500 IU		p
Weight						BMI					
0	83.20±10.30	(65 - 120)	88.00±14.70	(65 - 136)	0.056	0	31±5.42	(25 - 42)	31±1.14	(24 - 40)	0.151
1 m	78.20±10.50	(59 - 110)	83.10±13.50	(61 - 128)	0.064	1 m	29.4±4.35	(23 - 44.6)	30.2±3.82	(24.2 - 40.4)	0.169
3 m	77.50±10.40	(56 - 106)	80.80±13.20	(58 - 122)	0.302	3 m	29.2±4.27	(21.9 - 40.6)	29.4±3.85	(23.4 - 40.4)	0.673
6 m	78.90±10.70	(59 - 113)	80.20±12.80	(58 - 121)	0.810	6 m	29.6±4.31	(23.7 - 42.5)	29.2±3.73	(23 - 42.2)	0.648
12 m	79.90±10.30	(59 - 113)	84.40±14.20	(59 - 128)	0.109	12 m	30±4.13	(23 - 42.5)	30.7±4.02	(23.7 - 42.7)	0.400
TWL						BMIL					
1 m	5.02±5.04	(0 - 20)	4.89±5.04	(0 - 19)	0.493	1 m	1.90±1.97	(0 - 8.43)	1.75±1.09	(0 - 5.32)	0.539
3 m	5.64±6.53	[(-4) - 20]	7.18±4.79	[(-4) - 20]	0.054	3 m	2.13±2.50	[(-1.56) - 8.43]	2.58±1.65	[(-1.56) - 6.24]	0.065
6 m	4.32±7.07	[(-8) - 28]	7.86±7.07	[(-5) - 22]	0.002	6 m	1.64±2.73	[(-3.13) - 10.7]	2.82±2.06	[(-1.84) - 7.02]	0.002
12 m	3.30±8.16	[(-10) - 40]	3.66±8.16	[(-8) - 21]	0.077	12 m	1.25±3.12	[(-3.91) - 15.5]	1.32±1.77	[(-2.74) - 6.70]	0.095
%TWL						%BMIL					
1 m	6±6.05	(0 - 25.3)	5.44±6.05	(0 - 14.8)	0.718	1 m	47.80±70.4	(0 - 400)	32.5±30.50	(0 - 200)	1.000
3 m	6.63±7.5	[(-4.55) - 25.3]	7.99±7.5	[(-5) - 18.5]	0.118	3 m	52.90±85.7	[(-27) - 500]	51.00±51.59	[(-25) - 300]	0.242
6 m	5.03±7.83	[(-9.09) - 25.3]	8.64±7.83	[(-6.94) - 20.4]	0.004	6 m	41.1±73.7	[(-54) - 400]	54.30±68.00	[(-12.5) - 454]	0.052
12 m	3.67±8.42	[(-11.4) - 33.3]	4.05±8.42	[(-11.1) - 19.8]	0.101	12 m	33.2±105	[(-145) - 600]	31.80±86.80	[(-78.1) - 726]	0.131

The negative values represent gains in the related parameters. BTxA: Botulinum toxin A; BMI: body mass index; TWL: total weight loss; %TWL: percentage total weight loss; %EWL: percentage excess weight loss; BMIL: body mass index loss; %BMIL: percentage body mass index loss.)

icantly higher in IGBP patients. TWL and BMIL at 1, 3, 6, and 12 months were consistently greater in the IGBP group. After the third to sixth month—when the pharmacological effect of BTxA begins to wane—the gap in TWL and BMIL between groups widened further.

A major strength of our study is the inclusion of 12-month follow-up data comparing IGBTI and IGBP in a single cohort. However, several limitations should be acknowledged. First, the study's retrospective design and exclusion of patients under 18 or over 65 years limit the generalizability of our findings. Second, the predominance of female participants precludes a reliable gender-based comparison.

Overall, both IGBP and IGBTI were associated with significant reductions in weight and BMI. However, when comparing TWL, %TWL, and BMIL, IGBP consistently outperformed IGBTI at all follow-up intervals. In the IGBTI group, weight loss declined after the third month and reversed in some cases after the sixth month—coinciding with the waning effect of BTxA. In contrast, weight loss durability in the IGBP group was strongly linked to balloon implantation duration.

