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Aims and Scope

Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication organ of the Turkish Surgical Association, Turkish Hepatopancreatobiliary Surgery Association and Turkish Association of Endocrine Surgery (TAES). The financial expenses of the journal are covered by the Turkish Surgical Association. The journal is published quarterly on March, June, September and December and its publication language is English.

The aim of Turkish Journal of Surgery is to publish high quality research articles, review articles on current topics and rare case reports in the field of general surgery. Additionally, expert opinions, letters to the editor, scientific letters and manuscripts on surgical techniques are accepted for publication and various manuscripts on medicine and surgery history, ethics, surgical education and forensic medicine fields are included in the journal.

The journal is a surgical journal that covers all specialities and its target audience includes academicians, practitioners, specialists and students from all specialities of surgery.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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All expenses of the journal are covered by the Turkish Surgical Association.

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TURKISH JOURNAL OF SURGERY

Instructions to Authors

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Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Material and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods (with subheadings), Results, Discussion, Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Material and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Expert Opinions: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future stud-

ies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Surgical Methods: Images of remarkable, striking and rare cases that emphasize the basic mechanisms of diagnosis and treatment of diseases, express discrepancies and extraordinary situations and explain new treatment techniques and options are evaluated for publication. Display items are important in this type of manuscripts and supporting the manuscript with video (in WMV, AVI or MPEG formats) images can facilitate a faster evaluation process and increase the possibility of publication.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget - Are we spending too much? Vojnosanit Pregl 2013; 70: 709-711.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	250 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	250	15	No tables	10 or total of 20 images
Surgical Methods	500	No abstract	5	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIEID/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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TURKISH JOURNAL OF SURGERY

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Editorial

Dear Colleagues,

With this issue, we have published the third issue of this year.

We are pleased to observe that our journal is getting better and reaching wider audiences every day and this increases our determination and enthusiasm to work.

Turkish Journal of Surgery is one of the reference surgical journals in our country and it has taken an organizational structure with its previous experience. It is followed by our colleagues in other countries of the world, particularly in European and Asian countries, as well as those in our country and they submit articles to be published.

In this issue, we have published research articles and case reports from different areas of General Surgery. In the articles published in the journal, clinical studies have been highlighted.

In the next issues, we will continue to publish the guiding and innovative studies of our colleagues in their fields.

Our aim is to be one of the journals which are scanned and followed in international indices. We will accomplish this goal with the support and contributions of our colleagues.

I offer my gratitude and thanks to all those who have contributed.

Prof. Dr. Mustafa ŞAHİN

Editor in Chief

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Original Article

Obesity and Bariatric Surgery awareness in the Kocaeli province, a leading industrial city in Turkey

Sertaç Ata Güler, Tonguç Utku Yılmaz, Turgay Şimşek, Oktay Yirmibeşoğlu, Sertaç Kırnaz, Nihat Zafer Utkan, Nuh Zafer Cantürk

ABSTRACT

Objectives: An increase in the prevelance of obesity is a worldwide problem. It many serious health problems, especially cardiovascular diseases and type-2 diabetes mellitus. Conservative therapies such as diet modification and exercise are the most preferable obesity treatments. Bariatric surgery is the most appropriate treatment in suitable patients. Several studies showed that a very low number of patients prefer bariatric surgery even though it would be appropriate. This study aimed to assess and raise awareness about the obesity level, its complications, and treatment methods, especially bariatric surgery among obese patients in Kocaeli, which is one of the most socio-economically developed cities, as well as the leading industrial city in Turkey.

Material and Methods: A survey was designed to assess the knowledge about obesity, its complications, and bariatric surgery in the Kocaeli province. It was administered to 232 adult patients with a body mass index greater than 30 in different outpatient clinics where patients suffering obesity were treated.

Results: It has been seen that although the contribution factors and complications of obesity are well known, awareness of the body mass index was insufficient. Most of patients have tried to lose weight at least once and most patients have heard of bariatric surgery before. However, the details were not well known. The gastric band method is the most known method, and the most known risk of surgery was death. The main source of knowledge about bariatric surgery was television. The increasing body mass index affects patients' attitudes toward the surgery positively.

Conclusion: Knowledge of bariatric surgery is inadequate in the Kocaeli province, which is one of the most socio-economically developed cities, as well as the leading industrial city in Turkey. More social responsibility projects and more objective elucidating via television and social media are also needed to increase the awareness of bariatric surgery.

Keywords: Bariatric surgery, knowledge, Kocaeli, obesity

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INTRODUCTION

The rising prevalence of overweightness and obesity in several countries has been described as a global pandemic (1-3). Obesity and obesity-related diseases are replacing infectious diseases and malnutrition as the most significant health problem threatening the developing countries (4, 5). In 2008, the World Health Organization (WHO) pointed out that the worldwide obesity has nearly doubled since 1980 (1). This increasing trend is also shown by Lancet in 2014: more than 2 billion people are overweight, and of these, approximately 670 million people are obese (2). According to the data from the Nutrition and Health Research in Turkey—2010 conducted by the Republic of Turkey Ministry of Health, the obesity prevalence is 20.5% among adult men and 41.0% among adult women.

World Health Organization uses the body mass index (BMI) as a quantitative parameter to define obesity and being overweight. It defines obesity as a BMI greater than or equal to 30 kg/m^2 and being overweight as a BMI greater than or equal to 25 kg/m^2. The main risk factors that contribute to obesity are genetics, environmental factors, physical inactivity, energy intake, fetal nutrition, and cultural elements (1, 5). Obesity and overweightness can cause a wide range of serious health conditions including cardiovascular diseases such as stroke, hypertension, and heart diseases, diabetes mellitus; musculoskeletal disorders such as osteoarthritis; some types of cancers; and sleep-breathing abnormalities (1, 5, 6). Metabolic syndrome is also one of the most important complications of obesity, which comprises type 2 diabetes mellitus, hypertension, dyslipidemia, and insulin resistance (7-9). These obesity-related health problems cause significant treatment costs for these preventable diseases (10, 11).

When the prevention of obesity fails, the treatment of obesity may *become unavoidable. These* multidisciplinary treatment methods included lifestyle-based conservative interventions such as diet modification and exercise, medical approaches such as drug therapies, and bariatric surgery (10, 12). After previous unsuccessful attempts to lose weight with lifestyle-based conservative methods in patients with a BMI greater than 40 kg/m^2 or BMI ranging between 35 and 40 kg/m^2 with comorbidities, bariatric

surgery becomes the most effective treatment for obesity. It achieves a significant weight loss and eases comorbid illness in eligible patients (13, 14). Sleeve gastrectomy and gastric bypass are the most common techniques to perform a bariatric surgery. However, globally, the number of eligible patients who undego bariatric surgery is low. Bariatric surgery is not well-known as an alternative weight loss method (14, 15).

Kocaeli was the Turkey's 11th most populous city (population 1,722,795) in 2014, according to data of the Turkish Statistical Institute. More than 400 first-class and over 7,000 second- and third-class corporations are located in Kocaeli. Therefore, it is one of the leading industrial cities in Turkey. Kocaeli is also the fourth most developed city after Istanbul, Ankara, and Izmir, according to the Socio-Economic Development Ranking Survey of Provinces and Regions (SEGE-2011) data of the Republic of Turkey Ministry of Development. Therefore, this study aimed to assess and raise the awareness level of obesity, its complications, and treatment methods, especially of bariatric surgery among obese patients in Kocaeli.

Table 1. Cohort distribution of the study

1511 appointments for 4 outpatient clinics
203 duplicated appointments
1308
232 missed the appointments
1076
224 patients did not sign the informed consent form
852
589 participants with body mass index <30 kg/m^2
263
26 incomplete surveys
237
5 previously operated bariatric surgeries
232 final population of survey

Table 2. Demographic data of the patients

	Body Mass Index (kg/m^2)			
Variables	**30–34.9**	**35–39.9**	**≥40**	**p**
Gender				0.113
Female	89 (50.0)	63 (35.4)	26 (14.6)	
Male	34 (63.0)	11 (20.4)	9 (16.7)	
Outpatient Clinics				0.101
Endocrinology and Metabolism	54 (50.5)	35 (32.7)	18 (16.8)	
Diabetes and Obesity	34 (44.2)	30 (39.0)	13 (16.9)	
General Surgery	23 (71.9)	6 (18.8)	3 (9.4)	
Sleep Laboratory	12(75.0)	3 (18.8)	1 (6.2)	
Age groups (Year)				0.336
18–25	2 (25.0)	5 (62.5)	1 (12.5)	
26–35	18 (66.7)	6 (22.2)	3 (11.1)	
36–45	30 (46.9)	25 (39.1)	9 (14.1)	
46–55	39 (48.8)	24 (30.0)	17 (21.2)	
56–65	22 (61.1)	11 (30.6)	3 (8.3)	
66–75	10 (66.7)	3 (20.0)	2 (13.3)	
>75	2 (100.0)	0 (0.0)	0 (0.0)	
Total	123	74	35	

Datas are presented as n (%)

MATERIAL AND METHODS

This study started after obtaining an approval from The Ethical Committee of the Research Health Science Center, Kocaeli University. Then, 4 different outpatient clinics with the highest number of obese patients were determined by a preliminary study. The population of study consisted of patients who applied to these outpatient clinics (General Surgery, Endocrinology and Metabolism, Diabetes and Obesity Clinics, and Sleep Laboratory) during a 2-week period. The inclusion criteria for participation in the study were being over 18 years old, having a BMI greater than 30, signing an informed consent form, and not treated by bariatric surgery. A weighting machine (Beko W1; Beko, Istanbul, Turkey) was used to measure the weight and height of patients. A survey had been administered to these patients. The survey included questions that assess patients' personal info, awareness about obesity, BMI, obesity-related health problems, and weight loss methods, their previous experiences with weight loss, and their knowledge about bariatric surgery.

All statistical analyses were performed using the IBM Statistical Packages for the Social Sciences (SPSS) for Windows version 20.0 (IBM Corp.; Armonk, NY, USA). Kolmogorov–Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as median (IQR), and categorical variables were expressed as percentages. Comparisons of categorical variables between the groups were performed using the chi-squared test. The correlation between categorical variables was assessed by the Pearson correlation test, Kendal tau coefficient, and Cramer phi coefficient. A two-sided P-value <0.05 was considered to be statistically significant.

RESULTS

In two weeks, a total of 1511 appointments were made to the 4 outpatient clinics. The surveys were administered to 232 patients who were suitable according to the inclusion criteria (Table 1).

At the end of the study, it was seen that there was not a significant difference of distribution of patients' BMI between gender, applied outpatient clinic type, and age categories (Table 2).

The awareness of BMI was evaluated. Most of the patients (55.2%) had never heard of the BMI before, and only 13.4% knew their own BMI value. Among the 104 who knew the meaning of BMI, only 41 (39.4%) stated the obesity limit as 30 kg/m^2.

Some questions were about obesity-related health conditions. It showed that 79.7% of patients knew that diabetes, hypertension, and hyperlipidemia were complications of obesity. Heart attack (81.0%), sleep apnea and respiratory problems (58.6%), and joint diseases (69.0%) were stated as obesity-related health problems by patients.

Several weight loss methods had been tried by 86.2% of patients before. Among those patients, 89.0% tried diet modification, 72.0% exercise, and 9.0% used pharmacological methods to decrease their weight. After these attempts, 21.0% of them stated that they completely failed. On the other hand, 38.5% were partially successful, and 31.5% were successful. It has been observed that the most important factor of their failures was the lack of motivation (Table 3).

Knowledge of patients about bariatric surgery was assessed by the survey questions. Most of the patients (84.9%) stated that they had heard of bariatric surgery as a treatment method, but they didn't know the details of this method, its techniques, and risks. On the other hand, 15.1% of patients had never heard about bariatric surgery before. The gastric band technique (79.1%) was the most known bariatric surgery method among the patients who knew that bariatric surgery was a treatment method (Table 4). When patients had been asked about the sources of their knowledge about bariatric surgery, it was observed that television (76.1%) was the main source, and only 4.1% of patients stated that they had seen an informative brochure on this subject. Additionally, "death" was the most common answer (28.0%) when the patients were asked about complications of bariatric surgery (Table 5). At the end, it was seen that an increasing BMI significantly affects the positive attitude toward bariatric surgery (Table 6).

Table 3. Weight loss failure reasons

Weight Loss Failure Reasons	Ratio (%)
Resistance to weight loss	40.3
Economical	10.1
Lack of motivation	54.6
Stress and fear of failing	45.4
Family problems and lack of time	26.9
Others	36.1

Table 4. Knowledge of surgical techniques

Surgical Techniques	Ratio (%)
Intragastric balloon	37.2
Gastric band	79.1
Sleeve gastrectomy	51.2
Gastric bypass	25.6

Table 5. Knowledge about the complications of obesity surgery

Complications of Obesity Surgery	Ratio (%)
Death	28.0
Anostomotic leak and ulcer	11.2
Malnutrition	7.3
Severe weight loss	16.4
Gaining more weight	5.6
Psychological problems	10.3

Table 6. Attitudes toward obesity surgery

Would you prefer obesity surgery as a treatment method?	BMI: 30-34.9	BMI: 35-39.9	BMI: >40	p
No	80 (65.0)	42 (56.7)	9 (25.7)	
Maybe, if it's necessary	30 (24.4)	19 (25.7)	7 (20.0)	
Yes	13 (10.6)	13 (17.6)	19 (54.3)	
Total	123	74	35	<0.001

BMI: body mass index

Datas are presented as n (%)

DISCUSSION

Obesity is also one of the most important health problems in Turkey as it is in the rest of the world. This study was worked on to evaluate the latest data on obesity, its complications, treatment methods, and bariatric surgery in the leading Turkish industrial city, Kocaeli.

Even though there is no difference between the BMI ratios and gender categories, there were more women who participated in this study than men. This might be showing that obesity is more common in women. However, it shows that obesity is generally common in public because there is no difference between the BMI groups. The results are compatible with other studies in the literature that there are more cases in the 30–50 age category than in other age categories (16). These study data are similar to those from other studies that have been made in the country side of Turkey; however, ratios are higher when it is compared with other studies abroad (16, 17).

Obese patients applied to several different departments, so this shows that obesity does not belong to one department and that it requires a multidisciplinary approach. Contributing factors for obesity are observed as socio-economic status, dietary habits, and lack of physical activity. Moreover, the importance of self-motivation in weight loss has been shown in the literature (18, 19). As a matter of fact, both bariatric surgery's and other medical treatment's main goals are reducing the patient's energy intake and facilitating the weight loss process. Data showed that patients are usually willing to lose weight, but they also need additional assistance for that.

In this study, it was shown that most patients are aware of obesity and its complications. On the other hand, they are not well informed about the treatment methods. As the main definition of obesity, the BMI term is not well known. This is similar to other studies that were conducted in Turkey (17).

Unfortunately, most of the sources of patients' knowledge about bariatric surgery were non-medical sources. A similar issue is also apparent in other medical subjects. These sources are increasing the awareness of these treatment methods; however, it also is causing false or insufficient informing of individuals. It is necessary to inform people with more certain and correct information; furthermore, more health care professionals should be involved into these campaigns.

It was observed that patients' attitudes toward bariatric surgery is becoming more positive with a higher BMI. This expected result might be due to the failed weight loss attempts with other methods. Although most of the patients' attitudes are negative

due to the complications of bariatric surgery, a considerable number of patients view bariatric surgery positively. Patients stated the death as the most known complication of bariatric surgery. The source of this excessive fear were mostly television and the internet. It has also been understood that there are not enough brochures about this subject. If the true numbers about the bariatric surgery complication were told to patients, their fear would be decreased (20). The most known method for bariatric surgery was observed as a gastric band. However, it is less preferable nowadays as it is seen in the literature (20).

CONCLUSION

This study has shown that the knowledge of bariatric surgery is inadequate in the Kocaeli province, which is one of the most socio-economically developed cities, as well as the leading industrial city in Turkey. Public informative brochures that comprise updated scientific data about obesity and bariatric surgery are needed. In addition, more social responsibility projects are also needed to increase the awareness of obesity and bariatric surgery.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Kocaeli University Research Health Science Center.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Original Article

Protective effects of laparoscopic sleeve gastrectomy on atherosclerotic and hemocytic parameters in obese patients

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ABSTRACT

Objectives: The aim of this study was to evaluate the effects of the change in the body mass index following laparoscopic sleeve gastrectomy on the vascular morphology structure and biochemical and hemocytic parameters.

Material and Methods: A prospective evaluation of 60 patients who underwent sleeve gastrectomy was conducted. The relationship was evaluated between the vascular morphological parameters and biochemical and hemocytic inflammatory variables of the patients preoperatively and at 6, 12, and 18 months postoperatively.

Results: Compared to the baseline values, a significant decrease was determined in the carotid intima media thickness at 6, 12, and 18 months ($p<0.001$, $p<0.001$, $p<0.001$, respectively). The compliance and distensibility values were observed to increase over time ($p<0.05$, $p<0.001$, $p<0.001$, respectively). A statistically significant difference was determined in the carotid intima media thickness values according to gender, with males (n:7) measuring 0.618±0.123 mm and females (n:53) measuring 0.506±0.113 mm ($p<0.01$). When patients were grouped as neutrophil-to-lymphocyte ratio ≤2.54 (n:41) and neutrophil-to-lymphocyte ratio>2.55 (n:19), the increasing neutrophil-to-lymphocyte ratio values were observed to be in proportion to the carotid intima media thickness, and the difference was statistically significant ($p<0.001$). When factors affecting the vascular morphology parameters measured at baseline and throughout the study were evaluated with the correlation analysis, there was observed to be a positive correlation between the baseline carotid intima media thickness thickness and neutrophil percentage ($r=0.736$, $p<0.001$) and neutrophil-to-lymphocyte ratio ($r=0.676$, $p<0.001$), and between the negative correlation and lymphocyte percentage ($r=-0.628$, $p<0.001$).

Conclusion: Laparoscopic sleeve gastrectomy is not only a cosmetic procedure reducing the body mass index values, but it also has a beneficiary effect on vascular morphology, biochemical, and hemocytic parameters.

Keywords: Hemocytic inflammatory parameters, laparoscopic sleeve gastrectomy, vascular morphology

INTRODUCTION

The increasing global prevalence of obesity in the last 30 years has caused comorbidities such as Type 2 diabetes mellitus (DM), hypertension (HT), and dyslipidemia and serious health problems, primarily cardiovascular diseases (CVD) (1). Although it is not possible to explain the effect of obesity on cardiovascular functions by a single mechanism, previous studies have focused on the role of increasing arterial stiffness (AS) (2-5).

Similarly, the relationship between the increased systolic and diastolic blood pressures (SBP and DBP) and hyperglycemic status of obesity and CVD is also now known. In addition, inflammation has been suggested as a risk factor for coronary artery disease (CAD) as a result of the studies on the role it plays in the development of atherosclerosis and plaque instability (5-7).

Together with the use of diet, exercise, and various medications in the treatment of obesity, bariatric surgery, particularly sleeve gastrectomy (SG), has been increasingly used in recent years as it is easy to apply and has fewer complications compared to other surgical methods (8). Previous studies have shown that various surgical methods used in the treatment of obesity have improved several metabolic parameters and that with SG, besides the treatment of metabolic diseases such as Type 2 DM, the lipid profile has reduced the cardiovascular risks by showing positive effects on arterial elasticity, diastolic functions, and left ventricle mass (9-11). However, to the best of our knowledge, there has been no study on the change in hemocytic inflammatory markers such as the neutrophil percentage, lymphocyte percentage, neutrophil-to-lymphocyte ratio (NLR), the mean platelet volume (MPV), and vascular morphology parameters such as the carotid intima media thickness (cIMT), elastic modulus, distensibility, and elasticity in individuals who have lost weight as a result of SG.

The aim of this study was to evaluate the effects of a body mass index (BMI) change following laparoscopic sleeve gastrectomy (LSG) on the vascular morphological structure and biochemical and hemocytic inflammatory parameters.

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MATERIAL AND METHODS

Study Population

Approval for the study was granted by the local Ethics Committee. This prospective study was conducted on a total of 60 morbidly obese and super-obese patients who presented at the General Surgery Polyclinic for obesity surgery between October 2014 and July 2016. Informed consent was obtained from all the patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Clinical parameters, anthropometric measurements, biochemical and hematological parameters, and radiological variables such as cross-sectional compliance, cross-sectional distensibility, lumen cross-section area, wall cross-section area, and elastic modulus were analyzed at 0, 6, 12, and 18 months. The power of the study and the range of a sufficient number of patients were evaluated with power analyses and terminated when the sample size reached 60 according to the cIMT parameters with 91% power to detect the test hypothesis with a significance level of 0.05. To prevent the study bias, the radiological data and hematological and biochemical parameters were gathered separately (by Author 1 and Author 2, respectively) and were combined for statistical evaluation after the study was completed.

Initial Assessment

Before commencing the study, a detailed anamnesis was taken from all the patients, including cardiac and metabolic diseases, medications used, and information about cigarette smoking. Baseline anthropometric variables and the SBP and DBP values were recorded for each patient. Blood samples were taken from all the patients before the study for blood glucose, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, neutrophil percentage, lymphocyte percentage, platelet count, and MPV values. NLR was calculated from the obtained data.

Ultrasonographic Evaluation Before the Study

Measurements were taken using a high-resolution Doppler ultrasonography system (Aplio™ 400 Platinum, Toshiba Medical Systems Corporation, Tochigi, Japan) with a broadband linear probe (PLT-704SBT, Aplio™ 400 Platinum, Toshiba Medical Systems Corporation, Tochigi, Japan). First, the probe was placed in the right carotid artery bifurcation, and cIMT, diastolic, and systolic lumen diameters were measured. Pulse pressure measurements (SP, DP, ΔP) were taken with an automatic sphygmomanometer (Vitagnost 2015 OC, MARS, Taiwan). The vascular AS parameters were calculated as described in literature (12) using the following equations:

- Cross-sectional compliance=$(\pi.(SD^2-DD^2))/(4.(SP-DP))$
- Cross-sectional distensibility=$(SD^2-DD^2)/(DD^2.(SP-DP))$
- Diastolic wall stress=$(DD/(2.IMT)).((SP+SD)/2)$
- Cross-sectional area of lumen=$\pi.DD^2/4$
- Cross-sectional area of wall=$\pi.((DD/2)+IMT)^2-\pi.(DD/2)^2$
- Elastic modulus=(3/(1+(Cross-sectional area of lumen/ Cross-sectional area of wall)))/ Cross-sectional distensibility

Anthropometric Measurements

Body mass index was calculated as weight (kg)/height squared (m^2).

Laboratory Tests

Before taking the blood samples, the patients were questioned in detail, and physical examination was made to evaluate the presence of infection. Patients with suspected infection in the physical examination and elevated white cell levels were called for a follow-up examination 1 month after treatment. If no infection was determined, blood samples were taken between 08^{00} 10^{00} after a 10-minute rest.

Surgical Procedure

The same surgical method was applied to all patients by the same surgical team (FMY, EB). The procedure was applied with the 5-trochar method to the patient lying in the French position, in the reverse Trendelenburg position. The abdomen was inflated with 14 mmHg carbon dioxide, then starting from approximately 3cm prepyloric, the gastrocolic and gastrosplenic ligaments were cut with a 5 mm LigaSure (Covidien, Dublin,

Table 1. Baseline characteristics of the studied participants

Characteristic	Male (n=7)	Female (n=53)	P
Age (years)	35.14±11.30	38.86±10.39	0.38
BMI (kg/m2)	47.76±5.16	47.52±5.48	0.91
SBP (mmHg)	135.71±9.75	136.98±11.02	0.77
DBP (mmHg)	76.54±5.81	77.28 ±5.81	0.72
Blood glucose concentration	98.71±16.67	104.37±28.79	0.61
Total cholesterol (mg/dL)	194.50±28.29	207.94±30.77	0.31
Triglycerides (mg/dL)	114.71±19.28	170.18±88.66	0.10
HDL-cholesterol (mg/dL)	38.50±5.98	39.52±7.14	0.73
LDL-cholesterol (mg/dL)	123.71±27.93	122.56±30.44	0.92
VLDL	23.66±3.93	32.51±16.06	0.18
HbA1C	5.17±0.49	5.96±1.02	0.13
Neu percentage	62.50±3.65	62.12±6.65	0.88
Lymp percentage	28.22±2.79	28.41±6.07	0.93
NLR	2.23±0.30	2.34±0.79	0.73
Plt (K/μL)	306.42±39.34	308.62±75.06	0.94
MPV (fL)	9.55±0.74	9.43±1.40	0.82
Intima-media thickness (mm)	0.618±0.123	0.506±0.113	0.01
Compliance	0.128±0.024	0.183±0.083	0.09
Elastic modulus (N/m^2)	212.63±60.54	157.57±103.23	0.17
Distensibility ($mmHg\ 1\times10^3$)	0.0046±0.001	0.0071±0.004	0.13

Data are expressed as the mean±SD; unless otherwise noted.
Independent T-Test (Bootsrap)—Mann–Whitney U Test (Monte Carlo)—Fisher's Exact Test (Monte Carlo)
BMI: body mass index; DBP: diastolic blood pressure (mmHg); HbA1C: hemoglobin A1C; HDL: high-density lipoprotein (mg/dL); LDL: low-density lipoprotein (mg/dL); MPV: mean platelet volume (fL); NLR: neutrophil-to-lymphocyte ratio; Plt: platelet (K/μL); SBP: systolic blood pressure (mmHg); VLDL: very low-density lipoprotein

Ireland), and the stomach was mobilized. A 38Fr orogastric tube was placed in the prepyloric area. Then a laparoscopic 60 mm stapler (Echelon Flex Endopath Stapler; Ethicon Endo-Surgery, Cincinnati, OH, USA) was used, with the first two stapler cartridges 4.2 mm green, and the other cartridges 3.5 mm blue. After completion of the resection, the resected tissue was removed from the 12 mm trocar, and the procedure was terminated. Radiologically, cIMT, compliance, distensibility, and elastic modulus values were accepted, and NLR was accepted in the hematological parameters.

In the patients were evaluated with respect to their age, gender, comorbidities, BMI values, biochemical parameters such as blood glucose, HbA1C HDL-cholesterol, LDL-cholesterol, Triglycerides and hematological parameters such as neutrophil percentage, lymphocyte percentage, NLR, MPV, and platelet count and radiological variables such as cIMT, compliance, dıstensibilty, and elastic modulus.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA). Data were stated as mean±standard deviation (SD). Comparisons between groups were performed by one-way ANOVA test followed by Bonferroni correction. To evaluate factors related to cIMT, linear regression models were used, and data were stated as beta-coefficients at a 95% confidence interval (CI). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The patients included in the study comprised 53 (88.3%) females and 7 (11.7%) males (Table 1). The mean age of the patients was 38.43±10.47 years (range: 18–56 years), and the baseline mean BMI values were 47.55±5.40 (range: 39–61.73). At the 6, 12, and 18-month follow-up examinations, the mean BMI values were 35.19±4.56 kg/m^2, 30.84±4.00 kg/m^2, and 28.35±3.88 kg/m^2, respectively (Table 2). The reduction in the BMI values was more evident in the first 6 months, and the rate of decreased, although it continued. In the preoperative period, 29.5% of patients were using medication for high blood pressure, then together with the reducing the SBP and DBP values proportional to the weight lost, at the end of 18 months, only 3.3% continued to use medication for high blood pressure. The anthropometric changes of the patients are shown in Table 2.

Compared with the baseline biochemical values, the lipid profile and glycemic parameters of the patients were observed to have significantly improved (Table 2). Similar results were not seen in the anthropometric hemocytic parameters. At the end of 18 months, while a decrease was observed in NLR, MPV, and the platelet count, the lymphocyte percentage was seen to have increased compared to the preoperative values (Table 2).

A statistically significant decrease was determined in the cIMT values at 6, 12, and 18 months compared to the baseline values ($p<0.001$, $p<0.001$, $p<0.001$), and no difference was seen between the values at 6, 12, and 18 months

Table 2. Clinical, biological, biochemical, hematologic, and vascular morphologic parameters of the study group, preoperatively, and at 6, 12, and 18 months postoperatively

	Preoperatively	6 months postoperatively	12 months postoperatively	18 months postoperatively
Weight (kg)	124.66±15.24	92.20±12.28#	80.78±2.81#	74.35±9.14#
BMI (kg/m^2)	47.55±5.40	35.19±4.56#	30.84±4.00#	28.355±3.88#
SBP (mmHg)	136.83±10.81	127.17±12.78*	124.58±8.54*	117.50±4.73#
DBP (mmHg)	88.34±6.74	83.52±4.14	76.28±5.74*	73.57±5.18*
Blood Glucose (mg/dL)	103.71±27.61	83.52±10.30#	85.34±9.00#	84.97±9.99#
Total Cholesterol (mg/dL)	206.55±30.57	173.66±23.24#	189.33±33.17	179.50±34.15#
HDL-Cholesterol (mg/dL)	39.41±6.99	50.61±13.06#	45.11±10.82*	54.20±10.17#
LDL-Cholesterol (mg/dL)	122.69±29.92	105.71±27.24*	113.09±24.00	118.73±31.29
Triglycerides (mg/dL)	163.36±85.17	126.12±59.51*	116.67±70.14*	99.41±39.79#
Neu percentage	62.16±6.35	52.47±7.28#	50.68±7.11#	53.76±7.07#
Lymp percentage	28.39±5.77	36.92±6.74#	38.36±6.20#	36.34±6.59#
NLR ratio	2.33±0.75	1.50±0.45#	1.38±0.42#	1.55±0.46#
MPV (fL)	9.44±1.33	9.12±1.24	9.01±1.04	8.86±0.95*
Plt (K/µL)	308.36±71.58	256.55±61.67#	249.41±65.38#	249.84±48.51#
Intima-media thickness (mm)	0.519±0.11	0.384±0.06#	0.342±0.06#	0.353±0.06#
Compliance	0.177±0.08	0.213±0.07*	0.233±0.07#	0.232±0.07#
Distensibility (mmHg 1×10^3)	6.8±0.4	8.9±0.4*	10±0.5#	11±0.4#
Elastic modulus (N/m^2)	163.99±100.41	100.30±35.43#	85.20±27.00#	79.59±33.68#

Data are expressed as the mean±SD, unless otherwise noted. Analysis of variance post hoc Tukey honest significant difference with Bonferroni correction

BMI: body mass index; DBP: diastolic blood pressure (mmHg); HbA1C: hemoglobin A1C; HDL: high-density lipoprotein (mg/dL); LDL: low-density lipoprotein (mg/dL); MPV: mean platelet volume (fL); NLR: neutrophil-to-lymphocyte ratio; Plt: platelet (K/µL); SBP: systolic blood pressure (mmHg)

*$p<0.05$ vs. baseline, #$p<0.001$ vs. baseline

Table 3. Comparison of vascular morphology values according to different parameters

Groups		Intima-media Thickness (mm)	Compliance	Elastic Modulus (N/m²)	Distensibility (mmHg 1×103)
BMI	≤49.9 kg/m² (n:39)	0.501±0.122	0.177±0.077	157.168±105.26	7.08±0.4
	≥50 kg/m² (n:21)	0.548±0.109	0.180±0.088	171.79±91.36	6.6±0.4
P	0.15	0.87	0.60	0.72	
Gender	Male (n:7)	0.618±0.123	0.128±0.024	212.63±60.54	4.6±0.1
	Female (n:53)	0.506±0.113	0.183±0.083	157.57±103.23	7.1±0.4
P	0.01	0.09	0.17	0.13	
SBP	≤120 mmHg (n:39)	0.514±0.121	0.180±0.08	160.40±102.41	7.0±0.4
	≥121 mmHg (n:21)	0.514±0.104	0.154±0.07	187.33±88.57	5.7±0.3
P	0.42	0.40	0.48	0.42	
	≤106 mg/dL				
Glucose concentration (n:45)	0.517±0.12	0.175±0.07	157.19±81.40	0.0068±0.003	
	≥107 mg/dL (n:15)	0.542±0.11	0.182±0.08	184.42±145.15	0.0070±0.005
P	0.084	0.77	0.36	0.87	
Total cholesterol (mg/d) (n:38)	≤200 mg/dL				
	0.506±0.11	0.175±0.079	157.87±89.98	0.0068±0.004	
	≥201 mg/dL (n:22)	0.538±0.12	0.189±0.079	162.71±107.52	0.0072±0.004
P	0.33	0.53	0.86	0.68	
NLR	≤2.54 (n:41)	0.484±0.111	0.183±0.086	156.43±102.64	7.0±0.45
	>2.55 (n:19)	0.595±0.102	0.174±0.079	180.32±96.05	6.7±0.39
P	0.001	0.703	0.396	0.824	
MPV	≤10.4 (n:46)	0.492±0.119	0.185±0.082	153.32±85.04	7.2±0.42
	>10.5 (n:14)	0.527±0.118	0.150±0.071	199.06±137.83	5.4±0.36
P	0.335	0.163	0.137	0.151	

Data are expressed as the mean±SD, unless otherwise noted
Independent T-Test(Bootsrap)—Mann–Whitney U Test (Monte Carlo)—Fisher's Exact Test (Monte Carlo)—Pearson Chi-Squared Test (Monte Carlo)—One-Way Analysis of Variance
BMI: body mass index; MPV: mean platelet volume (fL); NLR: Neutrophil-to-lymphocyte ratio; SBP: Systolic blood pressure (mmHg)

(p>0.05). The compliance and distensibiity values were observed to increase over time (p<0.05, p<0.001, p<0.001) (Table 2).