These findings support the superior efficacy and sustainability of IGBP over IGBTI in endoscopic obesity treatment. The development of longer-acting balloon systems and the identification of predictors of non-response to IGBTI could help improve individualized treatment strategies in the future.

Disclosures

Ethics Committee Approval: All procedures performed in this study involving human participants followed the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the ethics committee (Date: 20/05/2024, No: TUTF-GOBAEK 2024/219).

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Changes in IL-6 and IL-37 levels before and after sleeve gastrectomy in obese patients with metabolic syndrome

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ABSTRACT

Introduction: Metabolic syndrome (MetS) is characterized as a cluster of metabolic disorders, with key components including dyslipidemia, insulin resistance, low-grade inflammation, and hypertension. Interleukins (ILs) are crucial cytokines secreted by the immune system, playing a significant role in inflammation and immune regulation. IL-37, a member of the IL-1 family (IL-1F7), is an anti-inflammatory cytokine. However, research investigating the role of IL-37 in the pathogenesis of MetS remains limited. This study aimed to evaluate plasma IL-6 and IL-37 levels in patients with MetS.

Materials and Methods: A total of 80 participants (33 males, 47 females) were included in the study. Venous blood samples obtained from individuals diagnosed with Metabolic Syndrome (MetS) (Group II, n=40) and healthy volunteers (Group I, n=40) were used for the analysis of plasma lipids, IL-6, and IL-37 levels. Among the MetS group, 20 patients underwent laparoscopic Sleeve Gastrectomy (SG) due to obesity. The total cholesterol, HbA1c, IL-6, and IL-37 levels in plasma samples collected before (Pre-SG) and after (Post-SG) the operation were compared. Plasma IL-6 and IL-37 levels were measured using a commercially available solid-phase competitive enzyme-linked immunosorbent assay (ELISA).

Results: Plasma IL-37 levels were significantly lower in Group II compared to Group I, whereas IL-6 levels were significantly higher (IL-6: Group I: 0.82±0.41; Group II: 2.06±0.5; p<0.001; IL-37: Group I: 1.47±0.51; Group II: 0.67±0.27; p<0.001). Preoperative IL-37 levels were lower compared to postoperative levels following SG, while IL-6 levels exhibited the opposite trend.

Conclusion: IL-37 may serve as a promising therapeutic target for preventing and slowing the progression of MetS. However, larger-scale, multidisciplinary studies with additional parameters are necessary to further validate these findings.

Keywords: Interleukin 37, interleukin 6, laparoscopic surgery, metabolic syndrome, obesity, sleeve gastrectomy

Introduction

Metabolic syndrome (MetS) is characterized as a cluster of metabolic disorders, primarily including dyslipidemia, insulin resistance, low-grade inflammation, and hypertension.[1] Since MetS is associated with dysfunctional adipose tissue and chronic low-grade inflammation, addressing these underlying mechanisms may provide significant benefits for its prevention and treatment.

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The development of MetS is influenced by multiple factors, including gender, age, ethnic differences, physical inactivity, diet, smoking, alcohol consumption, adipocytokines, as well as epigenetic and mitochondrial factors. Scientific evidence from experimental models and studies in both humans and animals with MetS highlights the crucial role of cytokines in the etiopathogenesis of the syndrome. Inflammatory cytokines are believed to contribute to insulin resistance and elevated plasma free fatty acids.[2,3] The discovery that precursor fat cells exhibit macrophage-like characteristics supports the hypothesis that adipose tissue is actively involved in inflammatory processes.

In healthy adipose tissue, T cells, eosinophils, and M2 macrophages produce IL-4, IL-10, and IL-13, fostering an anti-inflammatory environment that preserves insulin sensitivity. However, in obesity, M1 macrophages within adipose tissue secrete pro-inflammatory cytokines, thereby promoting inflammation and insulin resistance.[4] Additional alterations that contribute to this pro-inflammatory response include a reduction in eosinophils and regulatory T cells, as well as an increase in neutrophils, B cells, mast cells, and interferon-γ (IFN-γ)-secreting T helper (Th) 1 and cytotoxic CD8+ T cells. Scientific studies have identified key cytokines associated with MetS and its components, including tumor necrosis factor-alpha (TNF-α), IFN-γ, IL-1α, IL-1β, IL-6, IL-7, IL-8, IL-10, IL-12, IL-18, IL-21, and IL-33.[5,6]

Cytokines, which are structurally peptides or glycoproteins, play a fundamental role in modulating immune responses against foreign substances and antigens. They regulate both systemic and local inflammatory processes by facilitating intercellular communication and immune system interactions. Interleukins, a major subset of cytokines secreted by immune cells, primarily activate immune system components. By inducing the expression of proteins such as chemokines, nitric oxide synthase, and matrix metalloproteinases, interleukins are pivotal in controlling immune functions and inflammatory processes.[7-9]

IL-37, a member of the IL-1 family (IL-1F7), is an anti-inflammatory cytokine. It is secreted from various tissues at different stages of inflammation and exists in five isoforms (IL-37a, b, c, d, e). Some isoforms, however, are exclusive to specific organs: IL-37a is secreted solely from the brain, IL-37b from the kidney, IL-37c from the heart, and IL-37d from the bone marrow and testes. These isoforms undergo maturation and interact through currently unknown mechanisms involving mRNA sequencing and various enzymatic processes, ultimately forming IL-37.[10,11]

Despite its potential significance, the role of IL-37 in the pathogenesis of MetS remains poorly understood. This study is the first to evaluate IL-6 and IL-37 levels in patients undergoing sleeve gastrectomy (SG) for obesity.

Materials and Methods

Ethical Approval

The study was approved by the Biruni University Non-Interventional Ethics Committee (Decision No: 2023/79-33). It was conducted on patients diagnosed with MetS who applied to the Endocrine Clinic of Biruni University Faculty of Medicine Hospital, as well as healthy volunteers who visited the clinic for control purposes. The study was carried out in accordance with the ethical principles outlined in the World Medical Association Declaration of Helsinki (2000).

Inclusion Criteria

- Participants aged between 25 and 65 years were included
- For the patient group: diagnosis of MetS according to the NCEP ATP III criteria.
- For healthy volunteers: absence of a MetS diagnosis.
- Individuals who provided informed consent to participate in the study (for both patient and healthy volunteer groups).

Exclusion Criteria

- Were not diagnosed with MetS (for patient groups)
- Individuals with autoimmune, infectious, or malignant diseases; those taking anti-inflammatory or immunosuppressive medications; pregnant or breastfeeding women; and participants with incomplete data were excluded from the study.
- Did not consent to participate in the study or did not fall within the age range of 25-65 years (for both patient and healthy volunteer groups).

Study Group Determination

Sample size was determined using the G*Power software (version 3.1.9.4, Düsseldorf University), aiming for 80% power and an effect size of 0.7. Based on this, a minimum of 18 participants per group was calculated. A total of 80 participants were enrolled, including 40 individuals with MetS and 40 healthy controls. Of those in the MetS group, 20 underwent sleeve gastrectomy (SG) due to obesity and were evaluated both before and 6 months after surgery.

The study groups were classified as follows:

- Group I (40 individuals): Healthy volunteers
- Group II (40 individuals): Patients diagnosed with MetS. Among the patients diagnosed with MetS, only 20 underwent SG. Pre-SG (20 individuals): Patients diagnosed with MetS and obesity prior to sleeve gastrectomy. Post-SG (20 individuals): Patients diagnosed with MetS and obesity after sleeve gastrectomy (at the end of 6 months)

All participants provided written informed consent before enrollment in the study. Venous blood samples (2.5 mL) were collected from each participant into heparinized tubes.

Surgical Procedure History

The study included patients who had undergone laparoscopic sleeve gastrectomy (SG) as a surgical intervention for obesity.[12]

Analysis Method

Anthropometric measurements and blood samples were collected to assess plasma lipid levels and cytokine profiles. Plasma samples stored at -20°C were thawed in a water bath before analysis and subsequently centrifuged at 3000 rpm for 5 minutes. Changes in IL-6 (Cat. No: E0090Hu, BT LAB, China) and IL-37 (Cat. No: E1947Hu, BT-LAB, China) levels were comparatively analyzed across the four study groups. For patients with MetS who underwent laparoscopic SG, cytokine analyses were performed at the end of the 6-month postoperative period.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism 9.1.1 software. For between-group comparisons, Student's t-test was used for normally distributed variables and the Mann–Whitney U test for non-parametric data. For repeated measures within the same individuals, paired t-tests or Wilcoxon signed-rank tests were applied. Parametric data are presented as mean±standard deviation (SD), while non-parametric data are expressed as median with interquartile range (IQR). A p-value of ≤0.05 was considered statistically significant.