The basal vascular morphology values of the patients included in the study were compared taking into consideration some different clinicopathological factors (Table 3). Accordingly, the patients were grouped as morbidly obese (Group 1, n=39, BMI≤49.9 kg/m²) and super obese (Group 2, n=21, BMI≥50 kg/m²), and when the relationship between the BMI values and the vascular morphology values was examined, there was no statistically significant difference observed between the groups (p=0.15, p=0.87, p=0.72, p=0.60). When the vascular morphology values were evaluated according to gender, the cIMT values were 0.618±0.123 mm for males (n:7) and 0.506±0.113 mm for females (n:53), with a statistically significant difference between the genders (p<0.01). A significant difference was determined between the genders in respect to compliance values (p<0.09), but although the distensibility and elastic modulus values of females were determined to be better than those in males, there was no significant difference (p=0.17, p=0.13). When the patients were grouped according to biochemical values such as hyperglycemia and hypercholesterolemia, no statistically significant difference was observed between the groups. The statistical evaluation results are shown in Table 3.

The patients were grouped as NLR≤2.54 (n:41) and NLR>2.55 (n:19) (13). The cIMT values increased in proportion to the increasing NLR values, and the difference was observed to be statistically significant (p<0.001). Although the compliance, distensibility, and the elastic modulus values deteriorated with an increased NLR, the results were not observed to be statistically significant (Table 3). Classification was made as MPV≤10.4 and MPV>10.5. The vascular morphology values at high MPV values were observed to have deteriorated, although not to a statistically significant degree (Table 3).

In the correlation analysis of the factors affecting the vascular morphology parameters measured at baseline and during the study, a positive correlation was determined between cIMT and male gender (r =–0.304, p<0.01), neutrophil percentage (r=0.736, p<0.001) and NLR (r=0.676, p<0.001), and a negative correlation with lymphocyte percentage (r=–0.628, p<0.001).

Table 4. Comparison of factors affecting the vascular morphology structure preoperatively and at 18 months postoperatively

	Intima-media thickness (mm)				Compliance				Distensibility (mmHg 1×10³)				Elastic modulus (N/m²)			
	Preoperative		Postoperative 18th month		Preoperative		Postoperative 18th month		preoperative		Postoperative 18th month		preoperative		Postoperative 18th month	
	r	P	r	P	r	P	r	P	r	P	r	P	r	P	r	P
Gender	-0.304*	0.01	-0.106	0.102	0.22	0.09	0.102	0.11	0.197	0.13	0.06	0.40	-0.178	0.17	-0.146	0.05
BMI	0.135	0.30	0.521**	0.001	0.036	0.78	-0.234**	0.001	0.018	0.88	-0.297**	0.001	-0.003	0.98	0.353**	0.001
SBP	0.057	0.66	0.531**	0.001	-0.059	0.65	-0.234	0.01	-0.031	0.81	-0.336**	0.001	0.070	0.59	0.356**	0.001
Glucose	0.65	0.62	0.348**	0.001	-0.066	0.61	-0.07	0.33	-0.009	0.94	-0.115	0.11	0.100	0.44	0.272**	0.001
HbA1C	0.075	0.63	0.197	0.08	-0.079	0.61	-0.090	0.42	-0.046	0.77	-0.134	0.23	0.083	0.59	0.095	0.401
T Chol	0.004	0.976	0.285**	0.001	-0.088	0.51	-0.120	0.13	-0.067	0.61	-0.008	0.92	0.031	0.81	0.188*	0.019
HDL	-0.132	0.326	-0.232**	0.002	0.129	0.33	0.072	0.34	0.129	0.33	0.72	0.35	0.095	0.48	-0.187*	0.014
LDL	0.068	0.060	0.156*	0.037	0.063	0.63	-0.011	0.88	0.154	0.24	0.084	0.26	0.029	0.82	0.105	0.162
Neu percentage	0.736**	0.001	0.610**	0.001	-0.073	0.57	-0.173**	0.008	-0.172	0.189	-0.123	0.06	0.377**	0.003	0.384**	0.001
Lymp %	-0.628**	0.001	-0.596**	0.001	0.020	0.876	0.194**	0.003	0.133	0.310	0.157*	0.017	-0.296*	0.022	-0.379**	0.001
NLR	0.676**	0.001	0.653**	0.001	-0.043	0.746	-0.181**	0.006	-0.161	0.218	-0.145*	0.028	0.341**	0.008	0.391**	0.001
MPV	-0.241	0.063	-0.008	0.902	0.034	0.797	-0.012	0.855	-0.004	0.976	-0.092	0.166	-0.078	0.55	0.118	0.073
Plt	0.253	0.051	0.384**	0.001	-0.064	0.628	-0.152*	0.021	-0.099	0.45	-0.112	0.09	0.147	0.262	0.270**	0.001

BMI: body mass index; DBP: diastolic blood pressure (mmHg); HbA1C: hemoglobin A1c HDL: high-density lipoprotein (mg/dL); LDL: low-density lipoprotein (mg/dL); MPV: mean platelet volume (fL); NLR: neutrophil-to-lymphocyte ratio; Plt: platelet (K/μL); SBP: systolic blood pressure (mmHg) *: p<0.05; **:p<0.001

The vascular, hematological, and biochemical parameters in the preoperative period decreased over time, and when the correlations between the vascular, hematological, and biochemical parameters were re-evaluated at the end of the study, taking the significant differences into account, there was seen to be a significant correlation between several parameters and cIMT, compliance, distensibility, and elastic modulus. The data are shown in Table 4 and Figures 1, 2, and 3.

In the linear regression analysis of the results seen as significant correlations in the postoperative period, the factor with the most effect on cIMT was observed to be a decrease in the BMI value. The crude model shows the association between cIMT and BMI: β=0.453 (95% CI), p<0.001. The most important interactions between cIMT and variables within the biochemical and hemocytic parameters were determined to be between Neupercentage: β=0.797 (95% CI) and NLR: β=0.111 (95% CI) (p<0.01).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the relationship between changes occurring in BMI following LSG and the vascular morphology structure and hemocytic inflammatory parameters.

It was observed that as the BMI values of the patients decreased, there was a parallel decrease in the cIMT values, which was seen to be statistically significant at 6, 12, and 18 months compared to the baseline values. When factors related to the change in the cIMT values were evaluated, a strong relationship was observed with BMI and SBP. Of the biochemical parameters, a strong positive relationship was seen with hyperglycemia and total cholesterol values in particular, and the increase in the HDL cholesterol levels was observed to negatively affect cIMT. The correlation between NLR from the inflammatory parameters and cIMT was extremely strong and the increase in lymphocyte percentage was observed to have a negative effect on cIMT. Although a reduction was seen in the MPV values with weight lost, the correlation was not significant.

At the end of the study period, there was a strong negative correlation observed between the decrease in BMI and compliance and distensibility. While no correlation was observed between biochemical parameters and compliance or distensibility, of the hemocytic inflammatory markers, the increase in the lymphocyte percentage and the decrease in the NLR values were seen to have positive effects on both compliance and distensibility.

There is a known relationship between CVD and age and gender. Although previous studies have shown changes in vascular morphology parameters in males and those older than 45 years in particular (14, 15), no correlation was seen in the current study between age and vascular morphology changes. This was thought to be due to the low mean age of the patients in the study. However, when the results were evaluated in respect of gender, the mean baseline cIMT of the male participants (0.618 mm) were seen to be higher than those of the females (0.506 mm) (p<0.001). In a study by Dengel et al. (16), the cIMT values of males were reported to be higher, but after correction taking the carotid diameter into consideration, the difference was eliminated.

A high blood pressure is a well-known risk factor for CDV and cerebrovascular diseases. There is not only a direct effect of high BP, but increasing vascular cIMT through possible indirect mechanisms also causes an increase in AS (17). In the

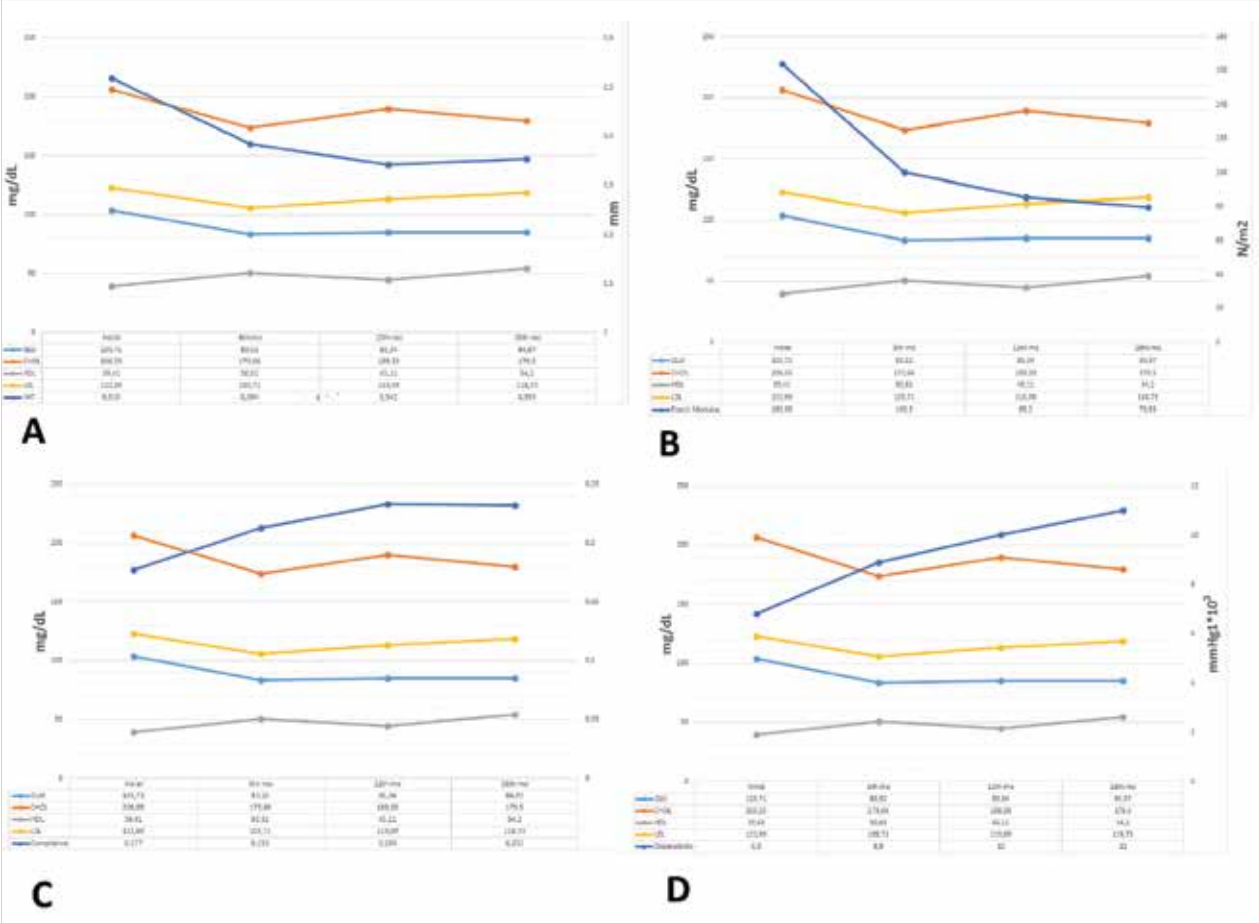

Figure 1. a-d. Temporal correlation of biochemical and vascular stiffness parameters. It is seen that IMT and biochemical parameters decrease with time (a). A positive correlation with elastic modulus and biochemical parameters (b). A negative correlation between compliance, distensibility, and biochemical parameters (c, d)

current study, while no correlation was observed between the traditional risk factor of SBP and baseline cIMT, a strong correlation was observed after treatment with the reduced cIMT values. At the beginning of the study, 29.5% of the patients had severe HT that required at least one medication, while at the end of the 18-month follow-up, only 3.3% of patients required medication. The improvement in hypertensive status was seen to have positive effects on distensibility although not as much as cIMT. Apart from the decrease in the SBP and BMI values, which were thought to have a direct effect on cIMT in the current study, an improvement was also observed in biochemical parameters and hemocytic parameters through indirect mechanisms.

When evaluation has been made in respect of biochemical parameters, several studies have shown a correlation between CVD and the hyperglycemic state and hyperlipidemia, and this has become a generally accepted status. Tropeano et al. (18) reported that hyperglycemia was one of the factors with an independent effect on cIMT. Sanches et al. (19) reported a relationship between an increased insulin resistance and cIMT. A recent study reported a significant decrease in the cIMT and insulin resistance in patients undergoing SG (20). In the current study, an extremely strong correlation was seen between the hyperglycemic status and both the cIMT and elastic modulus. However, similar results were not determined between distensibility and compliance. In the linear regression analyses of the current study, there was seen to be interaction between both the blood glucose level (10%) and the decrease in the HbA1C level (17%) with cIMT.

Dyslipidemia is an independent risk factor in the development of atherosclerosis, and the hyperlipidemic status has been shown to be related to an increase in cIMT (21). This relationship is known to be more evident based on familial hypercholesterolemia (22, 23). In studies that have evaluated the relationship between cIMT and cholesterol sub-types, the LDL cholesterol (LDL-C) concentrations have been reported to be related to an increase in cIMT (24, 25), and an increase in HDL cholesterol has been reported to have a positive effect (26). Similar to findings in the literature, in the current study, the HDL levels had a negative effect on cIMT, and no effect was seen with regard to compliance and distensibility. However, in contrast to literature reports, the LDL cholesterol levels, which showed a weak effect on cIMT in the current study, were not observed to be significantly correlated with any other parameters apart from cIMT.

Inflammation and lipid peroxidization are mechanisms held responsible for the development of atherosclerosis. However, there are different views related to whether immunological parameters, inflammatory cytokines, and lipid peroxidization products have an effect on cIMT. Previous studies have generally focused on the key role of inflammation in CAD (13, 27, 28). In contrast to the key role played by neutrophils in particular in coronary

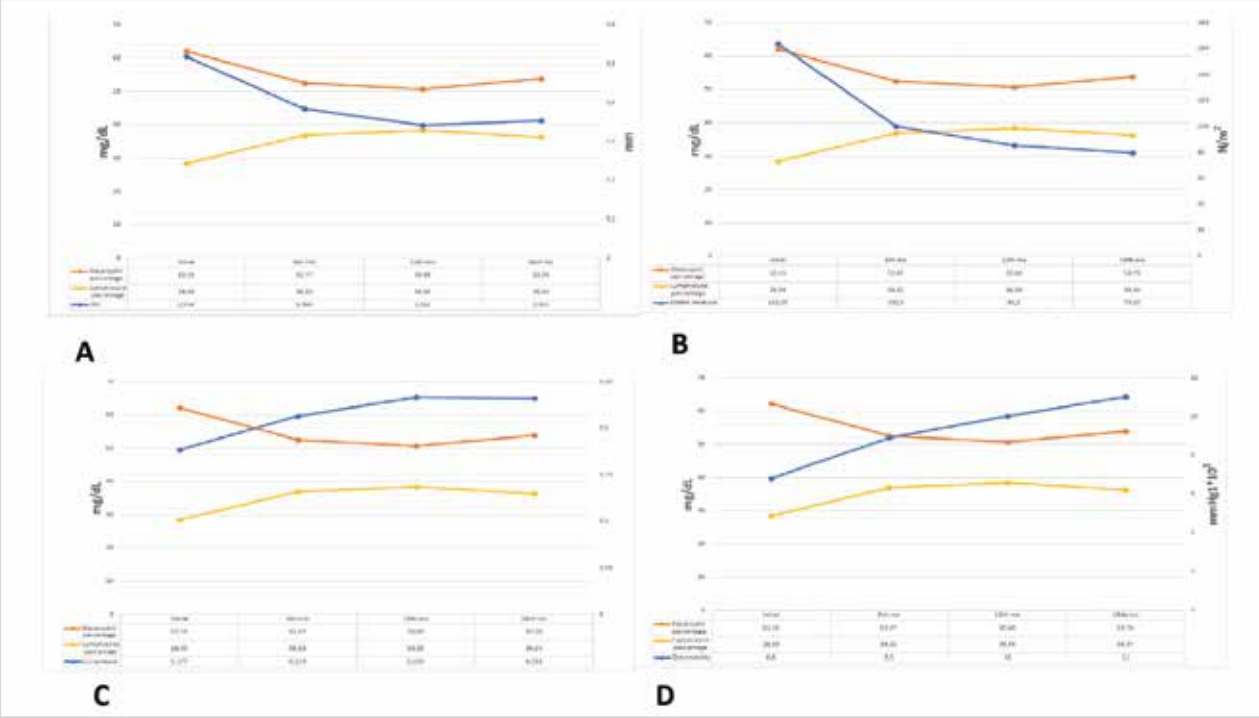

Figure 2. a-d. Temporal correlation of hemocytic and vascular stiffness parameters. Negative correlation with lymphocyte percentage and IMT, elastic modulus (a, b). Positive correlation between compliance, distensibility, and lymphocyte percentage (c, d)

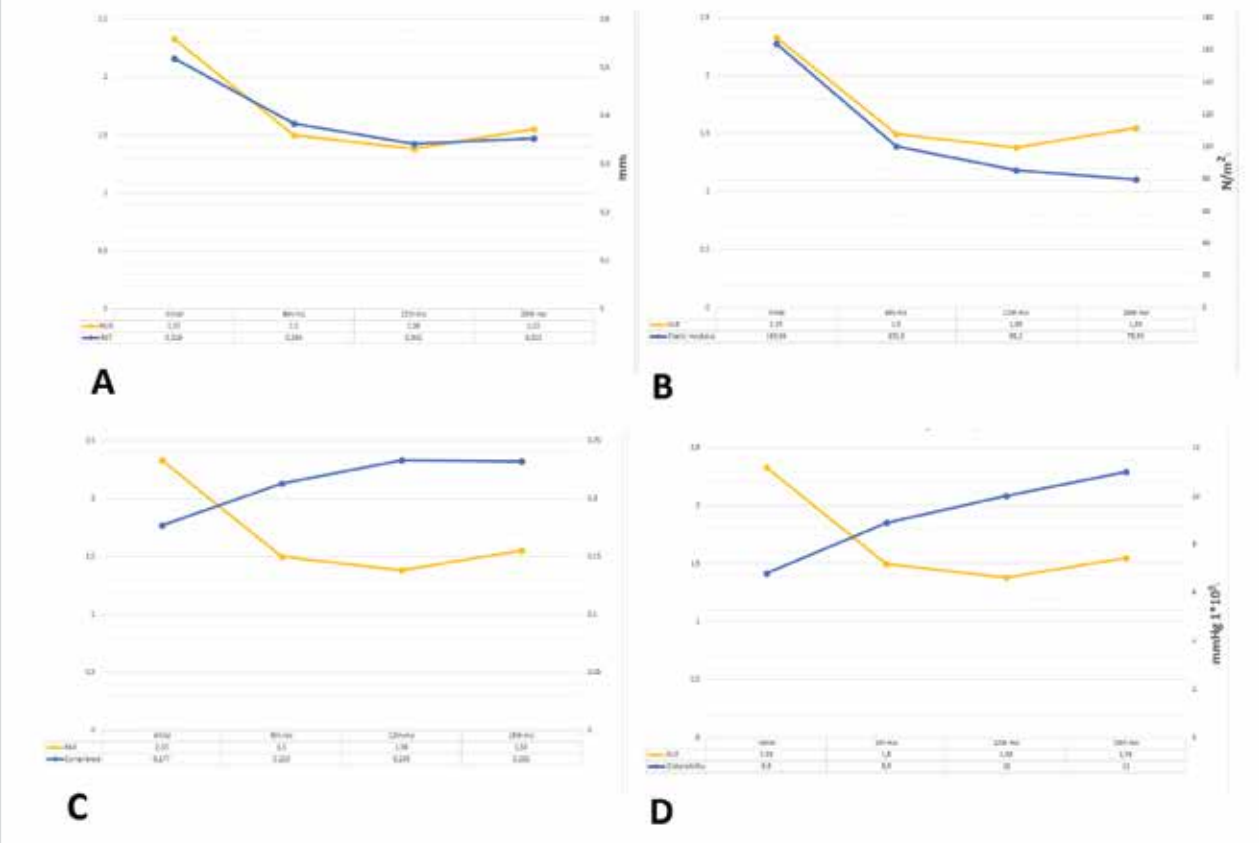

Figure 3. a-d. Temporal correlation of NLR and vascular stiffness parameters. Positive correlation between NLR and IMT (a). The elastic modulus decreases with the reduction in NLR (b). There is an opposite relationship between compliance, distensibility, and NLR (c, d)

events, it has been suggested that lymphocytes have a regulatory role in the inflammatory response and in atherosclerosis (13, 27, 28). It has also been emphasized that NLR is an indirect indicator of CAD and is an independent marker for adverse cardiac events and mortality in patients with stable CAD (29).

In a recent study, it was highlighted that NLR and MPV were independent markers of the presence of severe atherosclerosis (13). However, to the best of our knowledge, no previous study has examined the change in hemocyte inflammatory parameters in patients who have undergone bariatric surgery and evaluated

the relationship of this change with vascular parameters. In this study, by focusing on this main idea, we aimed to evaluate the relationship between the weight loss and the vessel wall and inflammatory response. There was an extremely rapid decrease in NLR, especially during the first 6 months in the patients from the current study who were seen to rapidly lose weight, and this decrease was thought to be associated with the decrease in neutrophil percentage and increase in lymphocyte percentage.

Parameters such as NLR and neutrophil percentage that were objective criteria of this study were seen to be strongly correlated with all the vascular stiffness parameters. Uysal et al. (13) emphasized that a cutoff value of 2.54 was extremely effective in showing the atherosclerotic process on coronary angiography in patients with no previous findings. This value was taken into consideration in the current study when the baseline NLR values were grouped, and it was seen that values >2.54 had a significantly positive effect on cIMT.

Recent studies have suggested that MPV is a potential biomarker for CDV (13, 30). High-volume thrombocytes are metabolically and enzymatically more active than small-volume thrombocytes, and they are thought to have a higher hemostasis capacity. Studies conducted on this subject have reported that CDV are seen more in patients with high MPV, and there is a greater possibility of the development of CDV in healthy individuals with high MPV (13, 30). In a recent study, it was reported that patients with MPV values >10.4 were a risk group for the development of atherosclerosis even if there was no previous cardiovascular pathology on angiography (13). In the current study, MPV values decreased together with the BMI values, and a statistically significant difference was determined in the values at the end of 18 months compared with the baseline values. Although there was no statistically significant difference when the baseline MPV values were grouped as above and below 10.4, the vascular parameters of patients with MPV >10.4 were seen to be worse.

The main limitation of this study was that there was no control group. However, as seen in Table 3, the study participants were separated into objective sub-groups. As it was considered that individual differences such as BMI, HT, and diabetes could change the biochemical, vascular, morphologic, and anthropometric hemocytic parameters, it was planned to use the pre- and postoperative values of the same individuals. Thus, it was aimed to minimize individual variations. Although the number of patients included was limited, according to the power analyses applied, the number was sufficient so that the results could be interpreted.

CONCLUSION

The study results showed that bariatric surgical procedures such as SG are not only cosmetic procedures reducing the BMI values, but they also have a protective effect on vascular parameters and thereby on CVD by bringing the hyperglycemic state under control, regulating HT, and controlling various inflammatory parameters.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects"

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.B., F.M.Y.; Design - E.C., M.B.,.; Supervision - E.B., F.M.Y.; Resource - M.B., F.M.Y., E.C.; Materials - E.B., F.M.Y., M.B.; Data Collection and/or Processing - M.B., F.M.Y., E.C.; Analysis and/or Interpretation - F.M.Y., M.B.; Literature Search - E.B., E.C.; Writing Manuscript - M.B., E.C.; Critical Reviews - E.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Original Article

Development of metabolic syndrome after bilateral total thyroidectomy despite the L-t4 replacement therapy: A prospective study

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ABSTRACT

Objectives: The literature about the frequency of metabolic syndrome in patients with multinodular goitre and a new onset of metabolic syndrome after total thyroidectomy is limited. The aim of this study was to investigate the effects of total thyroidectomy and thyroid hormones on a new onset of metabolic syndrome in patients who underwent total thyroidectomy and have received thyroid hormone replacement.

Material and Methods: Fifty-nine patients who underwent total thyroidectomy for multinodular goitre were included in this prospective study. Patients' height, weight, and waist circumference were measured, and the body mass index was calculated. Peripheral blood samples were obtained preoperatively and at the 12th and 24th month after total thyroidectomy to examine the lipid profile, glucose homeostasis, and thyroid function tests.

Results: The lipid profile and blood pressure parameters deteriorated, and the mean body mass index and waist circumference with the metabolic syndrome rates significantly increased at the 12th and 24th months follow-up. Preoperative body mass index (Exp[B] 1.60; p=0.003) was independently associated with metabolic syndrome at the 2nd year after total thyroidectomyin a multivariate regression analysis.

Conclusion: The frequency and severity of MetS is high in adult patients with non-toxic multinodular goitre after total thyroidectomy. The frequency of metabolic syndrome increased in patients with a high body mass index after total thyroidectomy.

Keywords: Metabolic syndrome, total thyroidectomy, subclinical hypothyroidism, body mass index

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INTRODUCTION

In the United States, according to the Centers for Disease Control and Prevention report on the National Hospital Discharge Survey 2010, surgical procedures involving thyroid disorders (303.000/year) rank second among the most frequently performed surgical procedures (1). The surgical practice has changed in favor of total thyroidectomy (TT) for the management of benign nodular disease in the last decade. The adherents of TT emphasize its potential advantages of a lower risk for recurrent nodular disease and a lower rate of thyroidectomy for incidental thyroid carcinoma (2-4). On the other hand, when the nodular disease relapse is considered as the primary endpoint in the treatment of multinodular goitre (MNG), two current prospective randomized studies have reported extremely good results with the Dunhill procedure (hemithyroidectomy plus subtotal resection) and demonstrated the safety and efficacy of leaving a small remnant of thyroid tissue without rendering the patient to total thyroid ablation (5, 6).

The prevention of metabolic complications after TT is as important as surgery-related complications, and it necessitates a close follow-up and treatment. In general, thyroid hormones regulate the basal metabolism, and by acting directly on carbohydrate and lipid metabolism, they determine the basal metabolic rate and energy expenditure, thus regulating thermogenesis (7-9). Thyroid hormones influence cardiac contractility, the heart rate, and systemic vascular resistance. Triiodothyronine (T3) via its direct effect on the vascular smooth muscle cells leads to vascular relaxation (10). Thyroid hormones increase the activity of lipoprotein-lipase with eventual degradation and utilization of triglyceride substrates. Severe hypothyroidism is usually associated with an increased serum concentration of total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and atherogenic lipoprotein profile represented by increased triglyceride (TGC) and decreased high-density lipoprotein-cholesterol (HDL-C) levels (11, 12).

With its growing importance, metabolic syndrome (MetS) is an epidemic public health issue (13). The frequency varies by country, but it ranges between 15% and 30% in Europe (14). The main components of MetS are systemic disorders such as insulin resistance-mediated abdominal obesity, glucose intolerance or diabetes mellitus (DM), and dyslipidemia and hypertension. Thyroid hormones and thyroid dysfunction play an active role in nearly all of these components (15). The effect of hypothyroidism on MetS is unclear, and the impact of total thyroidectomy has not been previously examined. In this respect, the thyroxine (T4) replacement therapy to prevent hypothyroidism and to obviate MetS after total TT is a major concern in surgical practice.

In this study, considering the side-effects of hypothyroidism mentioned above, we investigated the TT and thyroid hormons effects on a new onset of MetS in patients who underwent TT and have received a thyroid hormone replacement therapy. In addition, we aimed to draw attention to the new onset metabolic derangements following the operation.

MATERIAL AND METHODS

Patients and study protocol

This prospective study included patients with MNG who had been treated with TT. Sixty-five patients were allocated between October 2011 and July 2014 at the Department of University of Health Sciences, Izmir Bozyaka Research and Training Hospital, Department of General Surgery. The study protocol was approved by the local ethical committee. Informed consent was obtained from all patients. Six patients were excluded from the study for failing to attend regular visits. Analysis of the study was based on the laboratory, demographic and anthropometric data obtained during the preoperative period and at 1 and 2 years after the operation. The T4 replacement therapy was arranged to keep the thyroid-stimulating hormone (TSH) level within the normal range. It was considered that the patients with a TSH value below 4.24 mIU/mL at the 1st and 2nd year after TT had received effective treatment.

Patients' height (H), weight (W), and waist circumference (WC) were measured and recorded, and the body mass index (BMI) was calculated to assess the patients' body fat. A BMI from 20 to 25, from 25 to 30, and over 30 is considered normal, overweight, and obese, respectively. The definition of MetS is based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (16). The metabolic syndrome severity score (MetSSS) was calculated using the calculator available at http://publichealth.hsc.wvu.edu/biostatistics/metabolic-syndrome-severity-calculator (17). Patients were considered hypertensive based on double high reading of a systolic blood pressure (SBP) ≥140 mm Hg and/or a diastolic blood pressure (DBP) ≥90 mmHg (18). A clinical diagnosis of hypertension is established if the patient has already been under a treatment program or complied with the above criteria.

The criteria for the diagnosis of diabetes are based on the American Diabetes Association guidelines. Thus, patients with fasting plasma glucose level (FPG) ≥126 mg/dL (7.0 mmol/L) or HbA1C ≥6.5%, and those with a previous diagnosis of diabetes and/or regularly using antidiabetic drugs were considered to have overt diabetes (19). The homeostatic model assessment (HOMA-IR) test was used to assess the insulin resistance. A fasting insulin test less than 10 IU/mL was considered optimal. The test was calculated by the following formula: HOMA-IR=(fasting insulin [mU/l]xfasting plasma glucose [mg/dL])/405.

The diagnosis of atherogenic dyslipidemia (AD) required elevated TGC ≥150 mg/dL and low concentrations of HDL-C (<40 mg/dL in men and <50mg/dL in women) in a routine lipoprotein profile (20, 21).

Postoperative subclinical hypothyroidism is defined as an elevated TSH (above the upper limit of reference range) with normal FT4 and FT3 concentrations. Normal ranges for TSH, FT3, and FT4 were 0.41–4.24 mIU/mL, 2.5–3.9 pg/mL, and 0.61–1.06 ng/dL, respectively.

Peripheral blood samples were obtained after 12 hours of fasting, and low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), total cholesterol (TC), triglycerides (TGC), fasting blood glucose (FBG), fasting insulin (FI), thyroid stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), highly sensitive C-reactive protein (hsCRP), and hemoglobin A1c (HbA1c) levels were analyzed. Patients were invited to the hospital for 12- and 24-month visits, and the previous steps were repeated. The data and concomitant medication of the patients were recorded.