Results

A total of 80 participants were included in the study (33 men and 47 women). The mean age in Group I was 44.3 years (range: 27-65), while in Group II, it was 41.1 years (range: 25-65). The body mass index (BMI) was 20.88±3.1 kg/m² in Group I and 27.54±2.96 kg/m² in Group II. Plasma IL-37 levels were found to be significantly lower in Group II compared to Group I, whereas IL-6 levels exhibited the opposite trend (IL-6, Group I: 0.82±0.41; Group II: 2.06±0.5; $p<0.001$; IL-37, Group I: 1.47±0.51; Group II: 0.67±0.27; $p<0.001$).

When the results were analyzed based on gender differences, it was observed that plasma IL-37 levels were lower in men compared to women, whereas plasma IL-6 levels were lower in women compared to men. The analysis of lipid profiles (mean values) revealed that plasma triglyceride and total cholesterol concentrations were significantly elevated in the MetS group compared to the healthy group. Conversely, HDL-cholesterol (mg/dL) concentrations were significantly lower in the MetS group compared to the healthy group ($p<0.05$) (Table 1).

Our study identified four key variables that significantly influenced the improvement of MetS in patients undergoing sleeve gastrectomy (SG). These variables included total weight loss (%), body mass index (BMI, kg/m²), total cholesterol (mg/dL), and HbA1c levels at six months post-surgery. Furthermore, it was observed that all patients who underwent surgery for obesity had Type 2 diabetes mellitus (T2DM).

Pre-SG IL-37 levels were significantly lower compared to post-SG levels (IL-37, pre-SG: 0.61±0.33; post-SG: 1.65±0.47; $p<0.001$). Conversely, IL-6 levels demonstrated the opposite trend, indicating an antagonistic relationship between these two cytokines (IL-6, pre-SG: 1.97±0.38; post-SG: 0.96±0.36; $p<0.001$) (Table 2).

Table 1. Demographic data, anthropometric measurements, and IL-6 and IL-37 analysis results for patient and control groups

Variable	Control Group (Group I) (Mean±SD) (n=40)	MetS Group (Group II) (Mean±SD) (n=40)	p
Age (year)	44.3 (27-65)	41.1 (25-65)	>0.05
BMI (kg/m^2)	20.88±3.1	27.54±2.96	<0.05
HDL-cholesterol (mg/dl)	52.66± 2.09	38.4±1.29	<0.05
Total cholesterol (mg/dl)	142.22±1.87	241.16±4.53	<0.05
Triglycerides (mg/dl)	98.33±1.35	168.7±2.47	<0.05
Interluekin-6 (pg/ml)	0.82±0.41	2.06±0.5	<0.001
Interluekin-37 (pg/ml)	1.47± 0.51	0.67±0.27	<0.001

SD: Standard deviation.

Table 2. Changes in anthropometric measurements and IL-6 and IL-37 analysis before and after laparoscopic surgery for obesity

Variable	Pre-SG (Mean±SD) (n=20)	Post-SG (Mean±SD) (n=20)	p
Total Weight Loss (%)	-	25.25±4.28	-
BMI (kg/m^2)	39.75±5.44	30.03±4.92	<0.05
Total cholesterol (mg/dl)	224.56±35.77	182.43±61.68	<0.05
HbA1c	7.01±1.61	5.49±0.974	<0.001
Interluekin-6 (pg/ml)	1.97±0.38	0.96±0.36	<0.001
Interluekin-37 (pg/ml)	0.61±0.33	1.65± 0.47	<0.001

SD: Standard deviation.

Discussion

Inflammatory biomarkers play a crucial role in the etiology and progression of metabolic disorders. Several pro- and anti-inflammatory cytokines have been linked to MetS and its components (e.g., obesity, dyslipidemia, hyperglycemia); however, the combined relationship between IL-6 and IL-37 in MetS has not been extensively studied.