Laboratory Technology

A Roche cobas c 311 photometric analyzer was used for the measurement of substrates (albumin, total protein, Urea/Bun), enzymes (ALP, ALT, AST, GGT), the cardiovascular risk profile (TC, HDL-C, LDL-C, TGC), and hsCRP. The UniCel DxI 800; Beckman CoulterNyon, Switzerland, system was used for the determination of the FT3, FT4, and TSH levels. Applied FT3 and FT4 assays were paramagnetic particles; chemiluminescent immunoassays for the quantitative determination of free thyroxine and T3 levels in human serum and plasma. A hypersensitive hTSH/fast TSH Reagent (third-generation assay) made up of paramagnetic particles coated with goat anti-mouse IgG/anti-hTSH MAb complexes was used for the TSH measurement. The analytical sensitivity of the assay was 0.003 µIU/mL.

Statistical Analysis

Data were expressed as the mean±standard deviation of the mean. Proportions were compared by x2 analysis. The mean values of two groups (with or without MetS) were compared by the Student's T-test or by a nonparametric test if the data were not normally distributed. Comparisons of parameters with more than 2 groups (preoperative and postoperative 12th and 24th month values) were analyzed by the analysis of variance. Stepwise logistic regression analysis was used to determine independent predictors of MetS. $p<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS, version 15 (SPSS Inc.; Chicago, IL, USA).

Compared to patients with preexisting MetS before the operation, we assumed a 10% increase at the end of the 1st year after total thyroidectomy. Thus, determining the statistical power as 0.8 and alpha error level of 5%, we found that the required number of patients was 136. In our study, the percentage of patients with metabolic syndrome increased by approximately 12% in the first year after surgery. However, this analysis was based on 59 patients, and the statistical power was 0.64.

RESULTS

The mean age of the patients was 51.9±12.7 (23–75) years. The mean BMI and the average WC were 28.3±4.21 kg/m^2 (20.7–40.7) and 100.2±10.1 (76–123) cm. The mean systolic and diastolic BP were 120.2±11.4 mmHg (100–150) and 76.8±8.6 mmHg (60–90), respectively.

There was a female preponderance (50 pts. or 83.3% for females vs. 9 pts. or 16.6% for males for MNG). With respect to

pre-existing (preoperative) co-morbid diseases, 18 patients had hypertension (30.5%), nine had DM (15.3%), three had coronary artery disease (5.1%), and three had hyperlipidemia (5.1%). Of the hypertensive patients, 8.5% was on ss-a blocker treatment (n=5), 15.3% were using angiotensin-converting-enzyme inhibitors or angiotensin II receptor antagonists (n=9), 8.5% of them received thiazide diuretics (n=5), and 5.1% were using calcium-channel blockers (n=3). Seven patients with diabetes were using oral anti-diabetic drugs, and 2 were on insulin treatment.

The mean TSH, FT3, and FT4 values were 1.58±2.72 mIU/mL (0.01–19), 3.11±0.41 pg/mL (2.54–4.69) and 0.84±0.16 ng/dL (0.43–1.30). All but 1 patient had normal FT3 and FT4 values before the operation. A female patient presented with a FT4 level of 1.3 ng/dL and TSH value of 0.06 mIU/mL.

The indication for surgery was compressive symptoms causing neck discomfort, progressive growth of the dominant nodule or recurrence of cysts after aspiration in all, and additionally nodule(s) suspicious for malignancy in 2 patients. The final pathological diagnosis was MNG in 49 patients (83%), MNG with micropapillary carcinoma in 8 cases (13.6%), and MNG with papillary thyroid carcinoma in 2 (3.4%) patients. Postoperative replacement therapy with L-thyroxine is not implemented in any case until the final pathology result is obtained. This corresponded to an average period of 2 weeks.

Fifty-seven patients completed the 1st year, and 42 cases already completed the 2nd year controls, and the results were statistically evaluated.

Comparison of Pre-Operative Period vs. Post-Operative 1st Year

A preoperative TSH value of 1.58±2.72 µIU/mL increased to 2.13±3.64 (p=0.06), and preoperative FT4 value of 0.84±0.16 ng/dL improved significantly to 0.99±0.20 ng/dL (p<0.001) during the postoperative 12 months, indicating the adequacy of thyroxine replacement therapy. Indeed, the evaluation of the 12-month laboratory results revealed normal FT4 levels in all cases (Table 1).

Preoperative values of BMI, WC, and the ratio of patients with metabolic syndrome increased significantly statistically during the 1st year after the operation. With respect to BMI, 15 patients (25.4%) were normal weight, 24 (40.6%) were overweight, and 20 (34%) were obese before the operation. At the 1st year follow-up, the number of patients with normal weight markedly decreased, and the number of obese patients increased (Figure 1).

Similarly, SBP and DBP increased, and the TG and LDL values worsened significantly (Table 1). In addition, 1 patient had newly diagnosed hypertension, and 2 cases manifested with uncontrolled hypertension requiring a second drug. At the first year, 11 patients (19%) had TSH values higher than normal (>4.24 ml/mL). The comparison of patients with normal

Table 1. Comparison of laboratory and metabolic parameters in patients according to the follow-up period

	Pre-operative (N:59) (Mean±SD)	Post-operative 12 Months (N:58) (Mean±SD)	Post-operative 24 Months (N:42) (Mean±SD)	p
Free T3 (pg/mL) (N:2.5–3.9)	3.11±0.40	2.84±0.32	3.35±4.42	0.02
Free T4 (ng/dL) (N:0.6–1.1)	0.84±0.16	0.99±0.20	1.02±0.23	<0.001
TSH (mIU/mL) (N:0.4–4.24)	1.58±2.72	2.13±3.64	4.63±7.46	0.06
Subclinical hypothyroid patient rate (%)	10	19	31	0.46
Fasting glucose (mg/dL)	109±31	108±25	109±28	0.93
HOMA-IR	3.24±3.93	2.89±3.58	3.08±4.63	0.74
HgbA1c (%)	5.8±0.7	6.0±0.6	5.8±0.6	0.4
hsCRP (mg/dL)	2.55±3.51	0.55±0.62	2.72±3.78	<0.001
Total cholesterol (mg/dL)	190±31	208±36	216±34	0.179
HDL-C (mg/dL)	54±12	53±11	54±13	0.37
LDL-C (mg/dL)	118±26	139±28	143±28	0.002
Triglyceride (mg/dL)	116±53	146±88	149±77	0.004
Systolic BP (mmHg)	118±11	128±13	130±12	0.001
Diastolic BP (mmHg)	75±8.8	83±11	80±10	0.01
Weight (kg)	75±12	78±12	79±12	0.001
BMI (kg/m^2)	28.2±4.2	30.0±4.2	30.3±4.3	0.001
Waist circumference (mm)	100±10	105±11	106±11	<0.001
Obesity (%)	34	39.7	47.7	0.78
Metabolic syndrome (%)	39	51.7	61.9	0.01
Metabolic syndrome severity score	0.92±0.75	0.96±0.60	1.04±0.72	0.85

SD: standard deviation; TSH: thyroid stimulanting hormone; HDL-C: high-density lipoproteins cholesterol; LDL-C: low-density lipoprotein cholesterol; BP: blood pressure; BMI: body mass index

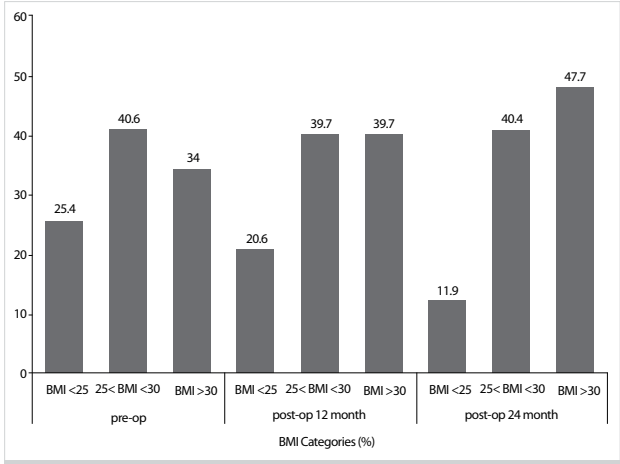

Figure 1. Body mass index (BMI) change over time

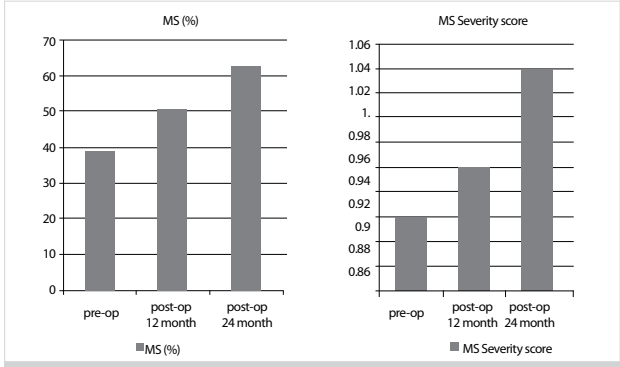

Figure 2. Metabolic syndrome and the severity score change over time

and high TSH levels at 1 year after the operation revealed no statistically significant difference in terms of the proportion of cases with MetS (55% vs. 36%; p=0.265), the mean BMI (30±5 vs. 29±4; p=0.44), and mean WC (105±12cm vs. 103±11cm; p=0.52). At the postoperative first year, the number of patients with MetS was 30 (51.7%) and their MetSSS was 0.96±0.60. Seven of them were newly diagnosed MetS (Figure 2).

The metabolic syndrome severity score of patients with former MetS (23 pts.) increased from 1.05±0.76 to 1.13±0.67; p=0.56. Compared to other patients, patients with MetS were in elderly, with higher baseline BMI and more often had a history of diabetes and hypertension, but they did not have significant difference with regard to the thyroid function test values (Table 2). Among the variables such as age, gender, the TSH level, basal BMI, history of DM and hypertension; the presence of DM (Exp[B] 14.34; p=0.03) and hypertension (Exp[B] 6.57; p=0.02) independently associated with the development of MetS in multivariate logistic regression analysis.

Comparison of Pre-Operative vs. Post-Operative 2nd Year

Forty-two patients have completed the 2nd year after BTT. Of the patients, the mean TSH, FT4, and FT3 values were 4.63±7.46 mIU/mL, 1.02±0.23 ng/dL, and 3.35±4.42pg/mL., respectively. The lipid profile and blood pressure parameters deteriorated, and the mean BMI and WC with MetS rates significantly increased at the 2nd year follow-up of patients (Table 1). The increase in the MetS rates was accompanied by an increase in MetSSS (Figure 2).

Subclinic hypothyroidism was observed in 13 cases (30.9%) at the 24th month after surgery. Eight of them (61.5%) had obesity, and 12 (92%) had MetS. Of the remaining 29 patients with normal TSH values, 12 (41%) were obese, and 14 (48%) had developed MetS. The difference between the MetS rates of patients with normal and high TSH levels was statistically significant (92% vs. 48%; p=0.001).

Those who had MetS were elderly, often had subclinic hypothyroidism, a higher basal and surveillance BMI, and had more frequently DM and hypertension (Table 2). Among the variables such as age, gender, baseline BMI, the history of DM and hypertension, and the TSH level; the baseline BMI (Exp[B] 1.60; p=0.003) independently associated with MetS in multivariate logistic regression analysis was identified.

DISCUSSION

In this study; despite the LT4 replacement therapy in patients who underwent TT, we observed worsening of metabolic parameters and an increase in the prevalence of MetS during the 2-year follow-up period. Indeed, the incidence of MetS increased from 39% to 52% at the postoperative 1st year and rose up to 62% at the 2nd year follow-up with simultaneous increase in MetSSS. Moreover, MetS rate rose to 92% in patients with the TSH level >4.2 mIU/mL at the 2nd year control.

The relationship between thyroid dysfunction and MetS has been shown in several studies. In these patients, the most common thyroid dysfunction is subclinical hypothyroidism (22-24). However, the literature about the frequency of MetS in patients with multinodular goitre is limited. In a study of 1422 Caucasian patients with thyroid disease, the presence of multinodular non-toxic goitre independently predicted the development of MetS (25). In our study, metabolic syndrome was present in 39% of patients referred for surgery because of MNG. More importantly, we detected a significant increase in the rate and severity of MetS after the operation. This indicates the importance of the choice of operation (total or subtotal thyroidectomy) and a close follow-up in these patients with high cardiovascular risk.

In our study group, we observed a significant increase in the prevalence of MetS at the 1st year follow-up despite the LT-4 replacement therapy. Several factors may be responsible for this process. First of all, keeping the target TSH levels lower for these specific patients can lead to a reduction in the development and progression of MetS. A significant relationship between the prevalence of MetS and the TSH levels existed in a large-scale cohort study including 7270 patients and by offsetting a normal TSH value between 0.35 and 1.38 mIU/mL; the prevalence of MetS increased 1.25-fold in patients with the TSH levels between 2.42 and 3.44 mIU/mL), and the MetS risk is increased 1.92-fold in cases with TSH>4.48 mIU/mL (26). In our study, the average TSH value at 1 year was in the normal range (2.13±3.64 mIU/mL); however, it was higher than the reference TSH value of the previously mentioned study. Relatively high TSH values may contribute to the deterioration of metabolic profile of patients after TT.

Two important features of this study were the progression of central obesity reflected by elevated body weight, BMI, and WC after surgery and the increasing rate of patients with MetS

Table 2. Comparison of patients with or without metabolic syndrome in three periods

	Pre-op MS(+) [(n:23),39%] (Mean±SD)	Pre-op MS(–) [(N:36),61%] (Mean±SD)	p	12 months MS (+) [(n:30),51.7%] (Mean±SD)	12 months MS (–) [(n:28),48.3%] (Mean±SD)	P	24 months MS (+) [(n:26),61.9%] (Mean±SD)	24 months MS(–) [(n:16),38.1%] (Mean±SD)	P
Age* (years)	57±10	49±13	0.01	56±10	48±13	0.01	58±10	49±14	0.02
Gender (female/male)	19/4	31/5	0.72	26/4	23/5	0.64	23/3	13/3	0.52
BMI* (kg/m^2) (basal)	30.5±4.3	26.8±3.5	0.001	29.8±3.96	26.7±3.78	0.004	30.9±3.89	25.7±3.10	<0.001
BMI* (kg/m^2) (Last control)				30.6±4.13	27.5±3.88	0.005	31.9±3.8	27.1±4.0	<0.001
Obesity# (basal)	11(47.8)	9(25)	0.08	13 (43)	7 (25)	0.14	16 (62)	2(13)	0.001
Obesity# (Last control)				14(46.6)	9(32)	0.26	17(65)	3(19)	0.002
Hypertansion#	14(60.5)	4(11,1)	<0,001	16(53)	3(11)	0.001	12(46)	2(12.5)	0.01
Hyperlipidemia#	3(11.5)	0(0)	0.08	10(33.3)	0(0)	0.08	3(11.5)	0(0)	0.08
Diabetes#	6(26)	3(8.3)	0.09	8(27)	1(4)	0.01	8(30.7)	1 (6.2)	0.03
HOMA-IR*	4. 20±5.69	2.45±3.61	0.154	3.91±5.42	2.37±3.46	0.20	3.82±4.33	1.60±0.61	0.08
Fasting Glucose* (mg/dL)	116±31	99±23	0.01	114±31	98±20	0.02	116±33	97±9.4	0.009
HbA1c* (%)	6.08±0.87	5.62±0.68	0.02	6.0±0.7	5.5±0.3	0.01	5.97±0.62	5.39±0.41	0.002
HsCRP* (mg/dL)	1.36±1.99	1.81±3.16	0.546	2.20±3.50	1.08±1.53	0.12	2.56±3.12	3.20±3.58	0.54
FT3* (pg/mL)	2.98±0.30	3.18±0.44	0.06	2.89±0.35	2.91±0.31	0.12	3.70±5.55	2.73±0.51	0.49
FT4* (ng/dL)	0.86±0.18	0.81±0.13	0.25	1.05±0.21	0.93±0.16	0.19	1.01±0.27	1.03±0.17	0.78
TSH* (mIU/mL)	2.22±3.97	1.10±1.21	0.20	1.95±3.03	4.78±1.95	0.10	6.59±8.54	1.36±2.97	0.007
Hypothyroid Patients Rate#	3(11.5)	3(8.3)	0.56	4(13)	7(25)	0.27	12 (46)	1(6)	0.002

Pre-op: preoperative; MS: metabolic syndrome; SD: standard deviation; FT3: free-T3; FT4: free-T4;
TSH: thyroid stimulanting hormone; BMI: body mass index
Datas are presented as *;mean±SD #; n (%)

(from 39% to 51.7%) at the postoperative 1st year (Table 1). The FT3 levels significantly decreased within the 1st year following the operation but improved thereafter. In our opinion, the most rationalistic explanation of the increase in WC appears to be diminished 3.3′-triiodothyronine-responsive energy expenditure and corresponding slow basal metabolic rate in these patients with the FT3 hormone levels within the lower limit of normal value (27, 28). It is very-well known that thyroid hormones affect the synthesis and particularly the degradation of lipids. Thus, both the utilization of lipid substrates and the mobilization of triglycerides stored in the adipose tissue should be reduced in these patients (29). Lipid disorders in our series were consistent with a Colorado study, which was reflected by the increased mean total cholesterol and low-density lipoprotein cholesterol levels. In the Colorado study, impaired lipid profile was observed particularly in subjects with subclinical hypothyroidism (TSH values between 5.1 and 10 mIU/L); however, in our study, a progressively deteriorating TC and LDL profile was present in the clear majority of patients independently from the TSH levels (30). Similarly, in a separate study, total thyroidectomy seriously deteriorated the lipid profile. By an effective thyroxine replacement, the patients have become euthyroid at least for 3 months after TT. However, compared with the the preoperative serum total cholesterol levels, the deteriorated TC values after TT remained unchanged at the 6th month follow-up (31). What measures to be taken to counteract the cardiometabolic adverse effects of impaired lipid profile and increased (W, BMI, WC) is a matter of concern in TT patients. An association between subclinical hypothyroidism and an increased risk of the coronary heart disease mortality has been shown particularly in those with a TSH level of 10 mIU/L or greater (32). None of the patients with hypertension and coronary heart disease required cardiac intervention or experienced myocardial infarction in our series. This may be attributed to shorter follow-up despite a high (31%) prevalance of subclinic hypothyroidism (13 cases at the 24th month after TT).

This study provides important data of various biochemical parameters and body composition and their effects in patients undergoing TT. However, it lacks a control group in terms of an optimal medical treatment after surgery; therefore, a controlled study is necessary to confirm our hypothesis that TT renders patients to metabolic complications that could not be managed by the levothyroxine treatment alone. This analysis is based on 59 patients, and the statistical power is 0.64. Although the statistical power is low, our results were noteworthy that especially preoperative BMI was statistically significant in predicting the postoperative MetS.

CONCLUSION

MetS is a major problem in adult patients with non-toxic multinodular goiter undergoing surgery. In these patients, an increased frequency of MetS can be observed even after the administration of levothyroxine replacement therapy following TT. Given the increased frequency of MetS after surgery in patients with preexisting DM, hypertension, and high BMI, if possible, a subtotal thyroidectomy and/or alternative thyroid replacement therapy may be considered.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.Z., A.U.; Design - A.U.; Supervision - V.S., A.U.; Materials - B.Z., G.O.; Data Collection and/or Processing - B.Z., G.O., A.A.; Analysis and/or Interpretation - A.D. E.T.; Literature Search - E.T., A.U.; Writing Manuscript - İ.Z., A.U., E.T.; Critical Reviews - V.S., E.T.

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Original Article

Evaluation of the effects of adipose-derived mesenchymal stem cells on intraperitoneal adhesions

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ABSTRACT

Objectives: The goal was to examine the efficiency of local implementation of adipose-derived mesenchymal stem cells, which have an anti-inflammatory effect, in preventing the intra-abdominal adhesions in rats.

Material and Methods: Twenty-one Wistar albino rats were randomly divided into 3 groups, 7 rats in each: Group 1 was defined as the control group, Group 2 as the sham group, and Group 3 as the adipose-derived mesenchymal stem cell group. A 6 cm mid-abdomen incision in the all the rats was performed. The cecum serosa and sub-serosa were injured by rubbing with a gauze. No agent was applied intraperitoneally for the rats in Group 1; 1.5 mL saline and $2x10^6$/kg allojenic adipose-derived mesenchymal stem cells in the 1.5 mL saline were injected into peritoneum of rats in Groups 2 and 3, respectively. Laparotomy was performed on the 14th day. Adhesion scores, histopathological examination, E-cadherin expression, and the tissue hydroxyproline level were evaluated.

Results: The general adhesion score and collagen deposition in Group 3 were found to be significantly higher than in Groups 1 and 2 (p=0.003 and p=0.009, respectively). In the inflammatory cell comparison, a significant decrease was found in Group 3 in proportion to Groups 1 and 2 (p=0.001, p=0.005, respectively). The E-cadherin levels were found to be higher in Group 3 (p=0.003).

Conclusion: Severe adhesion was observed in the adipose-derived mesenchymal stem cells group. Collagen intensity and E-Cadherin expression also increased in the adipose-derived mesenchymal stem cells group. The anti-inflammatory effect was also seen in the adipose-derived mesenchymal stem cells group.

Keywords: E-cadherin, rat, hydroxyproline, peritoneal adhesion, stem cells

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INTRODUCTION

Intraperitoneal adhesions that may develop after a great number of abdominal operations is an important problem that surgeons have to deal with after the abdominal surgical procedures. Although the incidence varies between 67% and 93%, the incidence of cases requiring surgical intervention due to intraperitoneal adhesion is 15%–18% (1, 2). The development of minimal invasive methods such as laparoscopy and their common usages decreased these rates (3). Intraperitoneal adhesions lead to hospitalization and surgical intervention due to mechanic ileus and pelvic pain. Furthermore, the intraperitoneal adhesions may cause secondary infertility in women during the fertility age (4). Since the exploration is very difficult in operations performed due to the adhesion, the iatrogenic injuries may be seen more frequently. Consequently, these complications lead to mortality and morbidity. Moreover, one of the most important results of adhesion-caused ileus is the increase in workforce loss and patient costs. For instance, in a study that has been carried out in the United States, it has been reported that the cost of surgeries performed due to the intraperitoneal adhesions was US$1.3 billion in a year (5).

To decrease and prevent the adhesions, the adhesion-barrier agents such as carboxmethylcellulose, steroids, and non-steroidal anti-inflammatory drugs, immunosuppressive drugs, clinoleic against, high molecular weight hyaluronic acid and low molecular weight hydroxypropyl methylcellulose, fibrin destruction agents, recombinant tissue plasminogen activator, bevacizumab, and Vitamin-E have been utilized (6-10). Different results have been reported for these agents. Except for the adhesion-barrier, others could not be put into the practice. Therefore, preventing the intraperitoneal adhesions and dealing with them have constantly remained on the agenda of surgeons interested in abdominal surgery.

It has been reported that post-operative inflammatory responses play a significant role in the formation of adhesions (11). The inflammatory response, especially the suppression of TGF-β1 and IL-6, may play an effective role in decreasing the intraperitoneal adhesion (12). Therefore, the anti-inflammatory feature of the selected chemical agent to prevent the peritoneal adhesion becomes very important. Adipose derived mesenchymal stem cells (ADSCs) show an anti-inflammatory effect by decreasing the inflammation in tissues (13, 14). Under the light of these observations, it can be hypothesized that ADSCs may decrease or prevent the adhesion formation by exhibiting the anti-inflammatory effect in the development of postoperative adhesions. In this study, the goal was to evaluate the effect of ADSCs on intraperitoneal adhesions that have an anti-inflammatory effect and on the intra-abdominal adhesions in rats.

MATERIAL AND METHODS

The present study was approved by the local ethic committee. The protocol was approved by the Animal Ethics Review Committee (Permit number 2016/01-02). All experiments were conducted in compliance with the relevant laws and institutional guidelines.

Rat groups

Twenty-one female Wistar albino rats weighing between 260 and 280gr were randomly divided into 3 groups, 7 rats in each: Group 1 was defined as the control group, Group 2 as Sham, and Group 3 as the ADSCs group. All rats were females to provide standardization in the study.

The cecum serosa of the rats was injured with a sterile gauze during laparotomy. For the rats in Group 1, no agent was implemented intraperitoneally. For the rats in Group 2, 1.5 ml saline was locally injected into the peritoneum. For the rats in Group 3, $2x10^6$/kg allojenic ADSCs in the 1.5 mL saline were injected locally into the peritoneum.

Anesthesia and Surgical Technique

Rats were kept between 18–24˚C (12 hours of day-night cycle) in cages (4–6 rats in each) with free water and food intake. Standard rat food and water were given to the rats. Before the operation, rats were fasting for 6 hours. As the anesthetics, ketamine (Ketalar, Pfizer, Turkey) 75 mg/kg and Xylazine 10 mg/kg (Rompun, Bayer AG, Leverkusen, Germany) were given intraperitoneally. For asepsis, polyvinylpyrolidone (polyvidon-iodine) 10% was used. Ceftriaxone 100 mg/kg was applied for the purpose of intramuscular prophylaxis. For postoperative analgesia control, a 0.25% bupiviocaine incision was implemented in all the rats. For liquid losses, 10 mg/L 0.09% NaCl was subcutaneously applied to all the rats. After the surgery, the rats were placed into separate cages and then followed up. Five hours after the surgery, the food and water intake was allowed.

After anesthesia, a 6 cm mid-abdomen incision was made in the rats. The cecum serosa and sub-serosa were injured by rubbing with a gauze. After the experimental procedures in the groups, the skin was closed with 4/0 polyglactin sutures subcutaneously.

ADSCs Extraction

To obtain ADSCs, 10- to 12-week-old Wistar albino rats weighing between 270 and 300 g were used. After the ketamine hydrochloride (75mg/kg İM) and xylazine hydrochloride (10mg/kg İM) anesthesia, the inguinal fatty tissues were taken (3–5 cm^3). After washing the fatty tissue with a phosphate buffer solution (PBS, Sigma Aldrich, St. Louis, MO, USA) containing penicillin-streptomycin, the tissue was cut into small pieces. After 1 hour of enzymatic degradation at 37°C with 5 ml Type I collagenase (1mg/mL, Sigma), 20–30 mL Low Glucose Dulbecco's Modified Eagle's Medium (L-DMEM, Gibco) with 1% penicillin-streptomycin (PS, Sigma), 1% L-glutamine (Sigma), and 10% fetal bovine serum (FBS, Gibco) were included. The mixture was centrifuged at 1.500 rpm for 10 minutes, and after removing the supernatant portion and by adding 15–20 mL of medium on the cell pellet, the centrifuge was continued for 10 min. at 1.200 rpm. After removing the supernatant portion, 12 mL of medium was added on the ADSC pellet and then, within a 75 cm^2 flask, incubated in a drying oven at 37°C with 5% CO_2. The ADSC cultures were used after the third passage.

Evaluation of the Adhesions and Tissue Sampling

On the 14th day, surgery was performed in rats under intraperitoneal anesthesia with ketamine (Ketalar, Pfizer, Turkey) 75 mg/kg and xylazine 10 mg/kg (Rompun, Bayer AG, Leverkusen, Germany). For the rats under anesthesia, to prevent the adhesion-caused injuries and to evaluate the adhesions on incision, laparotomy was performed via left paramedian incision.

A researcher, who did not know which group the rats belonged to, rated the rats on the scale between 0 and 9 points, and the levels of intra-abdominal adhesions were scored (15). In the assessment, the severity and the level of adhesion in the defect region were scored. The general score was calculated by adding up these three parameters.

After the rating, tissue samples were taken from the cecum and adjacent region adhesions to perform the histopathologic and other examinations. The samples taken were divided into two equal parts. One part of the tissue samples was fixed with 1 cc physiological saline solution, and kept at –80°C for hydroxyproline determination. The remaining part was fixed in formaldehyde for a histopathological examination. All rats were sacrificed by investigators via cervical dislocation.

Histopathologic Analysis

Histopathologic analyses were performed by the same pathologist. The pieces were prepared in a paraffin block, and their thin sections were analyzed under the light microscope with hematoxylin–eosin staining; the images were recorded via the computer. The histopathologic staging was performed in accordance with the Ehrlich–Hunt model (16) (Table 1).

In this model, the assessment criteria were determined to be inflammatory cells, fibroblast, neovascularization, and the collagen level. The cellular and histopathologic scoring were semi-quantitatively determined to be at the fourth level. Separate calculations were performed for inflammatory cells, fibroblast proliferation, neovascularization, and the collagen deposition.

Immunohistochemical Analysis

For the immunohistochemical analysis, tissue samples were taken from all the rats in study groups and the control group. For the sections, the formalin fixation, paraffin treatment, and blocking were performed, and then, the immunohistochemical staining was carried out. In the tissues of different groups, the level of E-cadherin was semi-quantitatively determined (absent (0), slight (1): up to 20% positive; moderate (2): 21%–50% positive; potent (3): 51%–100%).

Tissue Hydroxyproline Level Determination

The hydroxyproline content of the tissues was determined using the Hydroxyproline Assay Kit from Sigma (Cat. No: MAK008). The assay method is based on the reaction of oxidized hydroxyproline with 4-dimethylaminobenzaldehyde (DMAB) to give a colorimetric product at 560 nm (1). To explain briefly, 100 µL of water was added on 10 mg of wet tissue, and homogenization was performed by a sonicator equipped with a microtip (Bandelin, Germany) at the amplitude of 25% (0.7 s on, 0.2 s off cycle). Sonication was continued until the tissue suspension became completely homogeneous, which usually took approximately 1–2 min of total sonication time. 100 µL of homogenized tissue sample was mixed with 100 µL of concentrated HCl (12 M), and

the mixture was hydrolyzed at 120 °C for 3 hours. Once the hydrolysis was complete, the samples were centrifuged at 13,000 g for 10 min, and 20 µL of each hydrolysate was transferred into the wells of a 96-well plate. The plate was incubated at 60 °C for 3–4 hours to dry the samples completely. This was followed by the addition of 100 µL chloramine T solution to each well and incubation for 5 min at the room temperature for the oxidation of hydroxyproline. Afterwards, 100 µl of the DMAB reagent was added into the wells, and the plate was incubated at 60°C for 90 min. A microplate reader (Multiskan GO, Thermofisher Scientific) was used to measure the absorbance at 560 nm immediately after incubation. The hydroxyproline standards with known concentration were also measured in a similar way. The amount of the hydroxyproline content was calculated using a standard curve that was generated from the absorbance values of standards. The results were expressed as micrograms of hydroxyproline per milligrams of wet tissue (µg/mg).