Interleukin-6 (IL-6) is a cytokine with both pro-inflammatory and anti-inflammatory properties, known to promote the differentiation of monocytes into macrophages.[13] The association between elevated plasma IL-6 levels and an increased risk of diabetes suggests that inflammation plays a critical role in diabetes pathogenesis.[14] Previous studies have demonstrated significantly increased serum IL-6 concentrations in individuals with MetS.[15] and in diabetic dogs compared to healthy controls.[16] In experimental models, IL-6 administration in rats has been reported to stimulate gluconeogenesis, leading to hyperglycemia and hyperinsulinemia.[17] Similarly, subcutaneous administration of recombinant IL-6 in humans has been shown to stimulate gluconeogenesis, resulting in hyperglycemia and hyperinsulinemia.[18] These findings indicate that IL-6 increases insulin resistance in adipocytes. Moreover, studies using diet-induced MetS models have shown a correlation between IL-6 levels, MetS risk factors, and cardiovascular disease.[19] Our analyses are consistent with the existing literature, demonstrating that IL-6 levels were significantly higher in the MetS group compared to the control group.

Interleukin-37 (IL-37) is an anti-inflammatory cytokine that binds to the IL-18 receptor α (IL-18Rα) to form the IL-37/IL-18Rα complex, which transmits anti-inflammatory signals. IL-37 has been detected in various inflammatory and autoimmune diseases, including rheumatoid arthritis (RA), Mycobacterium avium infection, atherosclerotic coronary disease, and Crohn's disease.[20] Through its anti-inflammatory effects, IL-37 suppresses the production

of pro-inflammatory cytokines. Scientific studies have identified key cytokines associated with MetS and its components, including TNF-α, IFN-γ, IL-1α, IL-1β, IL-6, IL-7, IL-8, IL-10, IL-12, IL-18, IL-21, and IL-33.[21]

During inflammation, IL-37 regulates the activation of multiple signaling phosphokinases. It significantly reduces the activation of pro-inflammatory signal mediators such as FAK, STAT1, mTOR, p53, p38, paxillin, Pyk2, Syk, SHP-2, and AKT. Additionally, IL-37 upregulates anti-inflammatory mediators such as the phosphatase PTEN, thereby inhibiting inflammation mediated by the PI3K, mTOR, MAPK, and FAK pathways. In summary, IL-37 expression is upregulated by pro-inflammatory stimuli, which in turn suppress inflammation through multiple pathways.[22]

IL-37 exerts its anti-inflammatory effects through both extracellular and intracellular mechanisms. However, the factors determining the preference for one mechanism over the other remain unclear. Intracellularly, the IL-37/Smad3 complex reduces inflammatory pathways and enhances the production of anti-inflammatory cytokines. Extracellularly, IL-37 binds to IL-18Rα/IL-1R8, leading to the inhibition of pro-inflammatory pathways and the activation of anti-inflammatory pathways. However, excessive binding of IL-18BP to IL-37 reduces the anti-inflammatory activity of both IL-37 and IL-18BP. Since the IL-37 precursor undergoes processing both intracellularly and extracellularly in vivo, its N-terminus exhibits significant variability, making its functional role unclear. Studies examining IL-37 isoforms with different N-terminal ends in vivo and in vitro have revealed the biological complexity of IL-37 functions.[23]

A recent study demonstrated that IL-37 treatment (1 μg/mouse) in mice improved insulin sensitivity and reduced obesity-induced inflammation in adipose tissue after 22 weeks of a high-fat diet (HFD) compared to vehicle-treated controls. IL-37 treatment likely lowers plasma insulin levels and pancreatic islet mass by activating AMPK and inhibiting mTOR.[24-26] Thus, the anti-inflammatory effects of IL-37 may help mitigate metabolic disorders associated with obesity.