Statistical Analysis

For statistical analyses, Statistical Package for the Social Sciences (SPSS) version 13.0 (SPSS Inc.; Chicago, IL, USA). The

Table 1. Histologic Grading Scale*

Grade	Inflammatory cell/fibroblast/ neovascularization/collagen
1	A small amount and scattered
2	A small amount and all areas
3	A lot and scattered
4	A lot and all areas

*Ehrlich–Hunt Model

Table 2. Comparison of the Group Adhesion Scores

	Group 1	Group 2	Group 3	p*
General adhesion score	6±1.1[a]	4.4±1.1[a]	7.5±1.2[a]	=0.003
Adhesion severity	2.1±0.3	1.7±0.4	2.2±0.4	=0.278
Degree of adhesion	1.7±0.7	1.2±0.4[a]	2.5±0.5[a]	=0.038
Participation percentage	2.1±0.3	1.4±0.5[a]	2.7±0.4[a]	=0.003

*Kruskal–Wallis test: The results were given as the mean±standard deviation
[a]Subgroup comparison: Statistically significant groups

Table 3. Comparison of Histopathologic Findings and the Hydroxyproline Levels of Groups

	Group 1	Group 2	Group 3	p*
Inflammation	3 (3, 4)*	2 (3, 3)*	1 (2, 2)*	0.001[a]
Fibroblast activation	3 (3, 4)	3 (3, 4)	3 (4, 4)	0.135[a]
Neovascularization	3 (3, 4)	3 (3, 4)	3 (4, 4)	0.189[a]
Collagen deposition	3 (3, 4)*	3 (4, 4) *	4 (4, 4)*	0.009[a]
E-cadherin	0.4±0.5*	0.14±0.3*	1.5±0.5*	0.003[a]
Hydroxyproline (µg/mg)	0.38±0.23	0.48±0.31	0.40±0.06	0.690**

*Subgroup comparison: Statistically significant groups. Minimum (median, maximum)
**ANOVA
Group 1: Control; Group 2: Saline; Group 3: Adipose-derived mesenchymal stem cell

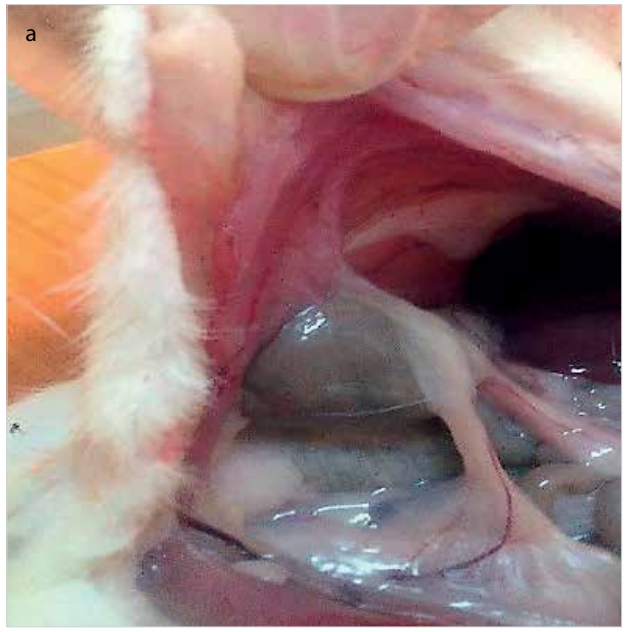

Figure 1. a-c. Macroscopic appearance of tissues. Control group: Intermediate increase adhesion is observed (a), Saline group: Intermediate increase adhesion is observed (b), Mesencimal stem cell group: Increased adhesion is observed (c)

Kruskall–Wallis test was used in the semi-quantitative group comparisons. In the paired comparison, it was done using the Kruskal–Wallis (post hoc tests) and Sida–Dunn test. The analysis of variance was used in comparing the quantitative parameters. The Tukey test was employed for multiple comparisons. The results were given as the mean±standard deviation. The values $p<0.05$ were considered significant.

RESULTS

Adhesion Scores

The general adhesion score was 6±1.1 in Group 1, 4.4±1.1 in Group 2, and 7.5±1.2 in Group 3. The general adhesion score of Group 3 was found to be statistically significantly higher compared to the Group 1 and Group 2 ($p=0.003$). No statistically significant difference was found between the general adhesion scores of Group 1 and Group 2 ($p>0.05$; Table 2, Figure 1).

Histopathologic Analysis Results

In neovascularization and fibroblast intensity, no statistically significant difference was observed between the groups. In terms of collagen deposition, the statistically significant increase was found in Group 3 in proportion to Groups 1 and 2 ($p=0.009$). In inflammatory cell comparisons, a significant decrease was seen in Group 3 relative to Groups 1 and 2 ($p=0.001$). No statistically significant difference was found between Group 1 and Group 2 ($p>0.05$) (Table 3; Figure 2).

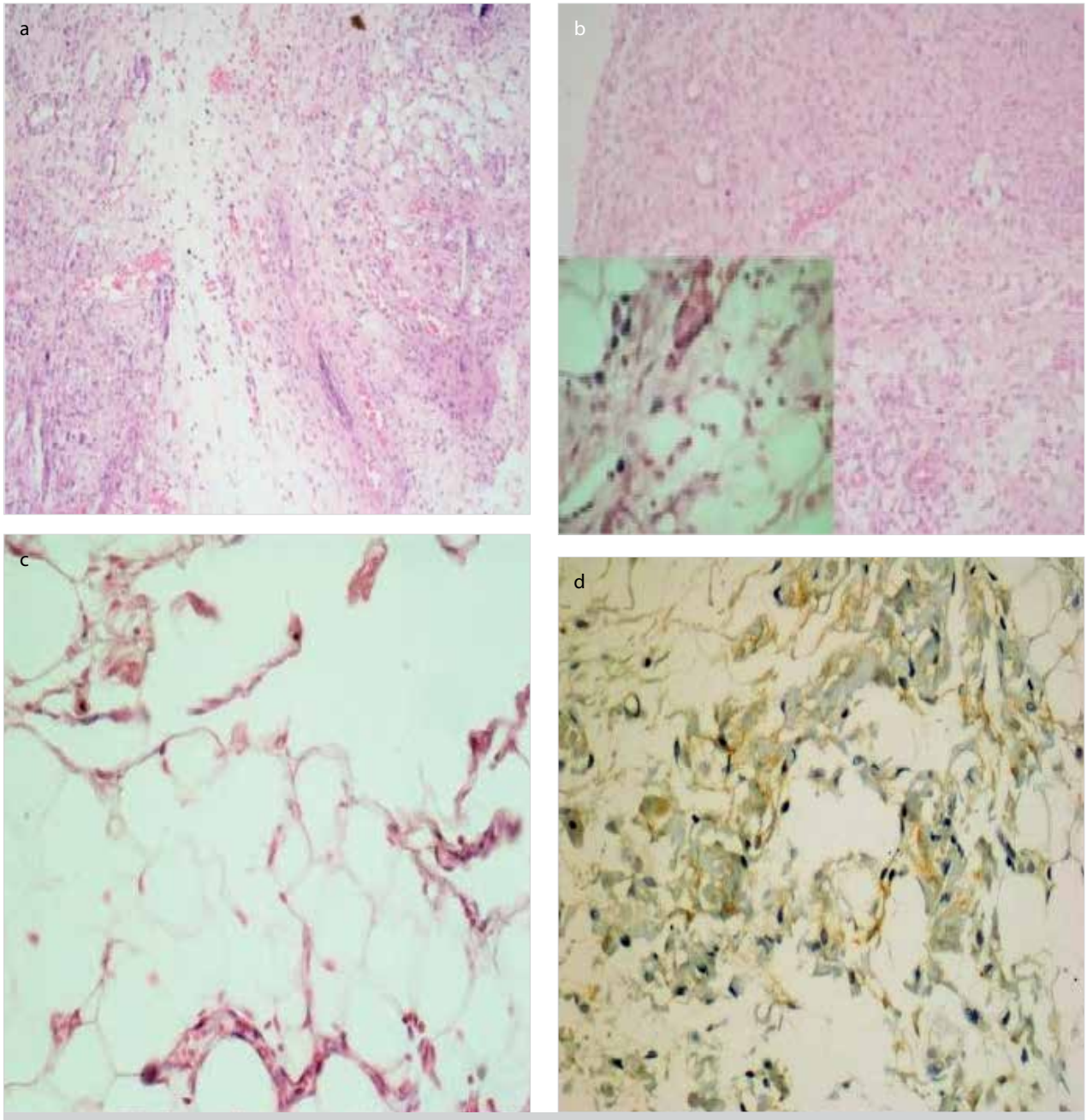

Figure 2. a-d. Histopathologic changes in Group 3. Grade 3 staining in Group 3: increase in the fibroblast intensity and a significant increase in neovascularization and the collagen fiber formation are observed (HE; X200) (a), Increase in collagen fiber and neovascularization in Group 3 (HE; X100) (b), Significant decrease in the number of inflammatory cells in Group 3 (HE; X100) (c), The pattern of Grade 3 staining with E-cadherin in Group 3 (immunohistochemistry; X400) (d)

Immunohistochemical Analysis Results

In comparisons performed between the groups, the pattern of positive staining with E-cadherin was found to be statistically higher in Group 3 compared with Groups 1 and 2 (p=0.003). No statistically significant difference was found between Group 1 and Group 2 (p>0.05) (Table 3).

Tissue Hydroxyproline Level Results

The hydroxyproline level was found to be 0.38±0.23 µg/mg in Group 1, 0.48±0.31 µg/mg in Group 2, and 0.40±0.06 µg/mg in Group 3. No statistically significant difference was found between the groups (p=0.69) (Table 3).

DISCUSSION

Intraperitoneal adhesions are an important problem that surgeons have to cope with after the abdominal surgical procedures. The clinical situations caused by intraperitoneal adhesions and the complications, which develop due to intraperitoneal adhesions, lead to an increased mortality and morbidity (17). For this reason, preventing the intraperitoneal adhesions and dealing with the adhesions have constantly remained on the agenda of surgeons interested in the abdominal surgery. The studies have been carried out with many agents to prevent the adhesions. However, there is no consensus on the ideal agent to be used.

In the formation of postoperative intraperitoneal adhesions, damaged tissues and the fibrin deposits are responsible for the inflammation. The inflammatory process continues with the restoration of damaged tissues by the cells such as macrophages and fibroblast cells. The permanent fibrous adhesions are formed with collagen and other matrix proteins expressed from fibroblasts.

In the study by Sekiguchi et al. (18), it was reported that the bone marrow stem cells played an important role in the peritoneal restoration process and mesothelial remodeling. In that study, it was shown that the anti-inflammatory effect of the mesenchymal stem cells lasted for 14 days. In another study, the IL-10 cytokine having an inflammatory property has been found in the mesenchymal stem cell. The same study noted that the intraperitoneally injected mesenchymal stem cells suppressed the TGF-β1 expression and prevented the phosphorylation of Smad 2 caused by TGF-β1. These results indicate that the TGF-β1 signal was suppressed, and consequently, the mesenchymal stem cells showed an anti-inflammatory effect (19).

Although the tissue repair function and the immunoregulation of mesenchymal stem cells (MSCs) have been known for a long time, their exact mechanisms of action are still not clear. Recent findings indicate that an intravenous injection of MSCs may attenuate the peritoneal injury by repairing mesothelial cells, reducing inflammation and fibrosis. There remains a controversy on the application of MSCs in peritonitis, and peritoneal injury is still being explored. Mesenchymal stem cells segregate many growth factors. They are the strongest mediators of the HGF and BMP-7 anti-fibrotic cytokines. They play a preventive role in the formation of peritoneal fibrosis (20). The secretion of TSG-6 by MSCs makes a major contribution to the therapeutic benefits of MSCs. Moreover, when mesenchymal stem cells have been transplanted into injured tissues, an improvement was achieved in neovascularization and wound healing (21). ADSCs have been shown to have an anti-inflammatory effect by decreasing inflammation in the tissue (14, 20). While planning our study, we were focused on that ADSCs would have an anti-inflammatory effect, decrease the intra-abdominal adhesion, and might prevent it. Under the light of these clinical and experimental observations, ADSCs were used in the intra-abdominal adhesion model in our study.

In comparisons in terms of inflammatory cells, the inflammatory cell intensity was found to be significantly lower in the ADSC group in proportion to the control and saline groups. Mesenchymal stem cells also affect many immune cells in terms of proliferation and function. Moreover, they contribute to the immune modulation by assisting the regulatory T-cell production, and the inflammatory response decreases (14, 20). Also, both of the bone marrow-derived MSC and ADSCs decreased the leukocyte infiltration and protected the tissue from inflammation (21, 22). In a study, it has been determined that an intravenous ADSC injection lowered the inflammatory response and the inflammatory cytokine levels such as cyclooxygenase-2, IL-6, and tumor necrosis factor-α. These results revealed the anti-inflammatory property of ADSCs (23). A decrease in the inflammatory cell density was found in the ADSC group from our study in accordance with the previous studies.

In previous studies, it has been reported that mesenchymal stem cells increased the neovascularization and collagen level in tissues (18). Moreover, the increased collagen level may be correlated with an increase in the fibroblast intensity. Fibroblasts are responsible for the secretion of extracellular matrix proteins and collagen, and therefore, they play key role in wound healing. Parallel with the previous studies, we also found a significant increase in the ADSC group in proportion to the saline and control groups in terms of an increased collagen intensity. In our study, no statistically significant fibroblast intensity was found between the groups. However, fibroblast was relatively higher in the ADSC group. Mesenchymal stem cells can contribute to the regeneration in many organs (24). MSCs also increase the fibroblast regeneration. In our study, the increase in fibroblast intensity was thought to be correlated with the regenerative property of mesenchymal stem cells on the fibroblasts.

Hydroxyproline that constitutes the main component of collagen plays an important role in the collagen stabilization (25). The hydroxyproline level is used as an indicator of adhesion severity. An increased hydroxyproline level leads to an increase in peritoneal adhesion severity (26). In our study, the level of hydroxyproline was not found to be statistically significant in the groups. An increase in the general adhesion score in the ADSC group cannot be correlated with an increased hydroxyproline level.

Adipose derived mesenchymal stem cells produce too much cytokines, bioactive matters, extracellular matrix proteins, as well as adhesion molecules (20). In a study, it has been shown that the co-culture with ADSCs increased both the N-cadherin and E-cadherin expression (27). In our study, an increase was observed in the rate of positive staining with E-cadherin in the ADSCs group. E-cadherin is one of the molecules responsible for the intracellular adhesion and communication. An increase in the E-cadherin expression leads to an increase in the rate of cell-to-cell adhesion. Cellular adhesion molecules play an important role in the process of peritoneal adhesion formation.

The increase in E-cadherin expression may contribute to the increase in general adhesion score found in the ADSC group.

According to our hypothesis, it was thought that ADSCs would decrease the adhesion by exhibiting an anti-inflammatory effect and might prevent the adhesions. Despite an anti-inflammatory response, it was observed that ADSCs led to severe and strong intraperitoneal adhesions. The ADSCs group had the highest general adhesion score. Although ADSCs showed a desired anti-inflammatory efficiency, it was observed that they increased the adhesions. An increase in the E-cadherin expression and collagen can be hold responsible for the adhesions.

Study Limitations

This study has several limitations. To the best of our knowledge, this is the first study in the literature that investigated the effects of ADSCs on the postoperative intraperitoneal adhesions formation. The ADSCs-associated histopathologic changes at the ultrastructural level need to be further analyzed. Therefore, further studies are needed to clarify the pathophysiological events. ADSCs were used 1–5x10^6 doses for different purposes and in different studies (28, 29). Although different time points could be considered, a single time point is used to evaluate the adhesion formation in this study. The vascular markers such as CD31 can be used for neovascularization. There are insufficient data on the rejection in allogeneic ADSCs. However, Kim et al. (30) studied immune reactions of allogenic adipogenic differentiated ADSCs. They showed that allogeneic adipogenic-differentiated ADSCs do not cause immunoreaction and maintain nonimmunogenicity. For this reason, they reported that allogenic ADSCs could be used safely in recipients. Since all these findings were obtained in vitro, there is an urgent need in vivo studies for the immune reaction and rejection of allogenic ADSCs. It is not known whether the allogenic ADSC used in our study caused rejection. Immunity can also be a response to the significant adhesion formation.

Adipose derived mesenchymal stem cells are not seen as an ideal agent for preventing the postoperative intraperitoneal adhesions. But, under the clinical conditions, where the formation of adhesions is desired, it can be used in the treatment such as closing the dead gaps via the formation of adhesion.

CONCLUSION

A severe adhesion was observed in the ADSCs-administered group. Also, the collagen intensity and E-cadherin expression increased in the ADSCs-administered group. The anti-inflammatory effect was also seen in the ADSCs group. The effect on the failure of adhesion improvement caused by an ADSCs intraperitoneal injection needs to be further analyzed. Further studies are needed to clarify the pathophysiological events.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Kahramanmaras Sutcu Imam University (2016/01-02).

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.U., A.H.K.; Design - M.D., E.U., T.K.; Supervision - E.U., T.K., M.D.; Resource - E.U., M.D.; Materials - E.U., A.H.K., M.D.; Data Collection and/or Processing - E.U., M.K., M.D.; Analysis and/or Reviews - T.K., A.H.K., M.K.; M.D., E.U.

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Original Article

TLR4 Asp299Gly and Thr399Ile and TLR2 intron 2 microsatellite gene polymorphism in patients with acute biliary pancreatitis: Does it cause the disease?

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ABSTRACT

Objectives: There has been coverage of Toll-like receptor 4 and Toll-like receptor 2 gene polymorphisms in inflammatory episodes in a number of studies. In view of the inflammatory nature of acute pancreatitis, we aimed to determine the predictive value of mutations in Asp299Gly and Thr399Ile of the Toll-like receptor 4 gene, and the intron 2 microsatellite polymorphism of the Toll-like receptor 2 gene on the occurrence of acute biliary pancreatitis.

Material and Methods: The study included 86 patients for the Toll-like receptor 4 Thr399Ile polymorphism, 100 patients for the Toll-like receptor 4 Asp299Gly polymorphism with acute biliary pancreatitis, and 101 healthy volunteers. At the same time, 93 patients and 92 healthy volunteers were included in the study to research the Toll-like receptor 2 intron 2 microsatellite polymorphism. Genotypes were determined using the restriction fragment length polymorphism analysis of PCR products and by an allele-specific PCR.

Results: The Toll-like receptor 4 Thr399Ile homozygotes mutant variants ($p=0.005$) and Toll-like receptor 2 MM genotype ($p<0.001$) were detected with a significantly higher frequency in patients with acute biliary pancreatitis than in the healthy blood donors.

Conclusion: The Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms and the Toll-like receptor 2 intron 2 microsatellite polymorphism are statistically associated with ABP.

Keywords: Acute pancreatitis, biliary, gene polymorphism, Toll-like receptor 2, Toll-like receptor 4

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INTRODUCTION

Acute pancreatitis (AP) is a disease common in the gastrointestinal system that induces acute abdominal pains and can lead to morbidity and sometimes mortality with an incidence rate of 13–45/100000 (1). According to the Atlanta Classification, the severity of pancreatitis has been classified into three distinct categories of mild, moderate severe, and severe pancreatitis. Although mild and moderate severe pancreatitis is seen at the rate of 80%, it recovers without any serious complications (2). Approximately 30% of the death cases have been reported to have arisen from acute pancreatitis (3). The causes of acute pancreatitis include iatrogenically toxic drugs following ERCP due to mechanical obstruction caused by gallstones, hypertriglyceridemia, alcohol, genetic predisposition, anatomical differences, primary inflammation (infectious, autoimmune), trauma, and idiopathic causes. In 60%–85% of patients, there is a history of gallstone or alcoholism (4-6). Of all these reasons, the most frequent etiological factor is the presence of gallstones (1). The most accepted theory in the pathophysiology of AP is the auto-digestion that occurs with trypsin activation in the pancreas parenchyma and the subsequent local and systemic inflammatory damage that develops (2, 4). Acute biliary pancreatitis (ABP) is the inflammation that develops as a result of auto-digestion and enzymatic parenchyma destruction with small gallstones, which as a gallstone complication, find a passageway to progress to the common bile duct and to be impacted to the ampulla of Vater (7, 8). In the pathogenesis of pancreatic inflammation, many immune factors and signaling pathways are involved in the innate immune system. The release of many proinflammatory factors plays a key role in the pathogenesis of AP (9). Toll-like receptors (TLR) with an important place in the pattern-recognition receptors (PRR) family have been researched in animal experiments and human-based clinical studies to investigate their role in the AP damage. Pathogen-associated molecular patterns (PAMPs), alarmins, and damage-associated molecular patterns (DAMPs) can serve as molecular signatures that can be recognized by the PRRs of innate immune system, starting an immunological response against the invasion, and if necessary, assisting in the activation of the adaptive immune system. Molecules found in microorganisms, but not in host cells are associated with PAMPs. Alarmins are endogenous molecules released into the extracellular compartment by activated or necrotic cells in response to stress or tissue damage. Even extracellular matrix molecules are alarmins when up-regulated upon injury or degraded following tissue damage. DAMPs constituted by alarmins and PAMPs, are the main targets of PRRs. PRRs are expressed on the cell surface or in intracellular compartments, but they can be secreted into the blood stream and tissue fluids as well (10).

TLR4 and TLR2 are members of the PRR family, which are frequently investigated as molecular mediators of the inflammation that constitutes AP (11). In different countries, genetic polymorphism has been in-

vestigated using TLR4 Asp299Gly and Thr399Ile with DNA isolation and guanine–thymine (GT) iterations in the TLR2 intron 2 region. The TLR4 Thr399Ile polymorphism and the TLR2 intron 2 microsatellite polymorphism have been found to be significant in patients who died due to AP compared to CG in patients with severe AP (SAP) and AP. In another study, no significant difference was found in terms of the TLR4 Asp299Gly and Thr399Ile polymorphism compared to CG in patients with AP (12-14).

In this study, it was analyzed whether the TLR4 Asp299Gly and Thr399Ile and TLR2 intron 2 gene polymorphisms caused a tendency for the development of acute biliary pancreatitis and whether there was a difference between patients in terms of these gene polymorphisms according to the imaging findings and recurrent disease.

MATERIAL AND METHODS

This study included 105 patients who were hospitalized with a diagnosis of ABP and treated in the General Surgery Clinic between January 2010 and September 2014. The ABP patients were determined according to a sudden onset of upper abdominal quadrant pain in the back, amylase and lipase values at three times more than the normal values, and the presence of gallstone in the ultrasonographic imaging (USI) (15). The control group (CG) comprised 101 individuals with no pancreatitis or gallstone history and no other etiological factor or gallstones on abdominal USI. Informed consent for the genetic study participation was obtained from all the participants in the study and control groups. Analysis was made of whether there was a statistically significant difference between the ABP patients and the healthy population in terms of the TLR4 and TLR2 genetic polymorphism. The pancreatitis findings of the patients were also evaluated through computerized tomography (CT). After the diagnosis of ABP, patients involved in the study were classified into categories according to the Revised Atlanta Classification of mild, moderate severe, and severe to evaluate the difference in genetic polymorphisms (16). In addition, the patients were compared in terms of the presence of polymorphism according to the factors considered important for the severity of inflammation, which were >1 attack, presence of pseudocyst, increasing prerenal fascia thickness on CT, and fluid collection in two or more areas. These factors were analyzed to determine any differences. This study was approved by the Ethics Committee of İstanbul Medeniyet University (No. 2014-0064).

DNA isolation and genetic polymorphism

Peripheral blood samples taken from the patient and control groups were withdrawn into EDTA tubes and stored at –20˚C. Then, the DNA isolations were obtained from these samples according to the manufacturer's protocol through a commercial kit (coded Bio Basic BS684-250 Ontario Canada). The PCR was performed with F: 5′- ATT AGC ATA CTT AGA CTA CTA CCT CCA TG R: 5´-GAT CAA CTT CTG AAA AAG CAT TCC CAC-3′ primers for the rs4986790 (Asp299Gly) polymorphism, and the obtained 249 bp amplicon was cut with Nco1 restriction enzyme and conducted in 3% agarose gel. Heterozygote gave AG allele 249+223+26 bp bands, while homozygote was expected to give GG allele 223+26 bp bands. For the rs4986791 (Thr399Ile) polymorphism, the PCR was performed with F: 5´-GGT TGC TGT TCT CAA AGT GAT TTT GGG AGA A-3′ and R: 5´- ACC TGA AGA CTG GAG AGT GAG TTA AAT GCT-3′ primers, and the resulting PCR products were cut through the (407 bp) Hinf I (Thermo Scientific) restriction enzyme and conducted in 3% agarose gel. Expected band profiles were 407+378+29 bp for heterozygous CT allele, and 378+29 bp for the homozygous TT allele. The resulting band compositions were photographed, and analyses were carried out. To reveal the GT iterations in the intronic region of the TLR2 gene, the PCR was performed through the primers that enclose this region which are F: 5′-GCA TTG CTG AAT GTA TCA GGG A ve R: 5′-CTT GAG AAA TGT TTT CTA GGC. The PCR products were conducted in the 10% polyacrylamide gel electrophoresis; the results obtained were monitored, and the analyses were performed. A number of 16 or fewer of these iterations were evaluated as the S allele, those between 17 and 22 were evaluated as the M allele, and those more than 22 were evaluated as the L allele.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA) program was used in the data analysis. Conformity of the data to normal distribution and variance homogeneity were evaluated respectively through the Shapiro–Wilk and Levene tests. In comparing two independent groups, the Independent-Samples T-test was used together with Bootstrap results, while the Mann–Whitney U test was used with the Monte Carlo simulation method. The one-way analysis of variance (Robust Test: Brown–Forsythe) was used together with the Bootstrap results, and Kruskal–Wallis H test was used with the Monte Carlo simulation method when comparing multiple groups with each other. In the comparison of categorical data, Pearson chi-squared and Fisher exact tests were used with the Monte Carlo simulation method. The quantitative data were expressed in the tables as mean±std. (standard deviation) and median range (Maximum–Minimum) values. The categorical data were stated as number (n) and percentage (%). The data were analyzed at the 95% confidence interval, and a value of $p<0.05$ was accepted as statistically significant.

RESULTS

Due to the development of hemolysis in the peripheral blood samples from patients, 100 patients were evaluated in the TLR4 Rs 4986790 polymorphism group, and 86 patients were evaluated in the Rs 4986791 polymorphism group. A total of 101 healthy individuals were included in TLR4-CG. The study was conducted with 93 patients in the TLR2 polymorphism group, and 92 healthy subjects for whom the genotypes belonging to TLR2 could work, to TLR2-CG. The mean age and sex ratios of all the patients were evaluated (Table 1). The TLR4 Rs 4986791 (Thr399Ile) polymorphism was found to be statistically significant in terms of pancreatitis disease for acute biliary pancreatitis patients compared to the control group

Table 1. Distribution of the gender and age median values in the ABPG genetic polymorphism comparison

ABPG n(%)		
Gender	Female	69 (65.7)
	Male	36 (34.3)
Age	Mean	60.3+15.58
	Median	61 (92–22)

ABPG: acute biliary pancreatitis group

Table 2. ABPG and CG TLR-4 Rs 4986791 genetic polymorphism comparison

		ABPG n (%)	CG n (%)	Total n (%)	p
TLR-4 rs4986791 (Thr399Ile)	CC	81 (94.2)	80 (79.2)	161 (86.1)	0.005[a]
	CT	5 (5.8)	21 (20.8)	26 (13.9)	4.3 (1.5–11.8)*
Total		86 (100)	101 (100)	187 (100)	
C allele		167 (97)	181 (90)	348 (93)	0.001
T allele		5 (3)	21 (10)	26 (7)	1.9 (1.76–2.15)[a]*

Pearson Chi-Squared Test (Monte Carlo); [a]Fisher Exact Test (exact); *Odds Ratio (95% Confidence Interval)
ABPG: acute biliary pancreatitis group; CG: control group; TLR-4: toll like receptor-4

Table 3. ABPG and CG TLR-4 Rs 4986790 genetic polymorphism comparison

		ABPG n (%)	CG n (%)	Total n (%)	p
TLR-4 rs4986790 (Asp299Gly)	AA	92 (92)	80 (79.2)	172 (85.6)	0.015[a]
	AG	8 (8)	21 (20.8)	29 (14.4)	3.02(1.3–7.2)*
Total		100 (100)	101 (100)	187 (100)	
A allele		192 (96)	181 (90)	373 (93)	<0.001[a]
G allele		8 (4)	21 (10)	29 (7)	2.11(1.89–2.34)*

Pearson Chi-Squared Test (Monte Carlo); [a]Fisher Exact Test (exact); *Odds Ratio (95% Confidence Interval)
ABPG: acute biliary pancreatitis group; CG: control group; TLR-4: toll like receptor-4

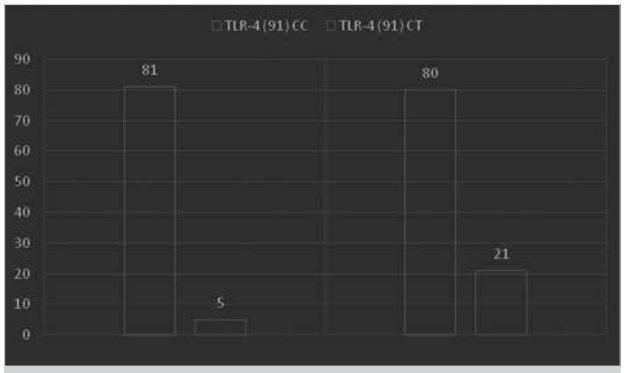

Figure 1. ABPG (n: 86, 94.2%) and CG (n: 101, 79.2%) Rs 4986791 genetic polymorphism comparison

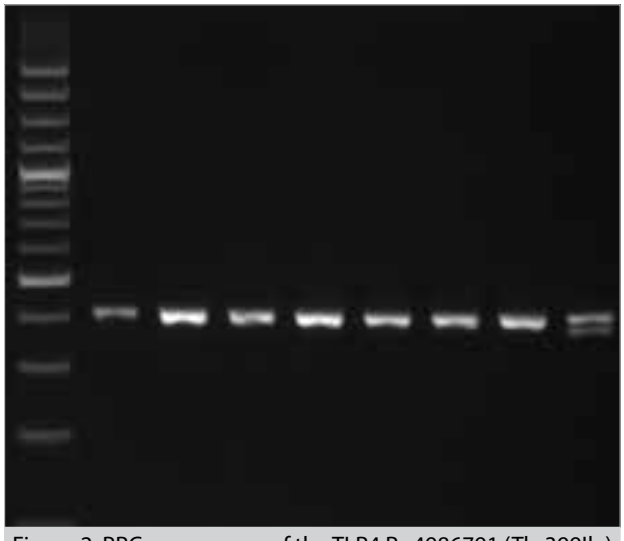

Figure 2. PRC appearance of the TLR4 Rs 4986791 (Thr399Ile) genetic polymorphism homozygous alleles

(p=0.005). The rates of C and T alleles in the CG and disease group were statistically significant (p=0.001), and they were determined at 1.9 times more in the ABPG and CG respectively (Table 2, Figure 1, 2). No statistically significant difference was seen in the TLR4 Rs 4986790 polymorphism compared to the control group (p=0.015). However, it was seen that the rates of A and G alleles in the CG and disease groups were statistically significant (p=0.001), and they were 2.11 times more in the ABPG and CG respectively (Table 3). A statistically significant difference was not found between the female and male gender for patients with ABP in terms of the TLR4 Rs 4986790 and Rs 4986791 polymorphism (p=0.255; p=0.151). No statistically significant difference was found between patients who had ABP for the first time and those who had experienced more than one attack in terms of TLR4 Rs 4986790 and Rs 4986791 polymorphism (p=0.562, p=0.407). No significant difference was seen in patients with mild, moderate severe, and acute pancreatitis according to the Revised Atlanta Classification (p=1, p=1). It was seen that the patients who had symptoms such as pseudocyst presence (p=1, p=1), fluid collection two or more areas (p=1, p=1) and increase in prerenal fascia thickness (p=1, p=1) had no significant statistical value in terms of polymorphism compared to those without these symptoms (Table 4). It was seen that the polymorphism of the TLR2 intron 2 region was significantly higher in the MM genotype ABPG compared to CG. M alleles were found to be significantly higher in the patients (p<0.001) (Table 5). As only 1 patient had the SS and SL genotypes during the preparation of the TLR2 gene polymorphism statistical data, the statistics between the different genotypes of the severity and independent parameters belonging to the ABPG were left out of the analysis. No significant difference was observed between the female and male gender in patients with acute biliary pancreatitis in terms of the TLR2 polymorphism (p=0.533; p=0.630). According to

Table 4. TLR4 Rs 4986790 and Rs 4986791 genetic polymorphism according to gender, number of ABPG attacks, and Revised Atlanta Classification among the ABP patients and CT findings in ABPG

		TLR4 polymorphism Rs 4986790			TLR4 polymorphism Rs 4986791		
		AG (n:8)	AA (n:92)	p	CT (n:5)	CC (n:81)	p
Gender*	Female	7 (87.5)	58 (63)	0.255	5 (100)	48 (59.3)	0.151
	Male	1 (12.5)	34 (37)		0 (0)	33 (40.7)	
Number of attacks **		1 (4–1)	1 (8–1)	0.562	1(4–1)	1 (4–1)	0.407
Atlanta Criteria*	Mild	8 (100)	84 (91.3)	1	5 (100)	75 (92.6)	1
	Moderate	0(0)	6 (6.5)		0 (0)	5 (6.2)	
	Severe	0 (0)	2 (2.2)		0 (0)	1 (1.2)	
Prerenal fascia thickness*	Absent	8 (100)	82 (89.1)	1	5 (100)	73 (90.1)	1
	Present	0 (0)	10 (10.9)		0 (0)	8 (9.9)	
Pseudocyst*	Absent	8 (100)	87 (94.6)	1	5 (100)	77 (95.1)	1
	Present	0 (0)	5 (5.4)		0 (0)	4 (4.9)	
Fluid collection in two or more areas*	Absent	8 (100)	82 (89.1)	1	5 (100)	73 (90.1)	1
	Present	0 (0)	10 (10.9)		0 (0)	8 (9.9)	

Independent T-Test (Bootstrap); Mann–Whitney U Test (Monte Carlo); Pearson Chi-Squared Test (Monte Carlo); Fisher Exact Test (Monte Carlo); *: n (%), **: median (range)
ABPG: acute biliary pancreatitis group; CG: control group; TLR-4: toll like receptor-4; CT: computer tomography

Table 5. TLR2 intron 2 microsatellite polymorphism comparison between the ABPG and CG

TLR-2 Genotypes	ABPG n=93	Control n=92	p	TLR2 Allele	ABPG n=93	Control n=92	p
SM	16 (17.2)	25 (27.2)		M	126 (68)	92 (50)	<0.001
SL	1 (1.1)	9 (9.8)		L	41 (22)	54 (29)	
MM	50 (53.8)	20 (21.7)	<0.001				
ML	10 (10.8)	27 (29.3)					
LL	15 (16.1)	9 (9.8)					

the Revised Atlanta Classification, no significant difference was found between patients who had mild, moderate severe, and acute pancreatitis (p=0.727, p=0.764). There was no statistically significant difference between patients who had ABP for the first time and those who had more than one attack in terms of the TLR2 polymorphism (p=0.438, p=0.175). Patients with symptoms such as pseudocyst presence (p=0.702, p=1), fluid collection in two or more areas (p=0.211, p=0.430), and an increase in the prerenal fascia thickness (p=0.211, p=0.430) had no significant statistical value in terms of polymorphism compared to those without these symptoms (Table 6).