A study by Moschen et al.[27] found that IL-37 expression was significantly higher in subcutaneous and visceral adipose tissue than in the liver in obese mice. Additionally, IL-37 transgenic mice fed a high-fat diet (HFD) exhibited reduced macrophage infiltration in adipose tissue, increased circulating adiponectin levels, and improved insulin sensitivity and glucose tolerance. In vitro studies have further demonstrated that recombinant IL-37 inhibits adipogenesis and activates the AMPK signaling pathway. Human studies have also reported a positive correlation between elevated IL-37 mRNA expression in adipose tissue, improved insulin sensitivity, and a lower inflammatory state. These findings suggest that IL-37 plays a crucial role in suppressing obesity-associated inflammation and insulin resistance. Our analyses are consistent with the existing literature, demonstrating that IL-37 levels were significantly lower in the MetS group compared to the control group. The findings of our study further support the potential regulatory role of IL-37 in metabolic diseases, highlighting its therapeutic potential.

Another study examined the impact of significant weight loss on the expression of IL-1F family members. The study revealed that IL-37 expression was substantially higher in subcutaneous and visceral adipose tissue than in the liver. Furthermore, weight loss following laparoscopic adjustable gastric banding surgery shifted the expression profile of the IL-1F family toward a more anti-inflammatory phenotype. Specifically, IL-1β expression significantly decreased in subcutaneous adipose tissue, whereas IL-37 expression increased.[28] These findings, along with our study results, further support the anti-inflammatory role of IL-37 in obesity-related inflammation.

This study aimed to investigate plasma IL-6 and IL-37 levels in patients with MetS. Our findings demonstrated that plasma IL-37 levels were significantly lower in the MetS group compared to the control group, whereas the opposite was observed for IL-6. Furthermore, our study identified four key variables that significantly influenced MetS improvement in patients undergoing SG: Total weight loss.(%), Body mass index (BMI), Total cholesterol levels, HbA1c levels at six months post-surgery. In conclusion, these four factors may influence the improvement of MetS in patients undergoing SG. Additionally, plasma IL-37 levels were lower pre-SG compared to post-SG due to obesity, while IL-6 levels exhibited the opposite trend, further supporting their antagonistic relationship.

Conclusion

Given the increasing prevalence of MetS with aging worldwide, effective management strategies and identification of contributing factors are crucial for reducing the global health burden. However, there is still insufficient knowl-

edge regarding the relationship between IL-37 and MetS. The activation of inflammatory signaling pathways in MetS results in alterations in circulating and tissue levels of pro-inflammatory and anti-inflammatory cytokines, leading to systemic inflammation and tissue damage. Modulating cytokine-mediated inflammation is considered a promising therapeutic approach for MetS prevention and treatment. The novelty of this study lies in the fact that IL-37 levels were analyzed for the first time before and after SG for obesity. Given its ability to regulate inflammatory, metabolic, and immune responses, IL-37 may serve as a promising therapeutic target with potential implications in metabolic disorders and cancer development. To further substantiate these findings, larger sample sizes and multidisciplinary studies with additional parameters are required to validate the potential therapeutic role of IL-37.

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Authorship Contributions: Concept – T.E., A.O.; Design – T.E.; Supervision – T.E., A.O.; Materials – A.O.; Data collection and/or processing – T.E., A.O., E.C.; Analysis and/ or interpretation – T.E., A.O., E.C., A.A.I.; Literature search – T.E., A.O., E.C., A.A.I.; Writing – T.E., E.C., A.A.I.;; Critical review – T.E., A.O.

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Letter to the Editor

Managing chilaiditi syndrome in laparoscopic surgery

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Chilaiditi syndrome is a rare condition in which a portion of the colon, typically the hepatic flexure, becomes interposed between the liver and the diaphragm.[1] This anatomical anomaly can mimic more serious conditions, such as pneumoperitoneum, on imaging and may be associated with symptoms like abdominal pain, nausea, or respiratory distress due to compression of the diaphragm.[2] In most cases, Chilaiditi syndrome is asymptomatic and discovered incidentally on radiographs or Computed Tomography (CT) scans. However, when symptoms arise or when the condition complicates surgical procedures, particularly in the upper abdomen, careful preoperative planning is essential. The syndrome can pose challenges during surgeries like laparoscopic cholecystectomy, as it alters the usual anatomical landmarks, potentially increasing the risk of bowel injury or complicating access to the liver and gallbladder.