DISCUSSION

Although it has been shown in many studies that an acute pancreatitis incidence is increasing, the mortality rate has been gradually reduced due to developments in diagnostic and therapeutic modalities (17). However, despite the advances in inspection modalities and research techniques, the ABP remains the most common cause of AP. With the presence of gallstones, it is known as a mechanical complication, but in general terms, the exact pathogenesis of APB has not yet been fully clarified (2, 18-20). Recently more and more solid evidence has demonstrated that the involvement of the immune system and, largely, release of multiple proinflammatory factors have played a fundamental role in the pathogenesis of AP. The early phase of severe AP progression is commonly accompanied by activation of monocytes, polymorphonuclear granulocytes, and macrophages, and the activated monocytes are the index of AP severity. Many factors and multiple pathways participated in the regulation of innate immune response of AP. TLRs can recognize pathogen-associated molecular patterns and protect bodies by initiating inflammatory reactions to destroy the invaders, thus playing pivotal roles in immune regulation. Studies on pathogenesis have shown that TLRs, which are members of the PRR family, are important components of the inflammation cascade, functioning as proinflammatory mediators affected by endogenous and exogenous sources in the TLR4 and TLR2 immune system (9, 10, 21). To date, 29 single nucleotide polymorphisms of TLR4 have been detected, and the studies have been most frequently performed on Asp299Gly and Thr399Ile (9). Studies of different ethnicities in different countries have tried to determine whether there is significant polymorphism susceptibility in AP patients compared to the healthy population, and whether the presence of polymorphism created a susceptibility to acute pancreatitis as defined in the Revised Atlanta Classification (9). In many studies performed on the Asp299Gly polymorphism, it has been shown that there was no genetic susceptibility due to the mutation of homozygous genotype in AP patients compared to CG (12-14, 22-24). Again, no significant result could

Table 6. TLR2 intron 2 microsatellite polymorphism according to gender, Revised Atlanta Criteria, number of attacks among the ABP patients and CT findings in the ABP patient group

		TLR2 polymorphism					TLR-2 polymorphism		
		ML n:10	LL n:15	MS n:16	MM n:50	p	Insignificant n:27	Significant n:66	p
Gender*	Female	6 (60)	11 (73.3)	12 (75)	29 (58)	0.533	19 (70.4)	41 (62.1)	0.630
	Male	4 (40)	4 (26.7)	4 (25)	21 (42)		8 (29.6)	25 (37.9)	
Atlanta Criteria*	Severe	10 (100)	15 (100)	15 (93.8)	44 (88)	0.727	26 (96.3)	60 (90.9)	0.764
	Mild	0 (0)	0 (0)	1 (6.3)	5 (10)		1 (3.7)	5 (7.6)	
	Moderate	0 (0)	0 (0)	0 (0)	1 (2)		0 (0)	1 (1.5)	
Number of attacks **		1 (4–1)	1 (4–1)	1 (2–1)	1 (8–1)	0.438	1 (4–1)	1 (8–1)	0.175
Prerenal fascia thickness*	Absent	10 (100)	15 (100)	15 (93.8)	43 (86)	0.211	26 (96.3)	59 (89.4)	0.430
	Present	0 (0)	0 (0)	1 (6.3)	7 (14)		1 (3.7)	7 (10.6)	
Pseudocyst*	Absent	10 (100)	15 (100)	15 (93.8)	46 (92)	0.702	26 (96.3)	62 (93.9)	1
	Present	0 (0)	0 (0)	1 (6.3)	4 (8)		1 (3.7)	4 (6.1)	
Fluid collection in two or more areas*	Absent	10 (100)	15 (100)	15 (93.8)	43 (86)	0.211	26 (96.3)	59 (89.4)	0.430
	Present	0 (0)	0 (0)	1 (6.3)	7 (14)		1 (3.7)	7 (10.6)	

One-Way Analysis of Variance (Brown–Forsythe) (Method: Bootsrap); Kruskal–Wallis Post Hoc Test (Monte Carlo); Independent T-Test (Bootstrap); Mann–Whitney U Test (Monte Carlo); Pearson Chi-Squared Test (Monte Carlo); Fisher Exact Test (Monte Carlo); *: n (%), **: median (range)

be obtained in studies on the other frequently investigated Thr399Ile polymorphism (12-14). In many studies performed on the Asp299Gly and Thr399Ile genetic mutations, it has been seen that the AP patient groups were heterogeneous etiologically. However, in the current study, genetic polymorphism was investigated in a more specific group by including the ABP patients.

According to the Revised Atlanta Classification, the severe form of AP, which is clinically divided as mild (MAP), moderate severe, and severe (SAP) and in which pancreatic necrosis may also be seen and there is high morbidity and mortality due to sepsis and SIRS, was investigated in terms of the TLR4 polymorphism disease, which is considered to possibly be the molecular reason for the increased inflammatory response and gram-negative bacteria infection effect. Studies where the Asp299Gly polymorphism has been analyzed in SAP patients compared to MAP, no significant result has been determined in respect of SAP (9, 12, 14, 23, 24). In another extensive study, no significant result was determined in favor of the TLR4 Asp-299Gly and Thr399Ile polymorphism. In the same study, no significant difference was seen between the SAP and MAP patients in terms of genetic polymorphism (25). However, in a study that involved 310 AP patients, 115 patients were diagnosed with pancreatic necrosis and the Asp299Gly polymorphism was investigated, and it was seen that morbidity due to gram-infection and incidence of pancreatic necrosis had increased in patients with mutation compared to the healthy control group and patients without polymorphism (11).

In the clinical analysis of the current study, which was performed according to the Revised Atlanta Classification, it was observed that the TLR4 Asp299Gly and Thr399Ile polymorphism and the TLR2 intron 2 microsatellite polymorphism did not create any significant differences in patients with different pancreatitis severities, and there was no connection between the genetic polymorphism and pancreatitis severity.

In several studies, it has also been attempted to evaluate the severity of illness with CT findings. The Balthazar classification, perirenal space findings, and fascia findings are important among these evaluations. Fluid accumulation in the peripancreatic area and an increase in the thickness of the perirenal fascia, which may be evaluated as the indicators of transition from mild to moderate severe illness, are remarkable imaging findings on CT (26-29). In addition, pancreatic pseudocyst, which rarely develops due to AP, occurs with the localization of peripancreatic fluid 4 weeks after the acute attack. Parenchymal necrosis development in the distal pancreatic remnant created by the neck and body sections of the pancreas may also cause the formation of pseudocyst and necrosis, is known to be an important indicator of the severity of AP (16). Although the severity of biliary pancreatitis seems to be connected with the predisposition of the patient, animal experiments and clinical studies have shown that the severity of illness could be more closely related to the continuation of the common bile duct obstruction (30-33). Gallstone disease represents the most common condition associated with acute recurrent pancreatitis (ARP) in Western countries. The most common causes of ARP are obstruction of the main pancreatic duct or pancreatico-biliary junction, genetic mutations, and alcohol consumption. If ABP is in question in ARP, mechanical obstruction and genetic mutation must be a relevant reason of more than one attack (34).

In this study, no relationship was determined between the CT findings, patients having more than one attack, and the TLR4 and TLR2 genetic polymorphism, which may be the indicators of the severity of illness.

As a member of the PRR family and a pro-inflammatory molecule, the TLR2 polymorphism has been investigated for AP as it has for different diseases. TLR2 is expressed on the plasma membrane of a large diversity of cells, including monocytes and macrophages, dendritic cells, polymorphonuclear leukocytes, B cells, T cells, and microglia. This PRR recognizes a wide

range of DAMPs. Usually associated with the innate immune response against Gram-positive bacteria. Besides its role in infectious diseases, TLR2 has also been reported to be involved in several non-infectious disorders including AP (11). In a study, the SS and SL genotypes were observed to be higher in AP patients, and S allele were observed to be higher in SAP patients compared to MAP and finally, it was attempted to reveal that the AP patients showed a higher rate of TLR2 intron 2 polymorphism compared to CG. However, as the study in question was limited to a certain population, more extensive studies are needed (11, 13). In another study where many TLR subgroups including TLR2 were analyzed, no significant finding could be determined in respect to AP and SAP in terms of the TLR2 genetic polymorphism (22).

In this study, the TLR2 intron 2 region microsatellite polymorphism was found to be significant in the MM genotype patients compared to CG ($p<0.001$). The MM genotype was observed to be associated with ABP. This study may expose that, role of TLR2 and TLR4 in early inflammation cascade, may be the cause of ABP, although there isn't no relationship between polymorphism and severity parameters.

CONCLUSION

The results of this study showed that although the TLR4 Rs 4986791 (Thr399Ile) polymorphism and the TLR2 intron 2 MM genotype polymorphism are not important for severe illness, they are significant in terms of creating susceptibility for the ABP disease compared to CG. More extensive genetic research should be conducted, to determine the possibility of eliminating the cause of disease with early cholecystectomy applied to patients with genetic polymorphism, before the development of pancreatitis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of of İstanbul Medeniyet University (No. 2014-0064).

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Original Article

Protective effects of St. John's wort in the hepatic ischemia/reperfusion injury in rats

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ABSTRACT

Objectives: The purpose of this study was to investigate possible protective effects of St. John's wort in the hepatic ischemia/reperfusion injury.

Material and Methods: The hepatic artery, portal vein, and bile duct were all clamped for 45 minutes to induce ischemia in rats, and after that reperfusion for 1 hour. SJW was administrated orally, once a day for 3 days before ischemia/reperfusion. The aspartate aminotransferase, alanine aminotransferase, tumor necrosis factor, and interleukin levels were measured in the serum samples. Luminol chemiluminescence, lucigenin luminol chemiluminescence levels; myeloperoxidase. The sodium–potassium ATPase (Na+/K+ ATPase) activity was determined in the liver tissue, and caspase-3 and caspase-9 activity with the bcl-2/bax ratio were measured by the western blot analysis.

Results: The St. John's wort administration recovered the aspartate aminotransferase, alanine aminotransferase, tumor necrosis factor, and IL-1β levels serum parameters meaningfully, while ischemia/reperfusion caused an increase in luminol chemiluminescence, lucigenin luminol chemiluminescence, myeloperoxidase, caspase-3, and caspase-9 activity and led to a decrease in the B-cell lymphoma-2/bcl-2-associated X protein (bcl-2/bax) ratio and the Na+/K+ ATPase activity.

Conclusion: The obtained results indicate protective effects of St. John's wort on the ischemia/reperfusion injury through various mechanisms, and we are able to suggest that St. John's wort can clinically create a new therapeutic principle.

Keywords: Apoptosis, inflammatory, ischemia/reperfusion, St. John's wort

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INTRODUCTION

The ischemia/reperfusion (I/R) injury occurs in various clinical situations, such as hepatic trauma, hemorrhagic shock, resection of a large intrahepatic tumor, and liver transplantation (1, 2).

The ischemia/reperfusion causes the hepatic neutrophil accumulation. In addition, the Kupffer cells become activated and release proinflammatory cytokines such as reactive oxygen species and the tumor necrosis factor (TNF-α) and IL-1 (3, 4). These cytokines activate most of the proteins involved in apoptosis, such as caspase-3 and caspase-9, bcl-2/bax ratio, as well as mitochondria cytochrome-c released to cytoplasm. Increased cytokine levels as a result of inflammation are associated with increased aldosterone levels, leading to the intensification of inflammation by inhibiting the Na^+/K^+-ATPase pump (5). The sequential events initialized by these substances results in the DNA damage and cell death (6). During I/R, with the myeloperoxidase-mediated neutrophil activation, the assay of excess production of free radicals was represented by using luminol chemiluminescence (CL) and lucigenin CL as indicators. By luminol-mediated measurements, the levels of hydroxyl (OH^-), hydrogen peroxide (H_2O_2), hypochlorite, and hydroperoxyl radicals were assayed, whereas by lucigenin-mediated measurements, the levels of superoxide (O_2^-) free radicals were assayed. During I/R, as a result of neutrophil activation, the levels of the luminol and lusigenin were found to be elevated (7).

Hypericum perforatum (St. John's wort; SJW) is commonly used in the treatment of mild to moderate depression. Apart from depression, SJW is used traditionally for in-wound healing, first-degree burns, and myalgia externally (8, 9). There are also arguments claiming that *Hypericum perforatum* or its' bioactive component, hypericin, may be useful in the treatment of various types of cancer (10).

In the light of such information, our study aims to investigate protective effects of SJW in the case of liver damage arising from the I/R implementation on the left and middle hepatic artery, portal vein, and bile duct.

MATERIAL AND METHODS

Animals and Conditions

The experiment was carried out with the permission of the Ethics Committee (date of permission: 11/18/2013 and protocol code: 95.2013.mar) of the Marmara University Experimental Animal Research Centre. The rats were procured from and the experiments were held in the same laboratory.

In this research, a total of 32 ten-weeks-old male albino Wistar rats were used, and they were weighing between 200 and 250 grams. The rats were randomly divided into four groups of eight. The rats were kept in wire cages under standard laboratory conditions, with each of the eight cages containing four rats. Tap water and standard rat food were released throughout the experiment.

Each rat was kept in a jar containing ether for 40 to 60 seconds for the purpose of anesthesia induction. After the anesthesia induction, 100 mg/kg ketamine (Ketalar, Parke-Davis, Eczacıbaşı-Istanbul), 1 mg/kg intraperitoneally (ip), chlorpromazine (Largactil, Eczacıbaşı-Istanbul) 1 mg/kg ip were applied as maintenance anesthesia.

In our research, rats were placed in supine position during anesthesia. The abdominal front walls were shaved by bistoury and sterilized using a povidone iodine solution. Afterwards, the abdomen was opened by midline incision. The hepatic artery, portal vein, and bile ducts of the rats were explored, and ischemia was induced by clamping for a 45 minutes. At the end of these 45 minutes, the rats were decapitated after undergoing a 60 min reperfusion (11). SJW (SOLGAR) (300 mg/kg, p.o.) (12) or a physiological saline solution (PSS) were administered for 3 days before ischemia and reperfusion.

Control (Sham opere-C) Group: Two cc. blood and liver tissue samples were collected 60 min after the standard operation without clamping the hepatic artery, portal vein, and bile ducts and without any further operation.

Saint John's Wort (SJW) Group: Three days before the sham operation of the rats and for 3 days before the sham operation, a 300 mg/kg SJW dose was administered orally.

Hepatic Ischemia/Reperfusion (HI) Group: The PSS was administered orally for 3 days before the day of hepatic I/R. Following the standard operation, ischemia was induced by the vascular clamping of the hepatic artery, portal vein, and bile duct. The rats were only subjected to a 45 min ischemia followed by a 60 min reperfusion.

Hepatic Ischemia/Reperfusion Group which was administered SJW (HI-SJW): For 3 days before the day of hepatic ischemia/reperfusion, a 300 mg/kg SJW dose was administered orally. The rats were only subjected to a 45 min ischemia followed by a 60 min reperfusion.

At the end of the reperfusion period, 2 cc. blood and liver tissue samples were taken from the decapitated rats. The resected liver tissues were washed with cold 0.9% NaCl and wrapped in aluminum foil to be stored at –80^{0}C for biochemical research. Some samples were also stored in formaldehyde for histological research. The luminol and lucigenin levels, bcl-2/bax ratio, Na^+/K^+-ATPase, caspase-3, and caspase-9 activities of the frozen samples were examined once thawed at the room temperature. Structural damage of the samples stored in formaldehyde was histologically evaluated . The plasma that was separated by centrifuging the blood sample (at 3000 rpm/15 min) was stored at –70 ^{0}C. The aminotransferase (AST), alanine aminotransferase (ALT), tumor necrosis factor (TNF-α), and interleukin (IL-1β) levels were measured after the frozen samples were thawed at the room temperature.

Examinations of Serum

Determination of AST (Biolabo Europe S.A. Catalog No: REF 92025, 02160 Maizy, France) and ALT (Biolabo Europe SA Catalog Number: REF 80027, 02160 Maizy, France) in the serum is a kinetic spectrophotometric method and is measured using the Opera Technican Bayer Autoanalyzer device. TNF-α (Bio Source Europe S.A. Catalog No.KRC 3014, Nivelles, Belgium) and IL-1β (ELISA, Bio Source Catalog No.KRC0011, Nivelles, Belgium) were determined using appropriate rat kits and measured by the enzyme-linked immunosorbent assay.

Examinations of Tissues

Determination of free oxygen radicals in tissues was conducted by the chemiluminescence method (13, 14). Tissues were placed into a 2 mL phosphate buffer solutions-4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (PBS-Hepes), and luminol (0.2 mM) and lucigenin (0.2 mM) were added to the two tubes (4 mL for each tube), which included the samples of the same tissue. The photonic activity resulting from the reactions between the reactive oxygen species, luminol, and lucigenin was recorded by using an illuminometer for 10 min, and the area-under-curve was calculated.

Determination of the *myeloperoxidase* (MPO) level in the tissues was performed by the Hillegeas method (15). The tissues that were removed immediately following decapitation were washed by PSS to remove any blood and environmental contamination. This step was followed by drying the tissues with filter paper and weighing them. By homogenizing the liver tissue by 50 mM K_2HPO_4 (pH: 6), a 10% homogenate was prepared, and the tissue was centrifuged at 41.400×g at a temperature of 4°C for 10 min. The supernatant was discarded, and the samples, which were homogenized again by adding 0.5% hexadesil-trimetil ammonium bromide to the solution, were re-frozen, thawed, and sonicated 3 times. Next, the samples were centrifuged at 41.400×g at a temperature of 4°C for 10 min. 50 mM K_2HPO_4 (pH: 6), 20 mM H_2O_2, and o-Dianisidine-2 HCl was added to the supernatant obtained, and it was incubated in a 37°C water bath for 3 min. Then the color reaction was stopped by adding 2% sodium azide. Later, the samples were centrifuged at 41.400×g at a temperature of 4°C for 10 min. The supernatant was obtained, and thus the absorbance of the color formed was measured using a spectrophotometer at 460 nm.

The Na^+/K^+-ATPase activity of tissues was determined using the method of Reading and Isbir (16). The liver tissue was homogenized with a 10% sucrose solution, and then was centrifuged at 3000 rpm for 10 min. 0.1 ml supernatant was obtained, and this was followed by the incubation of homogenates with an appropriate medium containing 3 mM ATP. The Mg^{2+}-ATPase activity was detected in the presence of 1 mM ouabain, while the total ATPase activity was determined in the presence of 100 mM NaCl, 5 mM KCl, 6 mM $MgCl_2$, 0.1 mM EDTA, 30 mM Tris HCl (pH: 7.4). The difference between the total ATPase activity and Mg^{2+}-ATPase was evaluated as the Na^+/K^+-ATPase activity (16), and the specific activity of the enzyme is expressed as nmol Pi mg^{-1} protein h^{-1}. The protein concentration of the supernatant was measured by the Lowry method (17).

Determination of the bcl-2/bax ration, caspase-3, and caspase-9 activities tissue homogenization

Protease inhibitors (0.2 mM PMSF, 1 µM pepsitatine, 1µg/mL leupeptin, and 10 µg/mL soybean trypsin), 10% glycerol, 50 mM NaCl, 2 mM DTT, 20mM Tris buffer with pH=7.4, which contains 1 mM EGTA and 1 mM EDTA, were used to prepare homogenates for molecular analysis of tissues that were stored at −80°C.

The tissues were transferred into 50 ml falcons and were homogenized on ice using the ultra-turrax homogenizer (90s) in the homogenization buffer, which was added according to their weight (1:2, w/v). After the homogenates were centrifuged at 2.000×g for 10 minutes, the supernatant portion was centrifuged again at 12.000× g for 60 min. The mitochondrial pellet formed as a result of the second centrifuge was centrifuged at 12.000× g for 1 h after being washed with a 500 µl homogenization buffer. Pellets containing 50 mM Tris-HCl (pH: 7.4), 5% glycerol, 1 mM EDTA, 5 mM DTT, protease inhibitors, and the fractions, which were incubated by vortexing for 1.5 h using 0.05% Triton X-100 buffer, were used as mitochondrial extracts. All processes were performed at +4 ^{0}C (16). The protein amounts of mitochondrial extracts were determined using the Lowry method (17).

SDS-PAGE and western blot

The tissues were analyzed by the Lowry method to determine their protein amounts and were then mixed with a 4X buffer (to include 100 µg proteins) and denatured for 6 minutes.

The samples were loaded to electrophoresis setup with gel containing 12% polyacrylamide for 120 min. The gel was transferred to the nitrocellulose membrane at 125mA for 90 min. Membranes were incubated by a buffer containing TBS-T (TBS containing 0.05% Tween 20) and 3% BSA for 14 h at +4°C. The day after bracketing, the membranes were incubated throughout the night using different concentrations of polyclonal antibodies of apoptosis [bcl 2 (1: 200), bax (1: 200), caspase-3 (1: 100), and caspase-9 (1: 100)] proteins.

Apart from the antibodies that were treated, all the membranes were incubated throughout the next night with the β-actin antibody (1: 200), at 4°C to be able to perform the normalization analysis. After each incubation, membranes were washed using a buffer containing TBS-T (TBS containing 0.05% Tween 20) for 3×15 min. In the next stage, they were incubated for another hour with a secondary antibody containing alkaline phosphatase conjugated to rabbit monoclonal anti-goat immunoglobulin G. After the secondary antibody incubation, membranes were washed once more using TBS-T for 3x15 min. Following the secondary antibody incubation, distinctive bands were identified on the membranes after being washed using TBS-T for 3×15 min one more time and usingn blue tetrazolium chloride/5-Bromo-4chloro-3indolyl phosphate color improvement solution (18, 19).

Histopathologic grading method (light microscope)

Having placed the tissues in 10% formaldehyde, they were washed by tap water for at least 3 h or 1 night. The remaining alcohol concentration was used for dehydration (15 min with 70% alcohol, 15 min with 90% alcohol, 30 min with 96% alcohol, 2x30 min 100% alcohol, 100% toluene for 2x30 min), and after that, they were steeped in paraffin for 1 night at 60°C. The next day the tissues were embedded in paraffin blocks. Following the blocking process, the tissues were sectioned to 5 to 6 mm thick pieces and placed onto the lames where they were left in toluene for 2 h to eliminate the paraffin. The aim of the process was to reduce to water as the alcohol concentration was gradually decreased (2 min with 100% alcohol, 2 min with 90% alcohol, 2 min with 70% alcohol, and finally placed into distilled water.). After a 15 min treatment with hematoxylin, they were steeped in tap water for empurpling. In addition to 5 minutes of staining with Eosin, distilled water was applied and as alcohol concentrations were increased again, the process was conducted (2 min with 70% alcohol, 2 min with 90% alcohol, 2 min with 96% alcohol, and 10 min with 100% alcohol). Then it was washed with toluene twice (1st bath for 5 min and 2nd one for 10 min), the tissue was covered with Entellan. Finally, it was examined with a light microscope.

Statistical Analysis

In our study, we compared the groups of the AST, ALT, TNF-α, IL-1β levels in serum and GSH, MDA, luminol, lucigenin levels, bcl-2/bax ratio and MPO, Na^{+}/K^{+}-ATPase, caspase-3 and caspase-9 activities, (which can be determined from the liver tissue) were investigated using the one-way analysis of variance. A Tukey test was used for pair-wise comparisons. P-values less than 0.05 were considered significant.

RESULTS

In the Hepatic Ischemia (HI) group, it could be observed that the AST, ALT, TNF- α, and IL-1β levels in the serum were significantly higher than in the control group. On the other hand, in the group to which SJW was applied, the increase was significantly slower in the levels of the HI group, approaching the values of the control group (Table 1).

Table 1. In the rat hepatic ischemia/reperfusion model (HI), The aminotransferase (AST), alanine aminotransferase (ALT), tumor necrosis factor (TNF-α), and interleukin (IL-1β) values of all groups. SJW: Saint John's wort.

	Control	SJW	HI	HI-SJW
AST (U/L)	66.2±7.5	68.2±5.4	120.5±9.3***	71.5±10.1^{++}
ALT (U/L)	61.3±5.6	68.7±6.2	133.8±14.6***	83.5±7.8^{++}
TNF-α (pg/mL)	55.4±3.2	48.2±3.1	82.2±3.9***	56.6±3.9^{+++}
IL-1β (pg/mL)	365±22	326±16	475±29*	380±18^{+}

Average value±standard error
*p<0.01, ***p<0.001 Comparisons with respect to control group
$^{+}$p<0.05, $^{++}$p<0.01, $^{+++}$p<0.001 Comparisons with respect to HI group

The luminol and lucigenin levels in the liver tissues of the HI group were found to be higher than in the control group. It was observed that this increase was prevented considerably in the HI group that was administered the treatment with SJW (Figure 1).

On one hand, HI increased the neutrophil infiltration in the liver in parallel with a significant increase of the MPO values with respect to the control group; on the other hand, the MPO activity decreased significantly in the SJW administered group, and the results of the MPO values were observed to be close to the control group MPO values (Figure 2a).

The Na^+/K^+-ATPase activities in the liver tissues were found to be low in the HI group with respect to the control group. It was observed that this decrease was prevented considerably in the HI group, which was treated with SJW (Figure 2b).

When the bcl-2/bax ratio was evaluated with respect to the control, the SJW and HI-SJW group's ratios were observed to be high, and the ratio was observed to be low in the HI group. The rate of decrease was considerably slower in the HI group treated with SJW (Figure 3a, Table 2).

The caspase-3 and caspase-9 activities with respect to control group were found to be low in the SJW group, while they were found to be high in the HI group. This increase was significantly recovered in the HI-SJW group (Figure 3b, c, Table 2).

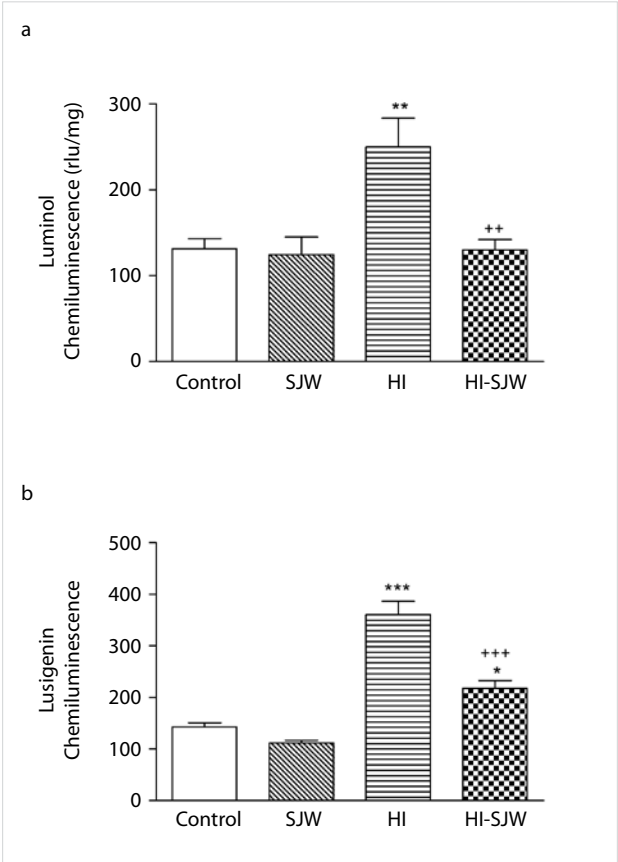

Figure 1. a, b. In the rat hepatic ischemia/reperfusion model (HI), tissues from all groups luminol (a) and lucigenin values (b)
SJW: Saint John's wort
*p<0.01, **p<0.01, ***p<0.001 Comparisons with respect to control groups, ++p<0.01, +++p<0.001 Comparisons according to the I/R group

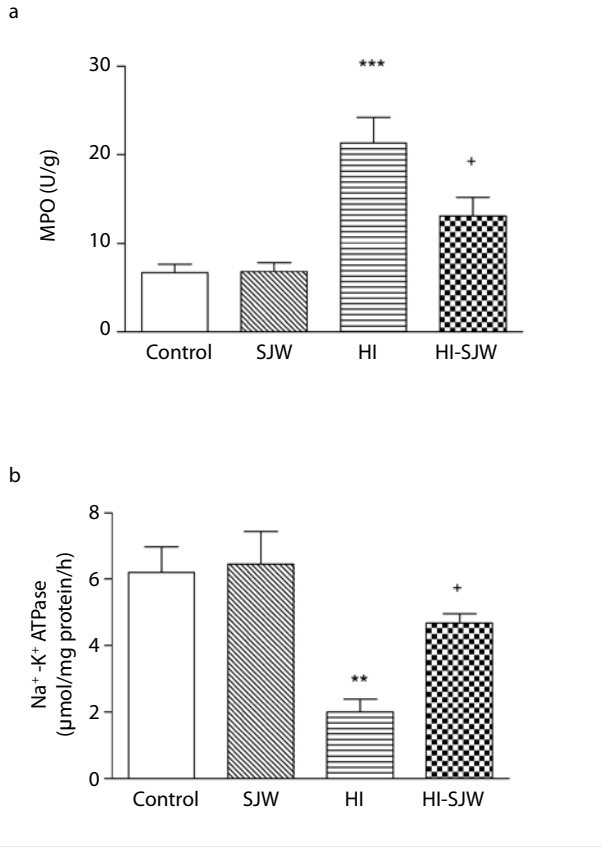

Figure 2. a, b. In the rat hepatic ischemia/reperfusion model (HI), tissues from all groups myeloperoxidase (MPO) (a), Na^{+-} K+ATPase values (b)
SJW: Saint John's wort
**p<0.01, ***p<0.001 Comparisons with respect to control groups, +p<0.05 Comparisons according to the HI group

Table 2. In the rat hepatic ischemia/reperfusion model (HI), the (b-cell lymphoma 2/ B-cell lymphoma 2 associated Xprotein (bcl-2/bax) ratio, and caspase-3 and caspase-9 activities in all groups. SJW: Saint John's wort

	Control	SJW	HI	HI-SJW
bcl-2/bax ratio	1	1.35±0.01***	0.76±0.02***	1.18±0.02***, +++
caspase-3/β-actin	1	0.75±0.02***	1.16±0.03***	0.87±0.02+++
caspase-9/β-actin	1	0.86±0.02**	1.19±0.03***	0.87±0.03**, +++

Average value ± standard error
** p<0.01, ***p<0.001 Comparisons with respect to control group
+++p<0.001 Comparisons with respect to HI group

In the histopathological examination of the control group, it is observed that hepatocytes and sinusoids were intact, and liver parenchyma was found to be maintaining a normal morphology (Figure 4a). In the SJW administered group, it was observed that hepatocytes and sinusoids were intact, and liver parenchyma was found to be maintaining a normal morphology (Figure 4b). In the HI group, a widespread congestion and hepatocyte degeneration, caused by HI, have been observed (Figure 4c). In the HI group that was administered the treatment with SJW, low sinusoidal and hepatocellular degeneration was observed (Figure 4d).

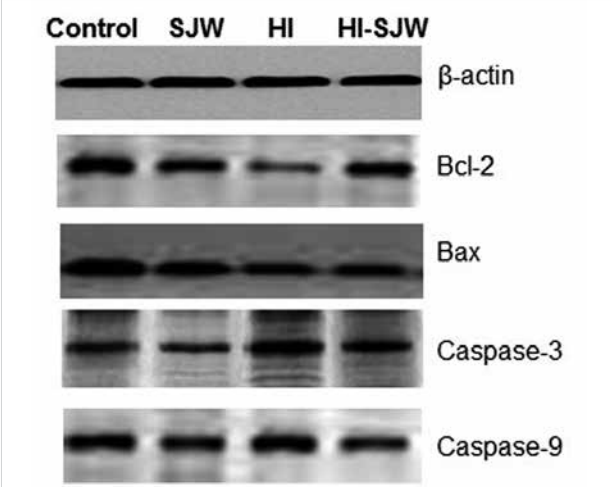

Figure 3. In the rat hepatic ischemia/reperfusion model, Bcl-2/Bax ratio and caspase-3 and caspase-9 activities of all groups.
SJW: Saint John's wort

DISCUSSION

A hepatic I/R injury may occur in most of clinical practices including transplantation of organs, hepatectomy, trauma, and vascular diseases (20, 21). Various factors contribute to the hepatic I/R injury, namely the Kupffer cell activation, oxidative stress, and upregulation of proinflammatory cytokine signaling.

During an ischemia period, several functional changes occur at cellular levels that promote cell injury. More specifically, the oxidative phosphorylation levels go down. This situation results in the ATP depletion. In addition, during the ischemia period, the lack of oxygen to hepatocytes causes mitochondrial deenergization, and finally the swelling of the sinusoidal endothelial cells and the Kupffer cells. The production of reactive oxygen species, activation of Kupffer cells, upregulation of proinflammatory cytokines, resulting in neutrophil-mediated injury are the major factors contributing to inflammation-associated damages (22).

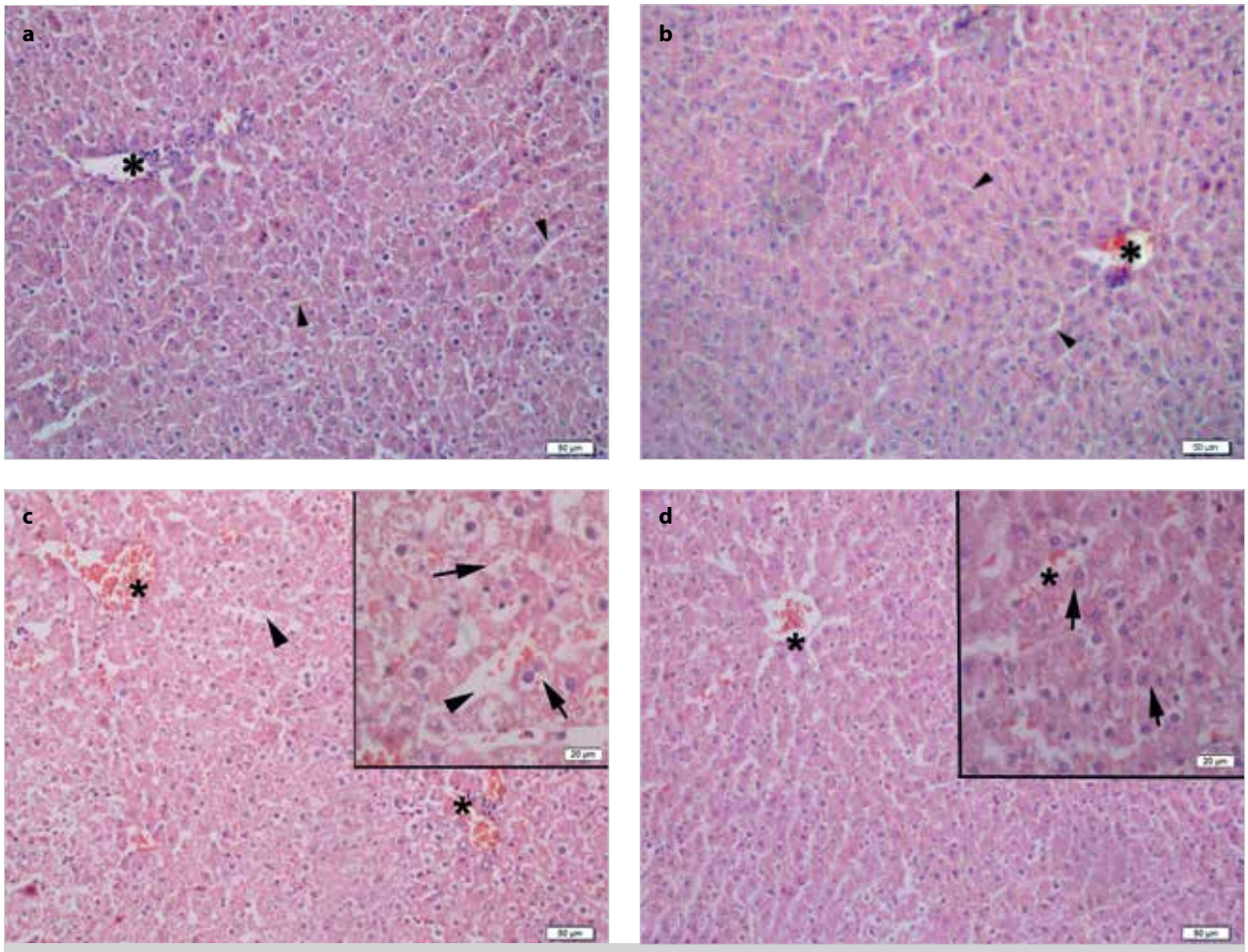

Figure 4. a-d. (a) Control group; central vein with smooth contours (*) and sinusoids (►) (a), SJW group, central vein with smooth contours (*) and sinusoids (►) (b), HI group, dilatation of sinusoids, hepatocellular degeneration (arrows) and widespread congestion in the central vein (*) (c), HI-SJW group, reduced dilatation in sinusoids (arrows) and reduced congestion in the central vein (*) (d)

Many agents have been investigated for prevention of the I/R injury (1, 22, 23). However, a study that would test SJW alone in the hepatic I/R injury and stated quantitative histopathological findings, has not yet been documented in the literature.

In a study conducted on rats, comparing the effects of the ischemia period, the rats were subjected to bilateral ischemia for 45 minutes, and this was followed by reperfusion for 1 hour. The values of AST and ALT were measured. This ischemia and reperfusion period were found to be associated with the extent of muscle edema as well as increased values of AST and ALT (23). In Kupffer cells isolated from the rat liver, an increase in the TNF-α levels after I/R were discovered to be 5 times greater than the increase of the TNF-α levels in the control group. Besides, it has been shown in studies conducted on rats that the use of anti-TNF-α antibodies in the hepatic I/R cases reduces liver damage. The effects of the oral use of *H. perforatum* in an animal model of acute inflammation, carrageenan-induced pleurisy, were evaluated. It was also determined that an acute inflammatory response characterized by fluid accumulation in the pleural cavity in animals contains an increased production of TNF-α and IL-1β. All parameters of inflammation were reduced by the administration of the *H. perforatum* extract (24). In our study, the AST, ALT, TNF-α, and IL-1β levels of the hepatic I/R group were found to be significantly higher than in the control group. On the other hand, in the SJW administered group was significantly reduced versus HI group and approached the levels in the control group.

Luminol is an indicator of the hydrogen peroxide and hypochlorous acid, hydroxyl radical formation, and lucigenin is an indicator of the superoxide anion radical formation (25). In this study, luminol levels in the liver tissues of the HI group were found to be higher than in the control group. It was observed that this increase was considerably prevented in the HI group that was administered the SJW treatment. Lucigenin levels in the HI group were found to be higher than the control group, and this increase was considerably reduced in the I/R group, which was administered with SJW.

Myeloperoxidase is an important enzyme that is found in neutrophils, and it is involved in the ROS production (26, 27). In recent studies, in the hepatic I/R injury, it is often stated that as an indicator of neutrophil infiltration, an increase in the MPO activity causes the endothelial dysfunction and inflammation (28, 29). Similarly, our study showed that HI increased the MPO values compared with the control group in the liver tissue, while in the SJW group in our study, the MPO activity was substantially reduced, and the results were close to the MPO values of the control group.

The Na^+/K^+-ATPase is an important membrane enzyme that plays a key role in the hepatocyte structure and physiology by ensuring that sodium and potassium are found in all cell membranes (30, 31). During liver transplantation, this is an indicator of the tissue viability and hepatic function. It is reported in a study that the Na^+/K^+-ATPase level was degraded after the hepatic I/R (32). Parallel to these studies, our study results also show that the Na^+/K^+-ATPase activity of the HI group was lower than that of the control group. In the HI group, which was treated with SJW, this decline was significantly prevented.

When the bcl-2/bax ratio was evaluated with respect to the control group, the ratios of the SJW group and the HI-SJW group were observed to be high, and the ratio was observed to be low in the HI group. This decrease was considerably prevented in the HI group treated with SJW.

The caspase-3 and caspase-9 activity with respect to the control group was found to be low in the SJW group, while it was found to be high in the HI group. This increase was significantly recovered in the HI-SJW group.

It is known that SJW have antidepressant, anti-inflammatory, analgesic, antibacterial, and wound-healing effects (33). In recent years, inflammatory models have shown a protective effect of SJW with antioxidant properties by inhibiting free radicals and lipid peroxidation (34). In addition to this, SJW has been shown to reduce the levels of proinflammatory cytokines and prevent PMN leukocytes from accumulating in the inflamed area (35). In our study, it has also been shown that either directly or indirectly, SJW prevents tissue damage by inhibiting both cytokine activation as a result of free radicals and the activation of apoptotic agents during inflammatory events.

CONCLUSION

We have, as a result, shown in our experimental study that the injury caused by hepatic I/R was significantly reduced by administering SJW. There is a need for further comparative experimental and clinical studies in the clinical use of SJW for this purpose. Particularly, the recovery effect of SJW in the I/R injury may lead to clinical and experimental research that will offer new treatment methods.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University Experimental Animal Research Centre (18.11.2013/95.2013)

Informed Consent: N/A.

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Original Article

Experimental pericardial tamponade–translation of a clinical problem to its large animal model

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ABSTRACT

Objectives: Pericardial tamponade is a life-threatening medical emergency, when the hemodynamic consequences of low cardiac output severely disturb the perfusion of the peripheral tissues. Our aim was to design a reliable large animal model to reproduce the clinical scenario with the relevant pathophysiological consequences of pericardial tamponade -induced cardiogenic shock.

Material and Methods: Anesthetized Vietnamese mini pigs were used (n=12). Following laparotomy, a cannula was fixed into the pericardium through the diaphragm without thoracotomy. A sham-operated group (n=6) served as control, while in the second group (n=6) pericardial tamponade was induced by intra-pericardial injection of heparinized own blood. Throughout the 60-min pericardial tamponade and the 180-min reperfusion, macro hemodynamics, renal circulation and the mesenteric macro- and micro-circulatory parameters were monitored. Myeloperoxidase activity was measured to detect neutrophil leukocyte accumulation and in vivo histology was performed by confocal laser scanning endomicroscopy to observe the structural changes of the intestinal mucosa.

Results: PT increased the central venous pressure, heart rate, and decreased mean arterial pressure. The mesenteric artery flow (from 355.5±112.4 vs 182.0±59.1 mL/min) and renal arterial flow (from 159.63±50.7 vs 35.902±27.9 mL//min) and the micro-circulation of the ileum was reduced. The myeloperoxidase activity was elevated (from 3.66±1.6 to 7.01±1.44 mU/mg protein) and manifest injury of the ileal mucosa was present.

Conclusion: This experimental model suitably mimics the hemodynamics and the pathology of clinical pericardial tamponade situations, and on this basis, it provides an opportunity to study the adverse macro- and micro-circulatory effects and biochemical consequences of human cardiogenic shock.

Keywords: Animal model, cardiogenic shock, mesenteric ischemia, mini pig, pericardial tamponade

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INTRODUCTION

This article will explore the line between patients and experimental subjects, in an attempt to provide a proper view on the role of classical surgical research in contemporary cardiac surgery. According to the proverbial quote of Francis D. Moore, a *"surgical investigator must be a bridge tender, channeling knowledge from biological science to the patient's bedside and back again"* (1). This traditional approach emphasizes the great potential of biomedical sciences to provide help for unsolved problems in surgery. An equally important aspect of this type of research is that it develops new data, or more comprehensible knowledge on a specific area of clinical practice. In this sense, the science of surgery, like any other area of biomedical sciences, has four main methodological steps: observation of a clinical problem, formulation of a hypothesis, and performance of test procedures to reach a conclusion, supporting or refuting the initial hypothesis. In this analytical circle, models are indispensable tools to check the validity of hypotheses and to generate clinically useful data. In pragmatic terms differences are always present between the clinical reality and the models and therefore these dissimilarities should be reduced by choosing the experimental setup as accurate as possible. Understandably, the demand is huge for developing high fidelity models to decrease existing limitations and to obtain better applicable results for human medical science and healthcare (2).

A specific problem addressed by our study is cardiogenic shock due to cardiac tamponade. Pericardial tamponade is one of the most dreadful complication of cardiac surgery and invasive cardiology. Tamponade can develop after myocardial infarction, it can be the corollary of intra- or post-operative complications, or the consequence of non-cardiac surgical procedures (NCSP) as well (3). During tamponade, fluid will accumulate within the pericardial space, which can be transudate or pus, however the most common cause is bleeding (4). The increasing pressure in the closed pericardial sac blocks the venous inflow and decreases stroke volume. The subsequently reduced cardiac output (CO) results in tissue hypoxia and multi-organ damage. The long-term systemic consequences of pericardial tamponade are pronounced and serious even after the primary cause has been diagnosed and the basic problem was solved, i.e., the pericardial pressure was decreased via pericardiocentesis, re-operation or other intervention (5). The main reason for late complications is ischemia-reperfusion injury of distant organs, including the lungs, kidneys, and splanchnic tissues. This circulatory condition results in an antigen-

Figure 1. The insertion of the pericardial cannula via the transphrenic route (1 diaphragm, 2 pericardium, 3 liver, arrow: the cannula fixed into the pericardium)

independent inflammatory reaction with cytokine storm and increased endothelial permeability, which finally leads to an overwhelmingly severe systemic immune response (6).

According to previous experiences, cardiogenic shock can be modelled if an animal is anaesthetized, mechanically ventilated, and the pericardial sac is accessible through thoracotomy (7). The disadvantage of the model is thoracotomy itself with significantly impaired lung function, extended wound surface with a high risk of bleeding, lung injury, and tissue damage. Based on the above, our aim was to develop an experimental procedure where thoracotomy can be avoided and thus to design a new model of iatrogenic cardiogenic shock, where the situation is realistic, similar to the clinical appearance.

MATERIAL AND METHODS

Animals

The experiments were performed in accordance with National Institutes of Health guidelines on the handling and care of experimental animals and European Union Directive 2010/63 for the protection of animals used for scientific purposes. The study was approved by the Animal Welfare Committee of the University of Szeged (approval number: V/148/2013).

Surgical interventions

Anesthesia was induced by a mixture of ketamine (20 mg kg^{-1} *im.*) and xylazine (2 mg kg^{-1} *im.*) and maintained by a continuous infusion of propofol (6 mg $kg^{-1}h^{-1}$ *iv.*). The animals were placed on heating pad in a supine position; the body temperature was kept between 36-37°C. After endotracheal intubation, mechanical ventilation was started with a tidal volume of 10 $mlkg^{-1}$. The left jugular vein was cannulated for fluid and drug administration and the left femoral artery for the measurement of mean arterial pressure (MAP), heart rate (HR) and cardiac output (CO) by transpulmonary thermodilution (PICCO Catheters; PULSION Medical Systems, Feldkirchen, Germany). MAP, HR, CO and SMA flow (SMAF) data were recorded, pressure signals (BPR-02 transducer; Experimetria Ltd, Budapest, Hungary) and superior mesenteric artery (SMA), renal artery (RA) flow signals (T206 Animal Research Flowmeter; Transonic Systems Inc., Ithaca, NY, USA) were measured continuously by surgically placing a urinary catheter in the bladder via the femoral incision. and registered with a computerized data-acquisition system (SPEL Advanced HAEMOSYS 1.17; Experimetria Ltd, Budapest, Hungary). Ringer's lactate was given at the rate of 10 $mlkg^{-1}h^{-1}$. After a median laparotomy, the SMA was dissected free and a flow probe was placed around the SMA (Transonic Systems Inc., Ithaca, NY, USA). The RA was dissected free and a flow probe was placed around it (Transonic Systems Inc., Ithaca, NY, USA). The wound of the abdominal wall was temporarily closed thereafter with clips. In addition, intra-vital examination of the intestinal microcirculation was carried out by an orthogonal polarization spectral imaging system (OPS; Cytoscan A/R, Cytometrics, Philadelphia, PA, USA), and the extent of damage of the gastric mucosa was evaluated by *in vivo* histology (Five1, Optiscan Pty. Ltd., Melbourne, Victoria, Australia). The diaphragm was accessed through a median laparotomy and a 3-cm incision was made at the sternal part, avoiding the muscular region of the diaphragm. The pericardium was opened and a cannula was fixed into the pericardial cavity with a pledgeted purse string suture (Figure 1). The tamponade was induced for 60 min by intra-pericardial administration of heparinized own blood (100±50 mL), and the MAP was kept between 40–45 mmHg. During the observation period and between microcirculatory imaging the abdominal wall was closed by surgical clips.

Experimental Protocol

The animals were randomly allocated into two experimental groups. Group 1 (n=6) served as sham-operated control, with the same surgical interventions, time-frame, and sampling as in group 2 (n=6) but without the induction of a tamponade. In both groups, the diaphragm was accessed through a median mini-laparotomy. A 3-cm incision was performed at the sternal part, avoiding the muscular region of the diaphragm. The pericardium was opened and a cannula was fixed into the pericardial cavity with a pledgeted purse string suture. In Group 2, after the end of 60-min tamponade the blood was released from the pericardial sac and the animals were monitored for 180 min. Blood gas and hemodynamic parameters were measured in every 30 min. *In vivo* histological examination on the ileal mucosa and determination of neutrophil granulocytes was performed at baseline, 30 min after the relief of tamponade (90 min) and at the end of the experiments (240 min). Myeloperoxidase enzyme activity was measured at the –5; 30; 60; 90 and 240 min of observation period.

Hemodynamic Measurements

Central venous pressure (CVP), mesenteric and renal artery blood flow (AMSF, ARF) signals were monitored continuously and registered with a computerized data acquisition system (SPELL Hemosys; Experimetria, Budapest, Hungary). The MAP, CO, and HR were measured with the PICCO Plus monitoring system (PULSION Medical Systems; Munich, Germany).

Myeloperoxidase enzyme activity

Blood samples (0.5 mL) were taken from the left jugular vein into precooled, heparizined (100 U mL^{-1}) polypropylene tubes, centrifuged at 1.200 g at 4°C for 15 minutes, and stored at

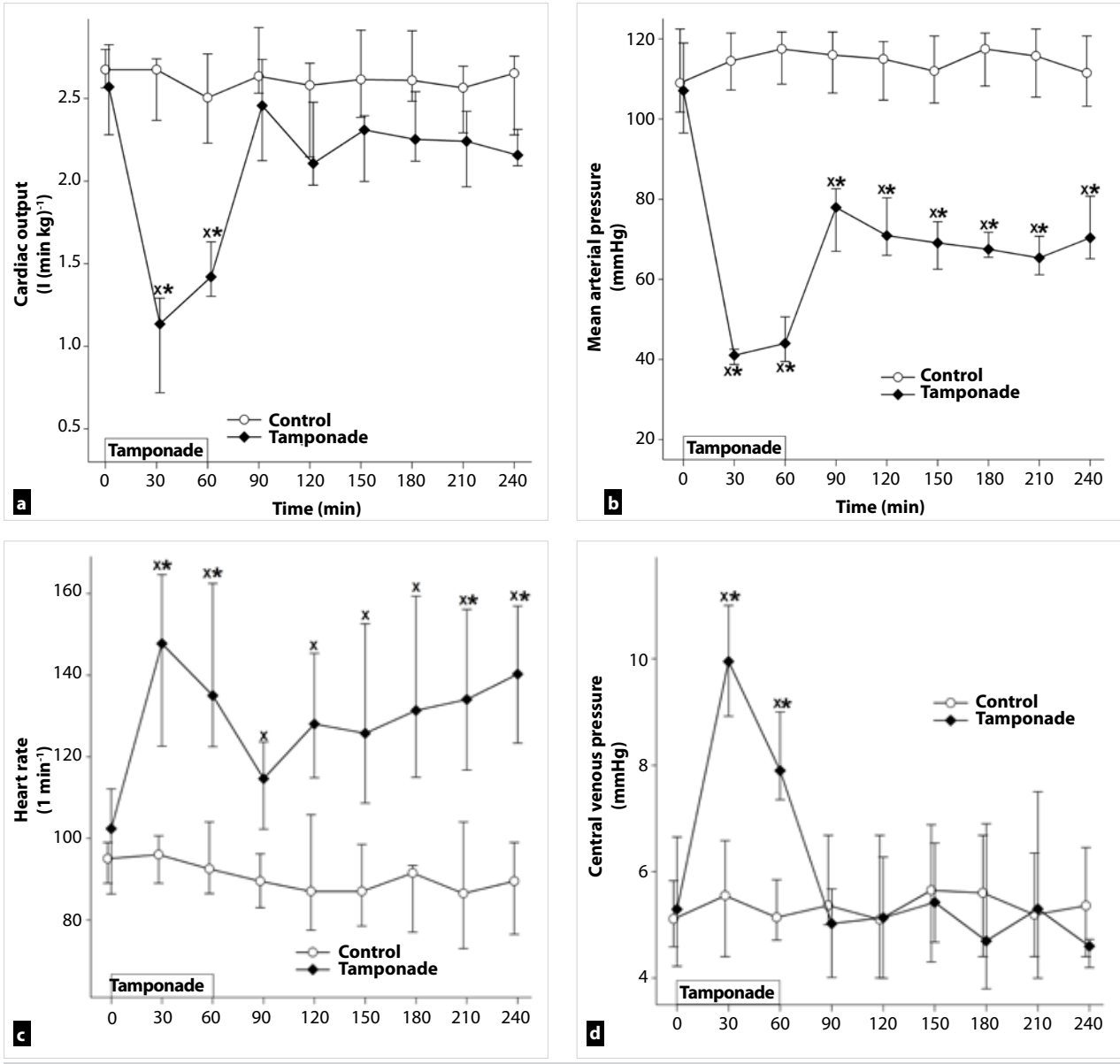

Figure 2. a-d. Changes in cardiac index (a), mean arterial pressure (b), heart rate (c), and central venous pressure (d) in control (white circle–solid line) and tamponade groups (black diamond–solid line). The plots demonstrate the median and the 25th (lower whisker) and 75th (upper whisker) percentiles
*p<0.05 for groups vs baseline values, xp<0.05 for cardiac tamponade vs control group values

–70°C until assay. Plasma MPO enzyme activity, a marker of polymorphonuclear leukocyte activation, was determined by the modified method of Kaszaki et al. (7).

Microcirculatory measurement

An intra-vital orthogonal polarization spectral imaging technique (Cytoscan A/R; Cytometrics, Philadelphia, PA) was used for non-invasive visualization of the mucosal microcirculation of ileum. This technique utilizes reflected polarized light at the wavelength of the isosbestic point of oxy- and deoxyhemoglobin (548 nm). As polarization is preserved in reflection, only photons scattered from a depth of 200 to 300 µm contribute to image formation. A ×10 objective was placed onto the mucosal surface of the small intestine, and microscopic images were recorded by a S-VHS video recorder 1 (Panasonic AG-TL 700; Matsushita Electric Ind, Osaka, Japan). Quantitative assessment of the microcirculatory parameters was accomplished off-line by frame-to-frame analysis of the videotaped images. Red blood cell velocity (RBCV, µm/s) changes in the capillary were determined in three separate fields by means of a computer-assisted image analysis system (IVM Pictron, Budapest, Hungary). All microcirculatory evaluations were performed by the same investigators (GB and GV).

***In vivo* detection of mucosal damage**

The extent of damage of the ileal mucosa was evaluated by means of fluorescence confocal laser scanning endomicroscopy (CLSEM) developed for *in vivo* histology. The analysis was performed twice, separately by two investigators (GV and GB). The mucosal surface of the ileum was surgically exposed and laid flat for examination. The ilaeal mucosal structure was recorded after the topical application of the fluorescent dye acriflavin (Sigma-Aldrich Inc, St. Louis, MO, USA). The surplus dye was washed off the mucosal surface of the ileum with saline 2 min before imaging. The objective of the device was placed onto the mucosal surface of the ileum and confocal imaging

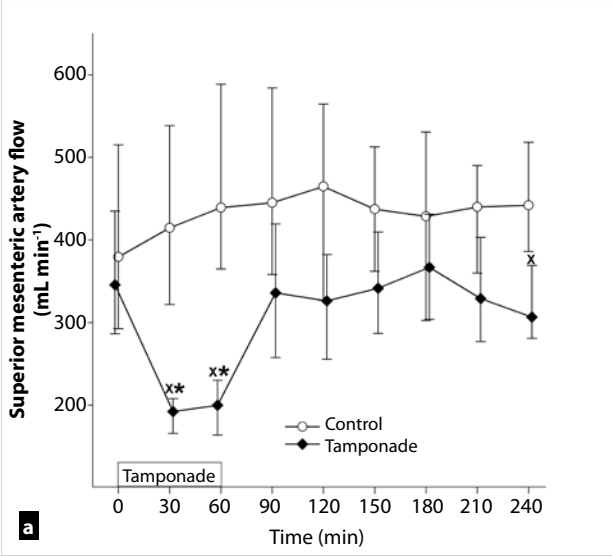

Figure 3. a-b. Changes in mesenteric artery (a) and renal artery flow (b) in control (white circle–solid line) and tamponade (black diamond–solid line) groups. The plots demonstrate the median and the 25th (lower whisker) and 75th (upper whisker) percentiles.
*p<0.05 for groups vs baseline values, xp<0.05 for cardiac tamponade *vs* control group values

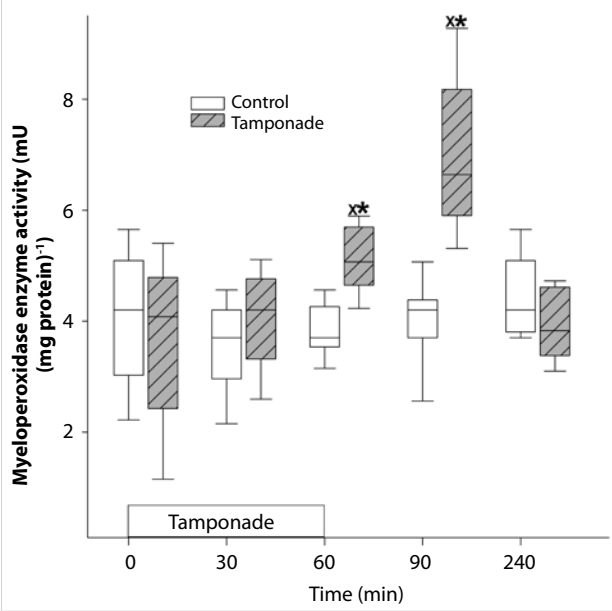

Figure 4. Changes in myeloperoxidase enzyme activity in control (white box) and tamponade (gray striped box to the right side) groups. The plots demonstrate the median and the 25th (lower whisker) and 75th (upper whisker) percentiles
*p<0.05 for groups *vs* baseline values, xp<0.05 for cardiac tamponade vs control group values

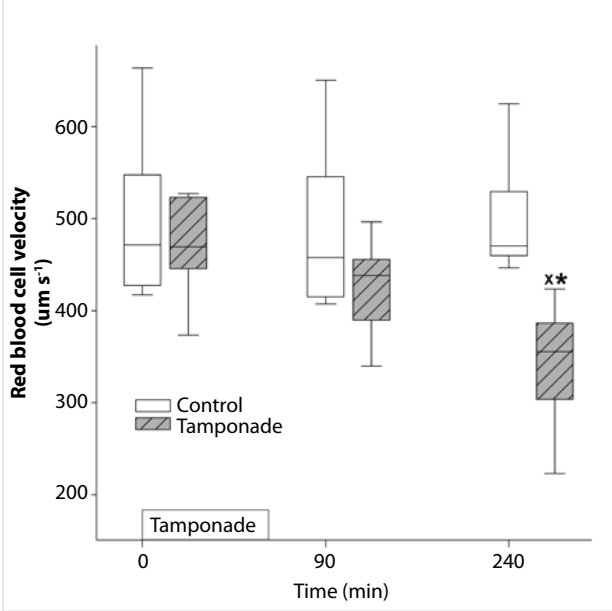

Figure 5. Changes in red blood cell velocity in control (white box) and tamponade (gray striped box to the right side) groups. The plots demonstrate the median and the 25th (lower whisker) and 75th (upper whisker) percentiles.
*p< 0.05 for groups *vs* baseline values, xp<0.05 for cardiac tamponade vs control group values

was performed 5 min after dye administration (1 scan/image, 1024x512 pixels and 475x475 μm per image). The changes in the mucosal architecture were examined by using a semi-quantitative scoring system as described previously (8). (I. oedema (0=no oedema, 1=moderate epithelial swelling, 2=severe oedema); and II. epithelial cell outlines (0=normal, clearly, well-defined outlines, 1=blurred outlines, 2=lack of normal cellular contours).

Statistical Analysis

Data analysis was performed with a statistical software package (SigmaStat for Windows, Jandel Scientific, Erkrath, Germany). Friedman repeated measures analysis of variance on ranks was applied within groups. Time-dependent differences from the baseline for each group were assessed by Dunn's method. The differences between groups were analyzed with Mann-Whitney probe. In the figures, median values and 75th and 25th percentiles are given; p<0.05 were considered significant.