The clinical significance of Chilaiditi syndrome lies in its potential to complicate both diagnosis and treatment of abdominal conditions. Due to the abnormal positioning of the colon between the liver and diaphragm, Chilaiditi syndrome can be misinterpreted as a more urgent pathology, such as pneumoperitoneum, leading to unnecessary interventions. In symptomatic cases, patients may present with abdominal pain, bloating, nausea, or even respiratory difficulties from diaphragmatic compression.[3] For surgeons, the condition presents additional challenges during abdominal surgeries, especially laparoscopic procedures, where altered anatomy increases the risk of bowel injury and complicates trocar placement and organ exposure. Recognizing Chilaiditi syndrome preoperatively is crucial, as it allows for appropriate planning and technique modifications to ensure safe and effective surgical outcomes.

In the management of uncomplicated, asymptomatic patients with Chilaiditi syndrome, no specific treatment is generally required.[4] Since the condition is often discovered incidentally during imaging for unrelated issues, most patients do not exhibit symptoms and can be managed conservatively.[5]

In Chilaiditi syndrome, the anatomical changes primarily involve the abnormal interposition of the colon between the liver and diaphragm, which can significantly affect the normal spatial relationship of the gallbladder. The gallbladder, typically positioned on the undersurface of the liver, may become less accessible due to the displacement of the liver and the presence of the interposed colon. This altered anatomy complicates the surgical approach, particularly during procedures like laparoscopic cholecystectomy. The liver may be positioned lower than usual, making traditional trocar placements less effective and increasing the risk of bowel injury. These changes necessitate careful preoperative imaging and intraoperative modifications

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Case

We present the case of an 84-year-old male with a history of biliary pancreatitis and cholelithiasis, who was scheduled for laparoscopic cholecystectomy. Preoperative imaging revealed Chilaiditi syndrome, with the colon interposed between the liver and diaphragm (Fig. 1). During surgery, the anatomical correction of the colon was straightforward, and the colon was easily reduced. However, the liver was found to be displaced lower than usual due to the syndrome, necessitating the insertion of trocars at lower points than standard laparoscopic practice (Figs. 2 and 3). Since the intestines are unusually located in the right upper quadrant, care must be taken to avoid damaging them when using the instrument.

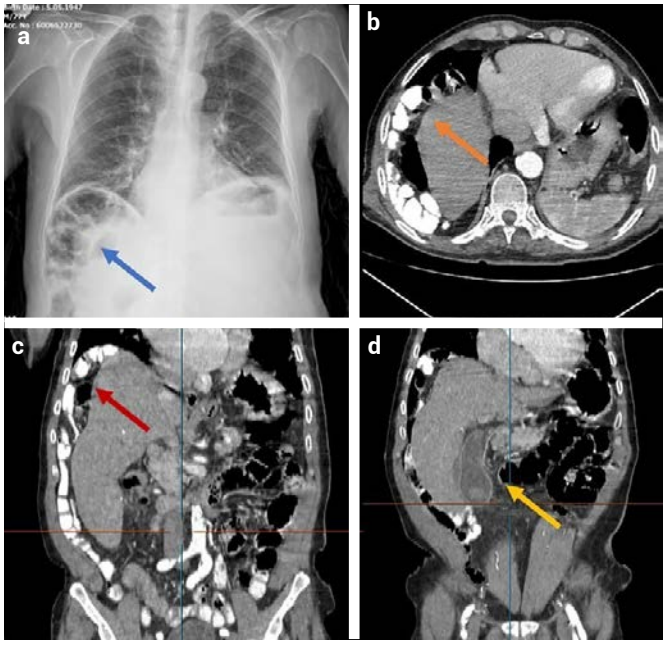

Figure 1. The preoperative images of an 84-year-old male patient with Chialiditis syndrome **(a)** demonstrate a pneumoperitoneum-like appearance under the right diaphragm on a chest X-ray (blue arrow). Computed tomography **(b and c)** reveals the colon between the liver and diaphragm, while **(d)** shows the gallbladder below the level of the umbilicus.

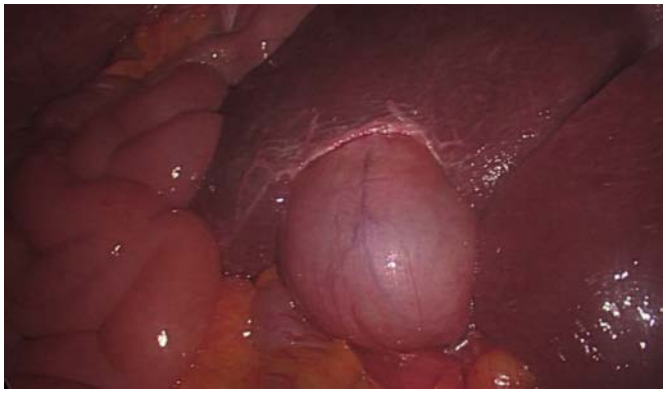

Figure 2. Intraoperative image showing anatomical position of liver and gallbladder due to Chialiditi's disease.

Figure 3. Segments of the small bowel and colon can be freely reduced and precisely repositioned.

Considering the anatomical changes associated with Chilaiditi syndrome and the preoperative imaging findings, the surgical team proceeded with meticulous care during the laparoscopic cholecystectomy. Trocar placement was modified to account for the lower positioning of the liver, ensuring the interposed intestines were not injured (Fig. 4). Despite these adjustments, the procedure was completed without intraoperative complications. Postoperatively, the patient was closely monitored for three days due to an increased risk of respiratory complications, including atelectasis and decreased lung function, exacerbated by both his underlying Chronic Obstructive Pulmonary Disease (COPD) and the pressure exerted by the interposed colon on the diaphragm. Following appropriate respiratory management, the patient's condition stabilized, and

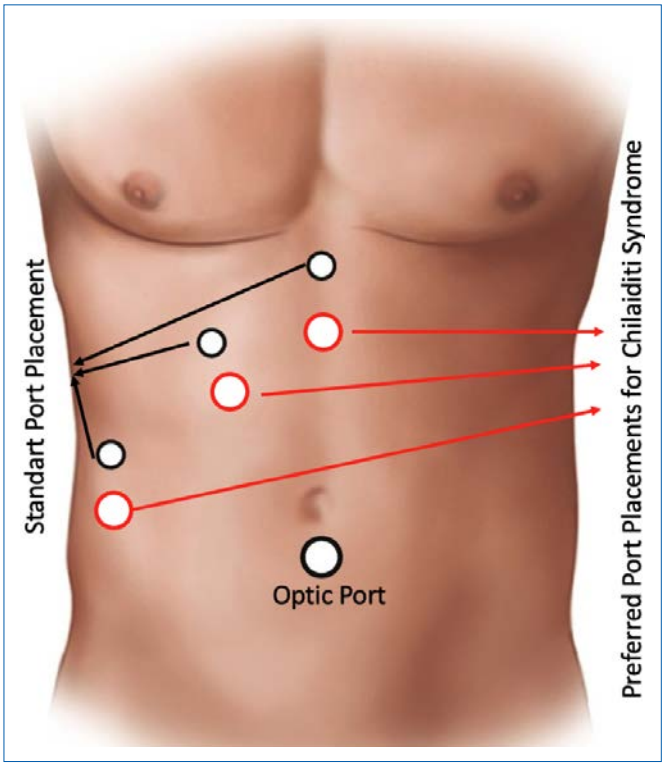

Figure 4. Preferred port placements for altered anatomical changes due to Chilaiditi syndrome.

he was discharged without any further issues. The patient was followed up postoperatively through outpatient clinic visits and imaging when necessary, during which no delayed complications were observed; considering the underlying anatomical variation, it was recommended that any future abdominal surgeries be preceded by detailed preoperative imaging to guide trocar placement and minimize intraoperative risks.

Conclusion

The presence of Chilaiditi syndrome presents a distinctive set of challenges during laparoscopic cholecystectomy, despite the relative ease with which the interposed intestine can often be reduced. While repositioning the colon is a relatively straightforward procedure, the altered anatomical relationships, particularly the change in the position of the liver, carry a risk of injury during instrument introduction. It is imperative that surgeons are mindful of these changes and adjust trocar positioning accordingly to avoid complications. Furthermore, the interposition of the colon and its pressure on the diaphragm may have implications for respiratory function, particularly in patients with preexisting pulmonary conditions. [6] It is therefore essential that both surgical technique and postoperative respiratory care are closely monitored in order to optimize outcomes in such cases.

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