RESULTS

Changes in Hemodynamic Parameters

The average duration of the surgical preparation phase was 70±20 min. The MAP remained at 40–45 mmHg as previously

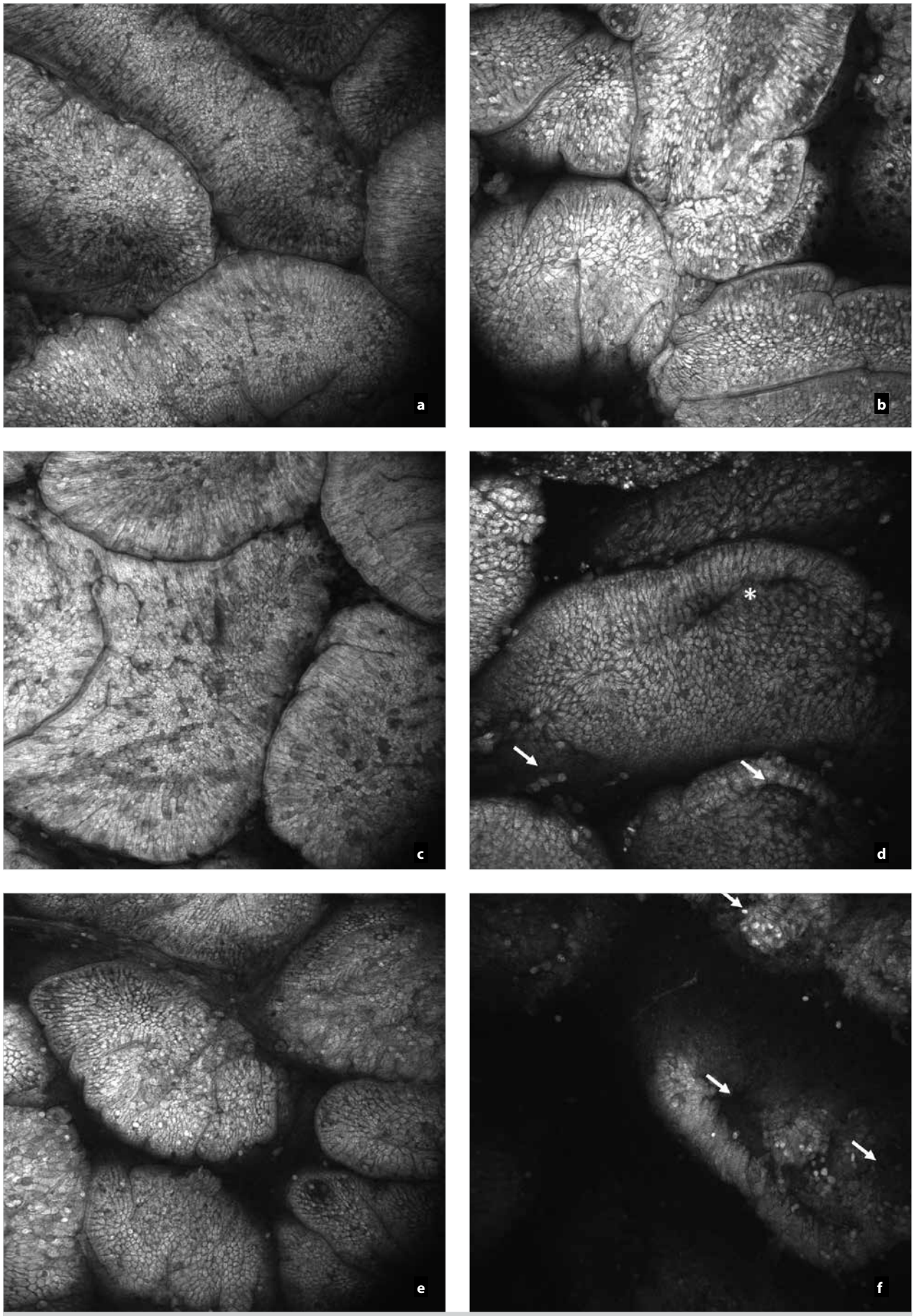

Figure 6. a-f. *In vivo* histology (CLSEM technique) showing the changes of the epithelial surface of the terminal ileum after acriflavin staining. Mucosal surface of control group (a, c, e); and structure of mucosal surface in tamponade group (b, d, f) are shown

planned throughout the 60 min of pericardial tamponade, accompanied by a concomitantly decreased CO. The CO increased to baseline levels after the reversal of tamponade (Figure 2a) but the MAP remained significantly depressed (Figure 2b). The elevation of CO was accompanied by a compensatory elevation of HR (Figure 2c). The decreased venous return was evidenced by a significant elevation of CVP throughout the tamponade phase.

Significant deterioration of artery mesenteric flow was observed during tamponade, but no significant differences were found in the post–tamponade phase as compared to the baseline values and the control group (Figure 3a). The renal artery flow was significantly and permanently reduced during tamponade and the post-tamponade period as well (Figure 3b).

Leukocyte accumulation

The plasma MPO activity increased during the tamponade period and its peak was reached 30 minutes after tamponade. At the end of the observation period the MPO activity decreased towards the control level (Figure 4).

Changes in microcirculation

The RBCV did not change in the control group, while in the tamponade group, a significant decrease from the baseline and control group was detected but at the end of the observation period (Figure 5).

***In vivo* Histology**

The mucosal morphology was examined by intra-vital CLSEM technique in real time. The epithelial morphology of the small intestinal mucosa presented normal morphological patterns in sham-operated animals and in the control samples of the tamponade group while 30 min after tamponade induction longitudinal fissures appeared and partial epithelium defects were detected (Figure 6a-e). The lack of epithelium was extended by the end of observation (Figure 6f).

DISCUSSION

Animal models have important, sometimes, decisive roles in today's medical research. Large animal models have many advantages for studying human pathophysiology and by their size they can provide additional benefits for the development of new surgical techniques and therapies. Experimental pericardial tamponade models using thoracotomy can be suitable to examine the complication of open cardiac surgical procedures or to monitor the hemodynamic changes (7, 9). Our purpose was to develop a suitable model based on experimental surgical standards for the investigation of cardiogenic shock, which evolves after NCSP where the duration, extent, characteristics, and outcome variables of impaired systemic circulation can be determined exactly. According to our results the presented experimental model can be used to study the acute pathophysiological consequences of low cardiac output states. Moreover, it may well reflect the signs of cardiogenic shock during NCSP. In addition, this pericardial tamponade setup can be useful for the practical training of surgical residents for the real-life demonstration and management of pericardiocentesis or emergency thoracotomy.

Increased pressure in the pericardium effects the low-pressure areas, like the superior and inferior caval veins and the right atrium. During the heart cycle, tension changes dynamically inside the atria and ventricles, thus the pericardial pressure blocks the right atrial inflow and consecutively the right ventricular diastolic filling. The high venous pressure leads to the distension of the jugular veins (Kussmaul-sign) the cardiac sounds are "muffled." In addition, the peripherial pulse cannot be palpated while cardiac auscultation detects heartbeats, this is referred as *pulsus paradoxus*. The ECG signs reveal the lower amplitude of R waves due to the increased resistance of intra-pericardial liquids (5, 10). The development of cardiogenic shock activates numerous compensation mechanisms to maintain the perfusion pressure to the vital organs. Besides the enhanced contractility, the heart rate is increased to maintain CO. Additionally, the body redistributes the circulating volume by systemic and local vasoactive responses, including the remarkable vasoconstriction of the muscle-, skin-, and mesenteric vessels (5, 10-12).

The decreasing diuresis could be the first sign of accumulating pericardial fluid and thriving pericardial tamponade on cardiac surgical ICU. In our experiments, the renal blood flow remained significantly depressed despite the resolving CO. The deteriorating renal function is a challenging problem in clinical practice, thus our porcine model could be an important tool for studies aiming to study the improvement of renal function.

CONCLUSION

Our model using anesthetized mini pigs reflects the local and systemic hemodynamic and inflammatory changes of the clinical picture correctly. In the absence of thoracotomy, the surgical procedure is relatively easy and fast while at the same time the experimental setup allows for extensive hemodynamic monitoring, tissue biopsies, and biochemical measurements. We tried to make the model as realistic as possible, thus the animal's own blood is used to fill the pericardium. Leakage of blood was not detected and therefore the amount of intrapericardial fluid could be standardized. The MAP level can be precisely controlled and the pressure response can be exactly modified throughout the experiments. Another advantage is that there is no explicit need for mechanical ventilation, and the lack of thoracotomy allows for longer duration or even chronic experiments with prolonged data collection. Besides, the transphrenic thoracal approach is definitely less stressful (refinement), and considering that the reduced invasiveness enables a reduction in animal numbers, this new model facilitates the adherence to the 3R principles as well.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Szeged University (V/148/2013).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.B., D.É., M.B., G.V.; Design - B.G., S.S., É.D., G.V.; Supervision - M.B. Resource - M.B., G.V.; Materials - B.G., S.S., É.D., G.V.; Data Collection and/or Processing - B.G., S.S., É.D., G.V.; Analysis and/or Interpretation B.G., S.S., É.D., G.V..; Literature Search - B.G., S.S., É.D., G.V.; Writing Manuscript - G.B., G,V.; Critical Reviews - D.É., M.B.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Original Article

Effects of different intraabdominal pressure levels on oxidative stress markers in laparoscopic cholecystectomy

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ABSTRACT

Objective: To evaluate the effect of laparoscopic cholecystectomy performed under different intraabdominal pressure on oxidative stress markers.

Material and Methods: This prospective, randomized, controlled study examined 90 consecutive healthy patients who underwent elective laparoscopic cholecystectomy with the diagnosis of symptomatic cholelithiasis. The patients were divided into three groups, 30 patients in each. Group 1 included patients who underwent laparoscopic cholecystectomy at a CO_2 pneumoperitoneum pressure of 7 mmHg, Group 2 patients who underwent laparoscopic cholecystectomy at a CO_2 pneumoperitoneum pressure of 10 mmHg, and Group 3 patients who underwent laparoscopic cholecystectomy at a CO_2 pneumoperitoneum pressure of 13 mmHg. Blood samples were collected preoperatively, perioperatively, and postoperatively for measurement of the serum levels of ischemia modified albumin and an analysis of total antioxidant status and total oxidant status. Intra-group comparisons were made.

Results: Group 1 experienced a significant increase in the postoperative ischemia modified albumin values compared to preoperative ischemia modified albumin values ($p=0.013$). Group 2 experienced a significant decrease in the perioperative total antioxidant status values compared to preoperative and postoperative total antioxidant status values ($p=0.009$). Group 3 experienced a significant increase in the perioperative total oxidant status and oxidative stress index values compared to preoperative values ($p<0.001$). Group 3 experienced a significant increase in the perioperative and postoperative ischemia modified albumin values compared to preoperative values ($p<0.001$).

Conclusion: Increased levels of oxidative stress markers were detected in patients who underwent laparoscopic cholecystectomy at a high intraabdominal pressure level.

Keywords: Antioxidant, intraabdominal pressure, laparoscopic cholecystectomy, oxidative stress, pneumoperitoneum

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INTRODUCTION

Laparoscopic cholecystectomy (LC) is a minimally invasive surgical procedure considered the gold standard and first choice in the treatment of symptomatic gallstones. This procedure has several advantages compared to open surgery, such as less pain and scarring and early return to activity (1). Nevertheless, adverse hemodynamic changes may occur with LC, including the increase of intraabdominal pressure (IAP). Besides the many advantages of LC, there are also risks, such as bile duct injury, bile leakage, intraabdominal organ and vascular injuries, perfusion defects due to rising IAP and oxidative tissue damage. Inappropriate pneumoperitoneum (PP) pressures can create life-threatening risks that are often not recognized, especially in elderly patients with chronic diseases. An increase in IAP depends on the presence of PP, which increases the systemic vascular resistance and decreases venous return, cardiac output, and stroke volume. Depending on the extent of PP, visceral perfusion, splanchnic perfusion, portal venous flow, and renal blood flow may also decrease (2-4). The reduction of abdominal visceral perfusion during laparoscopic surgical procedures increases oxidative stress (5, 6), which increases the production of lipid and protein oxidation products and decreases the production of antioxidant enzymes and circulation of vitamins.

There is a balance between oxidants and antioxidants that must be constantly controlled so that the biochemical functions in living beings may continue. Oxidative damage may occur when there is an imbalance in favor of oxidants. Some cellular and extracellular substances against the oxidative stress in the human body react with the free radicals, creating an imbalance between the oxidant and antioxidant levels, which is the main cause of tissue damage. There are many markers for assessing oxidative stress and antioxidant status. However, it is both time consuming and costly to measure these markers separately. To assess the risk of such a damage, the total antioxidant status (TAS) and total oxidant status (TOS) can be measured using a fully automated method (7, 8). Formation of the free radicals as a result of oxidative stress and hypoxia reduces the binding capacity for transition metals in the human N-terminal region of albumin, leading to the production of ischemia modified albumin (IMA). The IMA level can help in assessing the blood flow changes that may occur in the splanchnic area. The oxidant

and antioxidant levels can be demonstrated by the TAS, TOS, and IMA measurements appropriately and correctly (7, 8).

The LC procedure still shows diversity and differences due to the diversity of surgical instruments and techniques used, the number of trocars used, and the differences in the PP pressure created. During a LC procedure, keeping the PP pressure at the levels as ideal as possible without jeopardizing operational safety will ensure that the patient is protected from possible complications such as oxidative stress. Our aim in this study is to show the possible oxidative effects of the PP pressure and to draw attention to this issue. In our study, we formed groups of patients who underwent operation at low, medium, and high pressures, assuming that the 10–12 mmHg PP pressure was created while performing LC in the general practice. We performed surgical operations under 7, 10, and 13 mmHg PP pressures and investigated the effect of pressure differences on oxidative stress. Despite the importance of the IAP in LC, no study, to the best of our knowledge, has assessed the risk of performing LC under different pressures. To fill this research gap, our study examined the effect of LC performed under different IAP levels on oxidative stress markers.

MATERIAL AND METHODS

Patients

This prospective, randomized, and controlled study examined 90 consecutive healthy patients who underwent elective LC with the diagnosis of symptomatic cholelithiasis between June 2014 and April 2015. Patients with neoplastic diseases, diabetes mellitus, inflammatory disease, biliary pancreatitis, liver dysfunction, antihypertensive treatment, ischemic heart disease, chronic renal failure, or congestive heart failure were excluded. The approval for the study protocol was obtained from the local ethics committee of the Antalya Training and Research Hospital (2013-162). The study was conducted in accordance with the Declaration of Helsinki, and all study participants provided written informed consent before the study.

The 90 patients were divided into three groups, 30 patients in each. Group 1 included patients who underwent LC at a CO_2 PP pressure of 7 mmHg, Group 2 patients who underwent LC at a CO_2 PP pressure of 10 mmHg, and Group 3 patients who underwent LC at a CO_2 PP pressure of 13 mmHg. Preoperative (1 hour before the surgery), perioperative (20 minutes after the pressure generated PP), and postoperative (postoperative 24th hours) blood samples were taken from the patient groups. The samples were centrifuged at 3000 rpm for 15 min and stored in Eppendorf tubes at −80°C. The TAS, TOS, IMA, IMA-to-serum albumin ratio (IMAR), oxidative stress index (OSI), and albumin values were measured in serum. Intragroup comparisons were made following preoperative, perioperative, and postoperative measurements. A power analysis was performed. Preoperative and perioperative values were compared using the mean and standard deviation values. The power value of the analysis of the difference between the two values was found to be 0.999 according to the significance level of 0.05 and the effect size of 1.14.

Calculation of the TAS

TAS was measured with a Beckman AU5800 autoanalyzer (Beckman Coulter Diagnostics, BreaCA, USA), using the Erel method. In this colorimetric method, the presence of antioxidants causes a loss of color in dark-blue-green-colored ABTS, with the color change recorded at 660 nm and the results given in micromolar trolox liters. The measurement is calibrated with trolox equivalent vitamin E. The method's coefficient of variation (CV) has been reported to be <5% (7).

Calculation of the TOS

Total oxidant status was measured with a Beckman AU5800 auto analyzer (Beckman Coulter Diagnostics, BreaCA, USA) using the Erel method. This colorimetric method is based on the oxidization of ferrous-ion iron complex to ferric ion, which creates a colored compound in an acidic medium. The measurement is calibrated with H_2O_2, and the results given in μmol H_2O_2 Equiv./L. The method's CV has been reported to be <5% (8).

Calculation of the Oxidative Stress Index

The percentage ratio of TOS to TAS was accepted as the OSI (9). To determine the ratio, the resulting micromolar unit of TAS was changed to mmol/L, and the OSI value was calculated according to the following equation: OSI (arbitrary unit)=TOS (micromolar hydrogen peroxide equivalent/L)/TAS (micromolar trolox equivalent/L).

Measurement of the Ischemic Modified Albumin Level

After adding 50 μl of a 0.1% cobalt chloride solution to 200 μl of serum, the mixture was vortexed and then incubated for 10 min to induce the albumin–cobalt binding. After incubation, 50 μl of 1.5 mg/mL dithiothreitol (DTT) solution was added to form a color reaction with unbound cobalt and albumin, which typically occurs within 2 min. After 2 min, the reaction was completed by adding 1 mL of 0.9% NaCl to the mixture. The same steps were performed simultaneously to prepare a blind sample by using distilled water instead of DTT. After the reactions had been completed, the absorbance values of the experimental and blind samples as read at 470 nm were recorded as the IMA values (10). The equation IMA value/individual serum albumin concentration was used to maintain the IMAR to avoid introducing the confounding factor of the impact of albumin concentration differences between groups.

Statistical Analysis

Descriptive statistics were presented in terms of the frequency, percentage, mean, and standard deviation (SD) of the variables. In the test of normality, the Shapiro–Wilks test was performed if the sample size was <50, and the Kolmogorov–Smirnov test if the sample size was ≥50. The Kruskal–Wallis test was performed for non-parametric comparison of the three patient groups. In cases when the normal distribution was assumed, the analysis of variance was performed for comparison of the three groups, and the Turkey test for comparison of two groups. For the preoperative, perioperative, and postoperative values of the measurements for each group, the Friedman test was performed if the measurements were not in agreement with normal distribution, and normal distribution variance analysis for repeated measurements was performed if the measurements were in agreement with normal distribution. When the differences between the measurements were found to be significant in the binary comparisons, the Bonferroni–Dunn and Bonferroni tests were performed as post hoc tests. P-values less than 0.05 were considered statistically significant. All analyses were performed using the Statisti-

cal Packages for the Social Sciences (SPSS) version 20.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

The patients were divided into three groups. Group 1 (30 patients who underwent LC under a CO_2 PP pressure of 7 mm Hg) consisted of 11 males and 19 females of a mean age of 36.46 years (range, 26–52 years). Group 2 (30 patients who underwent LC under a CO_2 PP pressure of 10 mm Hg) consisted of 13 males and 17 females of a mean age of 43.63 years (range, 28–50 years). Group 3 (30 patients who underwent LC under a CO_2 PP pressure of 13 mm Hg) consisted of 12 males and 18 females of a mean age of 43.33 years (range, 33–52 years). The surgical duration for Groups 1, 2, and 3 was 38.67±34.11, 34.24±11.23, and 32.53±34.46 min, respectively. The difference in surgical duration among the groups was not found to be statistically significant (p=0.078).

The serum levels of IMA and analysis of TAS and TOS were done preoperatively, perioperatively, and postoperatively for measurement, and intra-group comparisons were performed.

Table 1 shows preoperative, perioperative, and postoperative TAS, TOS, IMA, IMAR, OSI, and albumin values of the groups. Group 1 experienced a significant decrease in the postoperative albumin level and a significant increase in the postoperative IMA level compared to the preoperative level of these variables (p=0.009, p=0.013, respectively). A significant increase was found in both the perioperative IMAR and postoperative IMAR values compared to the preoperative values of these variables (p=0.012, p=0.026, respectively).

Group 2 only experienced a significant decrease in the perioperative TAS value, a difference that was found to arise from an intraoperative reduction (p=0.009).

Group 3 experienced a significant increase in the perioperative albumin and postoperative albumin levels compared to the preoperative level (p<0.001, p=0.002, respectively). Group 3 experienced a significant increase in the perioperative TOS values compared to preoperative values and a significant decrease in the postoperative TOS values compared to perioperative values (p<0.001, p=0.001, respectively). Group 3 experienced a significant increase in the perioperative and postoperative IMA values compared to preoperative values (p<0.001), a significant increase in the perioperative OSI values compared to preoperative values (p<0.001), and a significant decrease in the postoperative OSI values compared to perioperative values (p<0.001).

Table 2 shows intra-group binary comparisons.

Table 1. TAS, TOS, IMA, IMAR, OSI, and albumin values of Groups 1, 2, and 3

	Preoperative Value Mean±SD	Perioperative Value Mean±SD	Postoperative Value Mean±SD	p
Group 1				
TAS	2.497±0.55	2.563±0.38	2.497±0.38	0.455
TOS	4.183±3.52	4.933±5.14	2.652±1.19	0.846
OSI	1.758±1.27	1.854±1.73	1.090±0.53	0.786
IMA	0.380±0.03	0.393±0.02	0.394±0.02	0.011*
IMAR	0.114±0.03	0.118±0.01	0.119±0.01	0.006*
Albumin	3.490±0.64	3.357±0.31	3.337±0.35	0.001*
Group 2				
TAS	3,160±0.64	2.861±0.54	2.964±0.63	0.007*
TOS	3.543±2.83	3.988±5.19	2.965±2.04	0.381
OSI	1.085±0.80	1.329±1.41	1.012±0.61	0.786
IMA	0.371±0.02	0.380±0.02	0.377±0.02	0.172
IMAR	0.114±0.02	0.117±0.01	0.114±0.01	0.356
Albumin	3.365±0.54	3.274±0.40	3.343±0.32	0.764
Group 3				
TAS	2.757±0.49	2.726±0.49	2.771±0.40	0.649
TOS	3.777±2.98	4.090±3.26	2.702±0.85	0.001*
OSI	1.368±0.92	1.496±1.01	1.150±0.91	0.001*
IMA	0.352±0.02	0.384±0.02	0.396±0.02	0.001*
IMAR	0.114±0.02	0.117±0.01	0.114±0.01	0.106
Albumin	3.160±0.47	3.307±0.40	3.493±0.34	0.002*

*Significant difference, p<0.05
TAS: Total antioxidant status (mmol Trolox Equiv./L); TOS: Total oxidant status (μmolH2O2Equiv./L); IMA: Ischemia modified albumin (ABSU); Albumin (g/dL); OSI: Oxidative stress index; and IMAR: IMA-to-serum albumin ratio (arbitrary unit)

Table 2. In-groups binary comparisons

	Preoperative–Perioperative p	Preoperative–Postoperative p	Perioperative–Postoperative p
Group 1			
IMA	0.078	0.013*	0.999
IMAR	0.012*	0.026*	0.999
Albumin	0.054	0.009*	0.999
Group 2			
TAS	0.009*	0.054	0.999
Group 3			
Albumin	0.001*	0.002*	0.072
TOS	0.001*	0.999	0.001*
OSI	0.001*	0.999	0.001*
IMA	0.001*	0.001*	0.897

*Significant difference, p<0.05
TAS: Total antioxidant status (mmol Trolox Equiv./L); TOS: Total oxidant status (μmolH2O2Equiv./L); IMA: Ischemia modified albumin (ABSU); Albumin (g/dL); OSI: Oxidative stress index; and IMAR: IMA-to-serum albumin ratio (arbitrary unit)

DISCUSSION

Cholelithiasis is one of the most frequent diseases of the gastrointestinal system, with a 15%–20% overall prevalence in the population aged between 15 and 50 years (11). The gold standard treatment for cholelithiasis is LC, an effective and minimally invasive surgical technique (12). However, the use of this method poses a risk of complications because of an increased IAP, thrombotic disease due to decreases in the perfusion of the abdominal organs, a decrease in the vena cava inferior blood flow, and significant changes in the respiratory and cardiovascular system and intestinal ischemia (13). Moreover, deterioration of the microcirculation due to oxidative stress occurs in the splanchnic region during LC insufflation. Although oxidative stress poses a significant risk due to high

intraabdominal pressure produced during LC, to the best of our knowledge, this was the first study to investigate the effect of LC performed under different levels of IAP on oxidative stress markers.

The splanchnic circulation results from the gastric, small intestine, colonic, pancreatic, hepatic, and splenic circulation occurring simultaneously. The three major arteries that supply the splanchnic organs, the celiac and superior and inferior mesenteric, give rise to smaller arteries that anastomose extensively. Numerous extrinsic and intrinsic factors influence the splanchnic circulation. Extrinsic factors include the general hemodynamic conditions of the cardiovascular and the autonomic and nervous system and circulating neurohumoral agents. Intrinsic factors include special properties of the vasculature, local metabolites, intrinsic nerves, paracrine substances, and local hormones (14). After an increase in IAP during LC, different oxidative stress markers are formed with the contribution of intrinsic and extrinsic factors. CO_2 pneumoperitoneum causes significant pathophysiological changes in many systems. The cardiovascular system is the most affected one during laparoscopy. Hypercarbia, acidosis, and an elevated IAP are the main reasons of the observed changes during CO_2 pneumoperitoneum (15). Generally, respiratory acidosis is well tolerated, and the blood is normalized by buffering systems. However, in patients with comorbid cardiorespiratory disease and in prolonged surgical procedures with elevated IAP, this recycling system might be challenging or impossible. IMA is formed by the pathophysiological causes of ischemia, such as the free radical formation, hypoxia, acidosis, and a decrease in the binding capacity for transition metals in the N-terminal region of the human albumin (16).

Ischemic events such as pulmonary embolism and myocardial ischemia alter the albumin binding, which may be a marker for ischemia pre-necrosis (10). In the antioxidant defense system developed by the human body, cellular, extracellular, and membrane-like substances are produced to prevent damage by oxidative stress by their reaction with free radicals. The resulting imbalance between the oxidant and antioxidant systems is the main cause of tissue damage.

While low levels of reactive oxygen species such as hydroxyl, peroxyl, and nitric oxide play the role in biological mechanisms such as defense mechanisms against pathogenic microorganisms and intercellular communication, an elevated concentration of such species may cause destruction in DNA, lipids, and proteins, and even cell death (17). Free radicals have the potential to cause damage to all cell components due to reactive structures. It is known that oxidative stress plays a role in the etiopathogenesis of many diseases, such as atherosclerosis, diabetes, cancer, and aging (18). Ortiz-Oshiro et al. (19) suggested that the restriction of pressure by 12 mmHg and a short surgery duration are the key points to prevent potential oxidative injury in laparoscopic surgery.

In another study, an increase in lipid peroxidation products and a decrease in endogenous antioxidants were reported in the early postoperative period in laparoscopic surgery when compared to open cholecystectomy (20). It was reported that the oxidative stress contributed to the pulmonary functions impairment in laparoscopic procedures with CO_2 insufflation (19, 20).

In a study measuring malondialdehyde in the tissue and blood, TAS, arterial blood gases, blood nitric oxide, and the end-tidal carbon dioxide volume after open and LC, Zulfikaroglu et al. (21) found the level of blood malondialdehyde to be high 30 min into surgery, but no significant changes in TAS. Based on their findings, they concluded that the antioxidant defense system is insufficiently stimulated when faced with a threshold level of oxidative stress. In another study, Koksal et al. (22) found that perioperative and postoperative TOS increased slightly but not significantly in LC patients. In a second study, Koksal et al. (23) found that the IMA values of blood samples taken during LC were higher than those of a control group, a difference that they explained by the improvement in splanchnic ischemia during LC due to PP.

This study tested the hypothesis that changes during LC can be generated by PP in the splanchnic area and the bloodstream of intraabdominal organs at different pressures. To test this hypothesis, albumin, TAS, TOS, OSI, IMA, and IMAR were measured in three patient groups. Oxidative stress markers were compared preoperatively, perioperatively, and postoperatively in the groups. In Group 1, the IMA and IMAR values increased significantly postoperatively, whereas in Group 2, the perioperative TOS and OSI values increased, and a postoperative decrease was observed. All markers showing perioperative oxidative stress, TOS, OSI, and IMA, were found to be significantly elevated in Group 3. At the postoperative 24th hour, the TOS and OSI values decreased significantly, while the IMA elevation continued. This status can be explained by a decrease in the splanchnic blood flow. During LC, high-pressure PP has several side effects, especially on the cardiovascular and pulmonary systems, and high CO_2 pressure may lead to acidosis, hypercapnia, deep vein thrombosis, and hypoxia (24).

The major limitation of our study is that the preoperative oxidative stress basal levels of the patients in the groups differ from each other. Differences in the baseline levels of preoperative oxidative stress limit comparing the groups with each other and interpreting the results. Because of this, preoperative, perioperative, and postoperative comparisons were made within the group, and it was observed that a high PP pressure may lead to adverse side effects.

CONCLUSION

The results of this study indicate that the creation of PP under low pressure during LC produces less oxidative stress than the creation of PP under high pressure. Laparoscopic surgery may alter the oxidative stress and pulmonary function due to IAP. Complications can be avoided with an appropriate anesthetic approach, pneumoperitoneum pressure, and surgical technique.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Antalya Training and Research Hospital (2013-162).

Informed Consent: Written informed consent was obtained from patient who participated in this study

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B.M.; Materials - U.D., H.Y.E., U.K., T.C.; Data Collection and/or Processing - U.D., T.C., A.A.; Analysis and/or Interpretation - U.D., B.M., M.H.; Literature Search - U.D., U.K., M.T.O.; Writing Manuscript - U.D., M.H., H.Y.E.; Critical Reviews - U.D., B.M., N.B.

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Original Article

Effects of prior abdominal surgery on laparoscopic cholecystectomy

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ABSTRACT

Objectives: With increased experience and technological advancement, laparoscopic cholecystectomy is reported to be safe and feasible even in the presence of most of the previously recognized contraindications. The purpose of this study was to explore the effects of prior upper and lower abdominal surgery on laparoscopic cholecystectomy.

Material and Methods: A retrospective evaluation of all sequential patients who underwent laparoscopic cholecystectomy from January 2014 to June 2016 was conducted. Patients were divided into three groups (Group A: patients without any prior abdominal surgical procedures; Group B: patients with prior upper abdominal surgical procedures; and Group C: patients with prior lower abdominal surgical procedures).

Results: A total of 329 patients were assessed. Group A consisted of 223, Group B of 18, and Group C of 88 patients. A statistically significantly higher operative time, postoperative pain, and complication rate after laparoscopic cholecystectomy were noted in patients with prior upper abdominal surgery. The groups were comparable regarding patients' demographics and surgery indications. The length of hospital stay was not statistically different between the groups (p=0.065).

Conclusion: According to the results of the current study, prior upper abdominal surgery leads to a significantly longer procedure time, higher postoperative pain, and complication rates after laparoscopic cholecystectomy. However, the length of hospital stay was not affected by the parameters investigated.

Keywords: Cholecystectomy, cholelithiasis, laparoscopy, previous abdominal surgery

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INTRODUCTION

Laparoscopic cholecystectomy (LC) is considered to be the gold standard approach in the treatment of cholelithiasis (1-3). Laparoscopic cholecystectomy has certain advantages over the open cholecystectomy procedure, such as a shorter hospital stay (LOS), faster return to daily activities, and lower morbidity and mortality rates, both in symptomatic cholelithiasis and acute cholecystitis (1, 4-6).

As a result of new developments in laparoscopic instrument technology and improved laparoscopic experience of the surgeons, laparoscopy is continuing to evolve (2, 7). Initially, pregnancy, obesity, cirrhosis, and previous abdominal surgery were accepted as relative contraindications for LC (2, 3, 7-9). In addition, previous abdominal surgery is reported to increase the complication rate and prolong LOS after LC (10). In this study, we intended to examine the effects of prior upper and lower abdominal surgery on LC.

MATERIAL AND METHODS

Patients who experienced LC between January 2014 and June 2016 at a tertiary care clinic were included into this study. All elective and emergency cholecystectomies were included except robotic, single-port laparoscopic, and mini-LC procedures. The procedures were performed by the same surgeons with an average expertise duration of less than 10 years. Study data were retrieved from REDCap (11) and from the hospital records retrospectively. The study was approved by the institutional review board (approval no: 2016-13/7), and informed consent was signed by all patients.

Included patients were divided into three groups as follows: patients who did not have prior abdominal surgery (Group A), patients who had prior upper abdominal surgery (Group B), and patients who had prior lower abdominal surgery (Group C). Only patients in whom the location of previous surgery was in the abdomen, considering it might affect the LC procedure, were assigned to Groups B and C. Patients with prior surgery through a midline incision were included in Group B.

Three groups were compared regarding demographic data, procedure duration, operative blood loss, indication for surgery, postoperative pain, duration of hospital stay, and early (<30 days) complication rates. The postoperative pain grade was assessed by the Visual Analog Scale (VAS) on postoperative Day 1. Operative blood loss was measured by means of aspirated blood from the operation field. Bleeding that could not be detected in the aspirator's container or was less than 1 mL, was recorded as 1 mL.

All patients included into the study underwent a conventional four port (one 10 mm camera port and three 5 mm working ports) LC. In patients with a median incision scar, open technique was used to establish pneumoperitoneum. In rest of the patients, to obtain pneumoperitoneum, a Veress needle was used with blind technique. The specimen was extracted through the 10 mm umbilical trocar.

Statistical Analysis

The statistical analysis for group comparison was done using the Kruskal–Wallis test. The origin of statistical significance was assessed by the Mann–Whitney U test. Pearson's chi-squared test or Fisher's exact test were used for qualitative data (gender, indication for surgery, American Society of Anesthesiologists [ASA], complications) comparison between groups. The results are reported as mean±standard deviation and range. Statistical analyses were performed using the Epi Info software. $p<0.05$ was acknowledged as statistically significant.

RESULTS

A total of 329 patients that met the criteria were included into the study. Groups A, B, and C consisted of 223, 18, and 88 patients, respectively. Patient demographics and pre- and postoperative data are presented in Table 1.

The overall mean age was 48.3±15.4 (range, 17–90) years, the body mass index (BMI) was 28±5.09 (range, 17–49) kg/m^2, the operative time was 58±27.5 (range, 25–260) minutes, blood loss was 11.34±23.4 (range, 1–240) mL, the VAS score was 2.8±2.1 (range, 0–10), and postoperative LOS was 1.6±1.8 (range, 0–28) days. There was no mortality. Age, BMI, ASA score, incidence of acute cholecystitis, and LOS were comparable between the groups.

Group C had a significantly higher percentage of female (87.5%) patients than Group A (51.6%) and Group B (44.4%) ($p<0.001$). Group B showed a significantly longer mean operative time (72.22±38.4, 25–155 min) compared to Group A (58.76±28.14, 25–260 min) and Group C (52.94±21.74, 25–115 min) ($p=0.031$). The operative time was similar between Groups A and C.

The VAS score was statistically significantly higher in Group B (4.11±2.22, 0–10) than in Group A (2.8±2.05, 0–10) and Group C (2.44±2.11, 0–10). Group A had a significantly greater blood loss than Group C (13.02±26.12 mL vs. 5.98±7.92 mL, $p=0.003$).

There was no conversion to open except for one patient. This patient in Group B was operated on for a cholecystocutaneous fistula. The patient had a history of right nephrectomy and tube cholecystectomy performed due to a perforated gallbladder. His gallbladder was sclerotic, and a choledochal injury was noted intraoperatively. After conversion to open, a Roux-en-Y hepaticojejunostomy was executed. Patient was discharged home uneventfully.

Table 1. Patients' demographics and pre- and postoperative data

	Patients Without Any Previous Abdominal Operations (Group A, n=223)	Patients With Previous Upper Abdominal Operations (Group B, n=18)	Patients With Previous Lower Abdominal Operations (Group C, n=88)	p
Gender*				
Female	115 (51.6)	8 (44.4)	77 (87.5)	
Male	108 (48.4)	10 (55.6)	11 (12.5)	<0.001
Age# (years)	48.61±15.6	55.5±16.97	46.06±14.16	0.080
BMI# (kg/m^2)	28.26±5.08	27.72±5.22	27.48±5.09)	0.244
ASA*				
I	164 (74.9)	12 (66.7)	77 (87.5)	
II	47 (21.5)	6 (33.3)	9 (10.2)	
III	8 (3.7)	0	2 (2.3)	0.061
Operation time# (minutes)	58.76±28.14	72.22±38.40	52.94±21.74	0.031
Operation indication*				
Acute cholecystitis	75 (33.6)	4 (22.2)	31 (35.2)	
Elective cholelithiasis	148 (66.4)	14 (77.8)	57 (64.8)	0.563
Operative blood loss# (mL)	13.02±26.12	16.89±34.22	5.98±7.92	0.003
Postoperative VAS score#	2.8±2.05	4.11±2.22	2.44±2.11	0.010
Length of hospital stay# (day)	1.5±1.08	3.11±6.31	1.36±1.02	0.065
Conversion*	0	1 (5.6)	0	
Early (<30 day) complications*				
No	213 (96.4)	12 (75.0)	86 (97.7)	
Yes	8 (3.6)	4 (25.0)	2 (2.3)	0.004

Continuous variables are described as the mean±standard deviation (range), and categorical variables are described as n (%). Statistical significance is emphasized in bold.
BMI: body mass index, ASA: American Society of Anesthesiologists, VAS: Visual Analog Scale
Datas are presented as *; n (%), #; mean±SD

Short-term (<30days) complications were statistically higher in Group B (n=4, %25) (p=0.004). Except one, all were minor complications including seroma, hematoma, infection, and fat necrosis in the trocar site. One patient in Group B who had a history of open rectum cancer surgery had an iatrogenic bowel injury. During LC, widespread intra-abdominal adhesions were noted. On postoperative Day 2, he was diagnosed with iatrogenic small bowel injury. A loop ileostomy was created through laparotomy. The postoperative course was uneventful.

DISCUSSION

According to the results of this study, in patients who had prior upper abdominal surgery, operative time was longer, and the VAS scores and complication rates were higher compared with those who had earlier lower abdominal surgery and those who did not have any abdominal surgeries.

In the present study, the conversion rate in 223 patients without previous abdominal surgery was nil. When both the upper and lower abdominal surgery groups were combined, the conversion rate was 0.9% (n=1). In a study performed by Ercan et al. (8) in 2009, a total of 677 patients were divided into three groups. When the conversion rate was compared, 27.27% of patients with prior upper abdominal surgery (n=66), 2.82% of patients with lower abdominal surgery (n=567), and 25% of patients with both upper and lower abdominal surgeries (n=44) were converted to open. In a similar study, Akyurek et al. (7) showed that the overall conversion rate in 192 patients with prior abdominal surgery was 2%. This difference may be due to wider laparoscopic surgery experience and defined safe cholecystectomy methods together with improved laparoscopic surgical tools. In addition, our 5.6% conversion rate with one patient from the prior upper abdominal operation group is not sufficient to draw any statistical conclusions. However, studies vary in terms of conversion rates, complications, and LOS after LC in patients with previous abdominal surgeries. Unal et al. (12) reported that prior upper abdominal surgery was not a risk factor for conversion. On the other hand, Karayiannakis et al. (9) demonstrated higher complication and conversion rates and longer LOS (3.4±2.1 days) for patients with prior upper abdominal surgery than without prior upper abdominal surgery. In contrast to this study, our increased complication rate and operative time did not result in a prolonged LOS (3.11±6.31 days, p=0.065) for patients with prior upper abdominal surgery.

In the current study, although a trend toward an increased LOS in the group with prior upper abdominal surgery was observed, the difference was not statistically significant (p=0.065). When complication rates are compared, the upper abdominal surgery group showed a significantly higher complication rates (p=0.004). However, this difference did not affect the LOS. In our opinion, the reason may be due to the fact that except in two patients, all complications were minor.

It is proposed that prior abdominal surgery increases the risk of iatrogenic intestinal damage by causing adhesions or obstructing the visualization of hepatobiliary structures and limiting the working area (10).

Obtaining pneumoperitoneum by the open technique instead of the closed needle technique, might prevent complications in patients with median incisions. Adhesions and scar tissue were reported to restrict safe entrance into the abdomen and cause bowel and other intra-abdominal organ injury (10). In this study, although the first trocar was inserted with open technique, iatrogenic bowel injury was observed not during the trocar entrance, but later, after the operation, in Group B. This draws attention to more attentive manipulation of the laparoscopic tools during surgery. It has been reported that the possibility of bowel damage is higher during the first trocar entry in patients with prior abdominal surgery, and these injuries are noticed later because of limited visualization due to adhesions (8). Despite the accepted superiorities of LC compared with its open equivalent, conversion to open can be necessary in difficult cases to prevent inadvertent injuries (8). It should be noted that meticulous adhesiolysis is necessary to prevent iatrogenic injury.

The mean operative time was statistically significantly longer in Group B compared with Groups A and C (p=0.031). The time spent for open trocar insertion and time for adhesiolysis around the gallbladder could be the reasons for this statistically longer operative time in Group B. There was a significantly greater number of females in the lower abdominal surgery group (Group C) (87.5%). This was because lower abdominal procedures including Cesarean section, hysterectomy, and oophorectomy were specific for females. However, adhesions in this region did not adversely influence the LC operation time. Further studies are needed to investigate the contribution of duration of adhesiolysis and open technique to total operative time. Akyurek et al. (7) demonstrated that adhesions were the most common cause for conversion to open surgery. In the same study, however, it was documented that adhesiolysis itself did not result with complications.

A certain limitation of our study is that adhesions of the patients were not assessed according to a scoring system, and the time for adhesiolysis was not recorded separately.

Adhesiolysis may increase postoperative pain, operative blood loss, and LOS (9, 10). In this study, the mean VAS score was statistically significantly greater in Group B compared with Groups A and C (p=0.01). This difference could be attributed to the increased amount of adhesions and subsequent adhesiolysis needed in Group B. However, an increased VAS score and operative blood loss did not lead to a longer LOS.

When groups were compared concerning the operative blood loss, it was interesting to see that the blood loss was statistically significantly greater in Group A than in Group C. The method of our blood loss measurement might be the reason for this unexpected difference. During the study, we measured the operative blood loss by the amount of aspirated blood volume. We recorded the amounts of bleeding that did not need aspiration or less than 1 mL as 1 mL. Different measurement methods may clarify this inconsistency.

We would like to acknowledge some limitations of our study. First, it was a retrospective analysis with inherent limitations. Thus, selection bias could not be prevented. Second, the sample size of the group with previous upper abdominal surgery

was small. Third, the adhesion scoring system was not used, or time for adhesiolysis and for open trocar insertion was not calculated separately from the total operation time. Finally, this study is also limited in its generalizability because the study population were patients who presented to a tertiary care center.

Additional studies are required to define the role of adhesiolysis. In addition, studies including a higher number of patients with prior upper abdominal procedures may further explain these concerns.

CONCLUSION

Prior upper abdominal surgery results in a lengthier operative time, higher postoperative pain, and greater complication rates after LC, compared to patients with earlier lower abdominal surgery and without earlier abdominal surgery. However, in this study, previous abdominal surgeries did not increase LOS and the conversion rate after LC. Further studies that would include patients with a higher number of prior abdominal procedures are needed.

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Original Article

Comparison of the non-mortal gunshot and handmade explosive blast traumas during a low-intensity conflict on urban terrain

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ABSTRACT

Objectives: We aimed to conduct a cross-sectional data analysis involving 60 patients wounded during a low-intensity conflict on urban terrain.

Material and Methods: Data of the 60 patients wounded during a low-intensity conflict on urban terrain between September 1st, 2016, and January 15th, 2017, and transferred to our hospital after the initial medical interventions conducted in the regional hospitals were probed retrospectively. Group A consisted of 25 (41.67%) patients suffering gunshot wounds, and Group B consisted of 35 (58.33%) patients with blast trauma injuries. Their Abbreviated Injury Scale scores were compared according to the injured body compartment.

Results: In both groups, extremities were the most common site of injury (17 [50%] for Group A, 18 [33.33%] for Group B). The difference between the two groups was statistically significant for only head and neck injuries and facial injuries ($p<0.05$). In each group, only one body compartment was affected in 19 patients, which represented 55.88% of patients in Group A and 35.18% of patients in Group B. Injuries of three compartments concurrently occurred in 3 (8.82%) patients in Group A and 4 (7.4%) patients in Group B. None of our patients died because of their injuries.

Conclusion: Contrary to the expected, gunshot casualties were found to be more likely to suffer from extremity injuries than blast casualties did, and it should be noted that blast trauma casualties tend to have multiple compartment injuries that should not be missed. Ocular ruptures are also common, especially with blast injuries, warranting equipping the personnel with protective goggles.

Keywords: AIS, blast trauma injury, gunshot injury, urban terrain

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INTRODUCTION

Early post-World War periods are known to change medical approaches to the injured patient suffering from trauma. Today, modern warfare is likely to take place, not in the fields, but on the urban terrain where once peaceful neighborhoods become battlefields. Combats of this kind made a paradigm shift in treatment approaches for high-kinetic-energy (HKE) injuries. The prime reason for this shift is the change in injury patterns. HKE injuries differ by means of affected body compartment according to its cause: bullets (B) or fragmented parts of handmade explosives (HE). Especially HE, which are widely used by terrorists, are known to cause complex and unpredictable damages (1, 2). In this study, we aimed to analyze the Abbreviated Injury Scale (AIS) compartments of patients who were affected by the B or HE traumas to reveal the anatomic locations which the protective measures should be directed at (3).

MATERIAL AND METHODS

This retrospective cross-sectional study is designed to examine the data of patients affected by the HKE injuries between September 1st, 2016 and January 15th, 2017, who were referred to our institution after their first medical intervention took place in the regional hospitals of the southeast region of our country. All patients were wounded in a low-intensity conflict on urbanized terrain (LICUT) during our national fight against terrorism and transferred to our center for further treatment after which they were considered to be medically stable. Patients were sorted according to their age, gender, the type of HKE trauma cause, and affected anatomical compartment. They were reclassified as Group A and Group B according to the cause of the HKE injury as B and HE explosives. The sites of penetration frequencies were determined using the AIS compartments for each group. Distribution of injured organs/tissues was also analyzed in the two groups. The SPSS for Windows version 22.0 (Statistical Software, Chicago, IL, USA) was used for statistical analysis, and chi-squared and Fisher's exact test were applied for data comparison. A p-value of <0.05 was considered to be statistically significant.

This study was performed in compliance with the Declaration of Helsinki.

RESULTS

All 60 patients were male with a mean age of 31 (23–57). Twenty-five (41.67%) patients injured by gunshot wounds were grouped as Group A, and 35 with blast injuries were grouped as Group B.

Two groups were compared according to their sites of injury according to AIS compartments (Table 1). The extremities were the most common compartment affected by trauma in 17 (50%) patients in Group A, and in 18 (33.33%) patients in Group B. Head and neck and facial injuries were significantly more common in Group B ($p<0.05$). Other compartment injuries showed no significant difference according to the type of the HKE trauma.

In each group, only one body compartment was wounded in 19 patients, which represented 76% of patients in Group A and 54.28% of patients in Group B. Two compartments were injured in 3 (12%) patients in Group A and 12 (34.29%) patients in Group B. Injuries in three compartments concurrently occurred in 3 (12%) patients in Group A and 4 (11.43%) patients in Group B. None of the wounded patients had 4 or more body parts affected.

In addition to compartments, anatomic injury sites were also analyzed according to the type of the HKE trauma (Table 2). Patients wounded by HE mostly suffered tibia fractures on the left side (n=3) and ulna fractures on the right side (n=3). The nerve damage and vascular injuries were the same for both sides, and the ocular globe rupture, which was only seen in patients in Group B, was the most common organ injury (n=9, 5 on the left, 4 on the right). The most frequently injured solid organs were the spleen (n=4) and liver (n=4). . Penetration of foreign bodies was mostly encountered in extremities (n=5) followed by eyeballs and the thoracic wall, and the second- and third-degree burns were mostly seen in the left upper extremities (n=2).

Gunshot wounds caused by bullets were common in extremities, mostly in the left humerus (n=3). Neurovascular injuries and amputations were same for both sides. Grade I–II splenic trauma was the most common type of solid organ injury. When the two types of injuries were compared according to the incidence of the organ/tissue injury, HE caused the fractures of the humerus, ulna, femur, and tibia (open), and gunshots caused the fractures of the humerus and tibia. Neurovascular injuries, amputation, and spinal cord injury rates did not differ among the two groups. In patients suffering blast traumas, the liver and spleen injuries were common, followed by eyeball ruptures and trapped foreign bodies on the anterior chest wall.

Although the mortality rate was 0% among our patients, 9 enucleations, 4 amputations, 7 splenectomies, and 7 colonic resections were performed by means of organ losses, all more common with blast injuries (n=21 vs. n=6).

DISCUSSION

It has been known that injuries caused by HKE are the most common cause of death among trauma patients (4). As HE is being used more frequently during LICUTs, blast injuries caused by them bring new challenges as well as contributing to the development of new treatment approaches (1). Furthermore, as Hoencamp et al. (5) reported, the frequency of blast injuries is 85% greater now than during the former combats and wars.

In this study, we aimed to analyze patients wounded during LICUTs and referred to our hospital after their initial resuscitative stabilization have been ensured at field hospitals. Wound patterns are investigated according to the cause of the HKE trauma: bullets or HE. Ever-changing and technologically improving pistols and rifles versus HE made from the everyday materials are also compared for their destructive effects.

Dubost et al. (6) reported their experience as the Seventh French Forward Surgical Team during military operations in Mali and the Central African Republic and concluded that gunshot wounds were the most common type of injury during their campaign. In our series, most of our patients were injured by HE, which clearly are a product of the tactical nature and reality of LICUT. A methodical review by Hoencamp et al. (7) revealed that 72% of combat injuries are due to blast traumas. In our study, 58.33% patients suffered from a blast trauma.

Abbreviated Injury Scale is one the most commonly used and well-defined trauma scoring systems that relies on objective findings according to the anatomic site of the injury (compartment) (3, 8). This severity scoring system provides important information that guides the treatment, helps to anticipate the outcomes, and is also handy for standardizing data when structuring retrospective analyses (8). Since patients were medically stabilized in the field hospitals prior to their transfer our hospital, the mortality rate was 0%. Thus, the Injury Severity Score was not applicable since we couldn't gather the initial data of the patients, so the AIS compartments incidence analyses are done. The AIS scores are reported to be indeterminable in some cases (9). The AIS scores of injured compartments were probably low, but not well-defined enough to give a quantitative value to our patients. Therefore, we grounded our study on compartments rather than AIS scores and aimed to interpret whether a flak jacket or similar protective garment had any relation to the site of injury.

With regard to the injured compartments according to the type of trauma, extremities were affected in 50%, the abdomen in 20%, and thorax in 20% of the patients with bullet

Table 1. Distribution of injuries according to their compartments

			Head and neck	Face	Thorax	Abdomen	Extremity	External	Total Compartments Involved
Gunshot n (%)	25 (41.67)	n	3	1	6	6	17	1	34
		%	8.8	2.9	17.6	17.6	50	2.9	100
Blast n (%)	35 (58.33)	n	6	13	8	8	18	1	54
		%	11.1	24	14.8	14.8	33.3	1.8	100
Total n (%)	60 (100)	n	9	14	14	14	35	2	88
		%	10.2	15.9	15.9	15.9	39.7	2.27	100

injuries. Blast traumas have caused damage to the extremities in 39.77% and to the face in 24.08% of the wounded. It is known that gunshot assaults, especially sniper attacks target deadly compartments. It should be stated that our analysis does not include lethal traumas, therefore extremity injuries made up the majority of cases with the gunshot trauma. Perhaps flak jackets provided a degree of protection against bullets, as mentioned in other studies so that the thoracoabdominal injuries were ranked after the extremity injuries (10). When considered together, nonfatal injuries caused by either gunshots or blast trauma are found to affect extremities in our series.

When the number of compartments involved is examined in both types of injuries, the caused damage was mostly confined in only one compartment (76% for gunshot injuries and 54.28% for blast traumas), and no more than three compartments were involved in either group. This could be explained by patients having more than three compartments injured who either lost their lives on the field or were not suitable for transfer.

The most commonly affected organ/tissue by both gunshot and blast traumas were extremities, as previous studies have reported (6, 7). Therefore, amputations due to neurovascular

Table 2. Injured organ/tissue incidence

Damaged Organ/ Tissue	Patients					
	Blast			Bullet		
	Left	Right	Total	Left	Right	Total
Extremity Damage - Fractures						
Humerus	1	2	3	3	2	5
Tibia	3	2	5	2	1	3
Fibula	0	0	0	1	0	1
Scapula	0	1	1	1	0	1
Talus	0	0	0	1	0	1
Calcaneus	1	0	1	1	0	1
Metacarpus	1	0	1	0	0	0
Maxilla	1	0	1	0	0	0
Metatarsus	1	0	1	1	0	1
Clavicula	0	0	0	0	1	1
Iliac Wing	1	2	3	0	0	0
Radius	1	0	1	0	0	0
Ulna	1	3	4	2	0	2
Shoulder	1	0	1	0	0	0
Femur	2	2	4	0	2	2
Neurovascular Injuries - Amputations						
Brachial Artery	0	0	0	0	1	1
Axillary Artery and Vein	0	0	0	0	1	1
Renal Artery	1	0	1	0	0	0
Ulnar Artery	0	0	0	1	0	1
Ulnar Nerve	1	0	1	1	0	1
Brachial Plexus Damage	0	0	0	1	0	1
Above Elbow Amputation	0	0	0	0	1	1
Below Knee Amputation	0	1	1	0	1	1
Hand Finger Amputation	1	0	1	0	0	0
Spinal Cord Injuries						
Nondisplaced C1 Fracture	1	0	0	0	0	0
Spinal Cord Injury T12	0	1	0	0	0	0
Spinal Cord Injury L1	1	0	0	0	0	0
Brain	3	2	0	0	0	0
Eyeball Rupture	5	4	9	0	0	0
Pneumothorax	1	1	2	0	2	2
Hemothorax	1	1	2	0	0	0
Lung Contusion	1	1	2	2	0	2
Liver Laceration (Grade I-II)	4	2	0	0	0	0
Spleen Laceration (Grade I-II)	4	3	0	0	0	0
Colon	4	0	0	0	0	0
Rectum	2	1	0	0	0	0
Renal Laceration	2	1	0	0	0	0
Bladder	0	1	0	0	0	0
Urethra	2	1	0	0	0	0
Rupture of Lateral Collateral Ligament	0	0	0	0	1	1
Rupture of Collateral Knee Ligament	1	1	2	0	0	0
Foreign Body Localization						
Extremity	3	2	5	0	0	0
Rectum	1	0	0	0	0	0
Eyeball	2	2	4	0	1	1
Abdomen	1	0	0	0	0	0
Thorax	4	0	0	0	0	0
Neck	1	0	0	0	0	0
Mandibula	2	0	0	0	0	0
2° and 3° Burns						
Shoulder	0	1	1	0	0	0
Back	1	0	0	0	0	0
Upper Extremity	2	0	2	0	0	0

injuries of the extremities were commonly encountered. The injuries causing brain damage were similar in both groups. However penetrating injuries were more common in gunshot traumas. This finding could only be interpreted if the data of mortal injuries were available.

We found that eyeball ruptures are common in blast injuries (n=9, 25.71% of blast injuries). When all wounded patients during LICUTs are considered, eyeball ruptures were present in 15%, which warrants the idea of wearing eye protecting goggles during LICUTs.

Solid organ injuries such as liver and spleen are more common among blast injury victims even when flak jackets are worn (10). This is because of fragmentation of shrapnel-like items such as nails, iron fragments, and screws embedded in HEs, as well as blunt trauma caused by the pressure.

Shacfor et al. (11) reported in their multicenter study that both gunshot and blast injuries tend to be mortal. Since our hospital played a referral center role in this particular situation, we had no mortalities. This allowed us to make a cross-sectional analysis of non-mortal gunshot and blast injury victims by means of their injury types and injured compartments.

Not having a standardized national database of trauma patients in Turkey is the main limitation of this study.

CONCLUSION

Although injury scores according to the AIS system could not be obtained, our cross-sectional study still provides useful information for the new era of modern warfare.

As a result, regardless of the injury type (gunshot or blast), non-mortal victims of LICUTs are likely to suffer from extremity wounds and especially blast injuries caused by HE, which tend to affect more than one compartment of the body, including a high incidence of eyeball ruptures. Every effort should be made to assess victims of blast trauma injuries not to miss any possible affected body compartment. Our series that was small in number also suggests that personnel facing low-intensity warfare like LICUTs or military operations on urban terrain should be equipped with protective goggles as well as flak jackets.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

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Original Article

Surgery for Intestinal Crohn's Disease: Results of a multidisciplinary approach

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ABSTRACT

Objectives: Crohn's disease is a chronic inflammatory bowel disease that requires lifelong multidisciplinary management. Seventy percent of patients affected by Crohn's disease will require at least one surgical procedure over their lifetime. The aim of this retrospective study was to present our series of patients suffering from Crohn's disease who were scheduled for surgery by a multidisciplinary team.

Material and methods: The data were retrieved from a review of 950 patients with Crohn's disease treated at our institution between March 2000 and March 2016. Only patients with intestinal Crohn's disease were included into the study. A multidisciplinary team assessed the decision to perform surgery.

Results: There were 203 patients who underwent surgery included in this study. One hundred and sixty-six were intestinal and 37 were perianal Crohn's disease. The mean age was 36±11.5 (range, 12–75) years. Ninety-two were stricturing, 45 were fistulizing, and 12 were inflammatory. The most commonly affected site was the ileocecal region (n=109, 65.7%), and the most common surgical procedure was the ileocecal resection (n=109, 65.6%). Laparoscopic approach was the procedure of choice in 56 (33.7%) patients. Of the patients enrolled, the most common early (<30 days) complications observed were the wound infection as the first (n=11) and anastomotic leak as the second (n=10). The mortality rate was 2.4% (n=4).

Conclusion: Multidisciplinary approach to Crohn's disease may decrease the surgical complications and recurrence rates leading to a better treatment.

Keywords: Crohn's disease, intestinal, multidisciplinary approach, surgical management

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory transmural bowel disease, which may present as a simple ulcerous luminal disease or a complicated fistulous, stenosing disease. The mean annual incidence of CD is 2.2 per 100.000 people in Turkey (1). Affected patients require a clinical follow-up due to risk of recurrences and long-term complications. Seventy percent of patients affected by CD will require at least one surgical procedure over their lifetime (2, 3). Postoperative management of CD is complex; therefore, coordination between patients, surgeons, and gastroenterologists is essential. The main treatment is medical, while surgery is reserved only for complications of the disease and treatment (3).

The aim of this retrospective study was to present our series of patients suffering from CD who underwent surgery as decided by a multidisciplinary team.

MATERIAL AND METHODS

This study was performed after an approval (approval code number: 2016-12/8) was obtained from the Ethics Committee of Acibadem University, School of Medicine, Istanbul, Turkey. A retrospective chart review was conducted and informed consent was not acquired. The medical records of the patients admitted between March 2000 and March 2016 with the diagnosis of CD followed by a multidisciplinary team were analyzed. Only patients who underwent surgery were included into the study. A surgical decision was made by the final agreement of different disciplines (gastroenterology, radiology, surgery, and pathology). All procedures were performed by the same colorectal surgeons.

The patient demographics, postoperative hospital stay, medications used in the preoperative period, the American Society of Anesthesiologists score, presence of extra-intestinal disease manifestation (EIM), previous abdominal operations for CD, type of procedures, indications for resection (inflammatory, stricturing, fistulizing, or perianal CD), and postoperative complications were evaluated. All data were obtained from the patients' records.

Patients who used steroid therapy until the day before surgery, patients who received azathioprine, 6-mercaptopurine, and methotrexate within 1 month before surgery, and patients who received anti-tumor necrosis

Table 1. Patients' characteristics and perioperative outcomes

	Patients With Intestinal Crohn's Disease (n=166)
Gender*	
Female	78 (47)
Male	88 (53)
Age#	36±11.5
ASA*	
I	125 (75)
II	40 (24)
III	1 (1)
Disease site*	
Ileocecal region	109 (66)
Large bowel	35 (21)
Small bowel	11 (7)
De novo Crohn's disease	11 (7)
Indication for surgery*	
Stricturing	92 (55)
Fistulizing	45 (27)
Inflammatory	12 (7)
De novo Crohn's disease	11 (7)
Right colon cancer	3 (2)
Toxic colitis	3 (2)
Medical treatment*	
AZA	70 (42)
Corticosteroid	19 (12)
Anti-TNFα	10 (6)
MTX	2 (1)
6-MP	2 (1)
Non-regular (non-compliance with) medical treatment	63 (38)
Operative approach*	
Open	104 (63)
Laparoscopic	56 (34)
Laparoscopic to open	2 (1)
Robotic	4 (3)
Operative procedures*	
Ileocecal resection	109 (65)
Colon resection	35 (21)
Small bowel resection	11 (7)
Restorative proctocolectomy	11 (7)
Early (<30 day) complications*	
Anastomotic leak	10 (6)
Intra-abdominal bleeding	2 (1)
Stoma-related complication	2 (1)
Acute mechanical intestinal obstruction1 (0.6)	
Wound infection	11 (7)
Late complications*	
Incisional hernia	2 (1)
Intestinal obstruction	2 (1)
Mortality*	
Renal failure	2 (1)
Electrolyte imbalance	1 (0.6)
Epileptic seizure	1 (0.6)

Continuous variables are described as the mean±standard deviation; categorical variables are described as n (%)
ASA: American Society of Anesthesiologists; AZA: azathioprine; Anti-TNFα: anti-tumor necrosis factor alpha; MTX: methotrexate; 6-MP: 6-mercaptopurine
*: n (%) #: mean±SD

factor alpha within 8 weeks were regarded as under preoperative medical treatment. Patients who received immunosuppressive therapies and discontinued them at least 1 month before the surgery were regarded as "not under medical treatment." Previous surgical history was defined as having abdominal operation for CD.

The procedures were grouped into four categories: ileocecal resection, small bowel resection, colectomy, and restorative proctocolectomy (RPC). The operations were performed open, laparoscopic, or robotic. Bowel resections were either one-segment resection or more than one-segment resection. Ostomy was added depending on the operative findings (presence of intra-abdominal abscess, multiple fistulas, etc.) and patients' medical status. The ostomy was closed 2 to 3 months after the first operation.

Early complications within postoperative 30 days and long-term complications were retrieved. Early complications were divided into two types: major complications including anastomotic leak, ostomy-related complications (perforation of the ileostomy and bleeding from ileostomy), intra-abdominal hemorrhage and acute mechanical intestinal obstruction, and minor complications including wound infection.

RESULTS

For the study period, data of 950 patients were retrieved. A total of 203 patients underwent operation. Of these, 166 patients were operated on for intestinal CD, and 37 were operated on for perianal CD. Patient characteristics and pre- and postoperative data were shown in Table 1.

Among the enrolled patients, 78 (47%) were women, 88 (53%) were men with an overall mean age of 36±11.5 (range, 12–75) years. Whereas 104 (63%) patients had open, 56 (33.7%) patients had laparoscopic approach. The most common indication for surgical resection was stricturing disease (n=91, 55%). Of the patients operated on, 3 (1.7%) had right colon cancer, and 3 (1.7%) had acute toxic colitis. Eleven (6.5%) patients who underwent RPC were preoperatively diagnosed as ulcerative colitis, and after 2 years, they were diagnosed as *de novo* CD.

Recurrence was assessed by symptomatic recurrence (the presence of symptoms attributable to CD that required surgical treatment). Reoperation for recurrent disease was performed in 4 (2.4%) patients. Three patients with previously performed ileocecal resection underwent ileocolic anastomosis resection due to disease recurrence within 1 year. One patient who developed disease relapse and a history of fistulizing medically refractory CD underwent multiple intestinal resections and is being followed up with short bowel syndrome.

The overall early complication rate was 15.6% (9% major complications). Major complications were the anastomotic leak (n=10), intra-abdominal bleeding (n=2), complications related to ostomy (n=2), and acute mechanical intestinal obstruction (n=1). The early minor complication rate was 6.6%, including 11 patients with wound infection. Patients diagnosed with anastomotic leakage underwent proximal intestinal diversion. Patients with intra-abdominal bleeding were operated on for hemostasis. Regarding ostomy complications, 1 patient had bleeding control surgery, and the other had stoma revision surgery. Minor complications required wet dressing or vacuum assisted closure.

The mean postoperative hospital stay was 8.5±5.76 (range, 2–33) days. For minimally invasive approach (laparoscopic/robotic) group, the mean postoperative hospital stay was 8.5±6.34 days, and for the open group, it was 9.5±5.49 (range, 2–27) days.

In the current study, 35 (21%) patients who underwent intestinal resections had EIMs including arthralgia in 14, ankylosing spondylitis in 4, and other EIMs in 17 (pyoderma gangrenosum, sacroileitis, uveitis, erythema nodosum, sacroileitis, etc.). Of the patients with EIMs, 8 were with colonic CD.

The long-term (>30days) complication rate was 2.4% (n=4). Two of these patients underwent laparoscopic incisional hernia repair, and the other two underwent laparoscopic adhesiolysis for intestinal obstruction. The mortality rate was 2.4% (n=4). The mean follow-up time was 70±44.9 (range, 2–194) months.

DISCUSSION

In this study, nearly one-fifth of the patients with CD were observed to require surgical treatment during their surveillance.

Once the need for a surgical intervention has been established in CD, surgical strategy will vary depending on the intestinal segment affected (4), on disease complications (stricture under medical treatment, uncontrolled fistulizing disease that cause abdominal abscesses, and/or electrolyte imbalance), and failed medical therapy (3). Depending on patient's general condition, severity of disease, and the involvement of intestinal segments, surgical treatment of CD may include ileocecal resection, subtotal colectomy with ileorectal anastomosis, total proctocolectomy, segmental small bowel resection, and strictureplasty (5). Stoma may be added to these procedures when necessary. In the current report, the most commonly performed surgical procedure was the ileocecal resection (n=109, 65.7%).

In this study, the symptomatic recurrence rate was 3% (n=5). Four patients developed recurrence 1 year after primary operation, and 1 patient developed recurrence 10 years after primary operation. All underwent intestinal resections. In our opinion, this low rate could be explained in terms of coordinated teamwork and careful indications for surgery. Several other reasons could also be attributed to our low symptomatic recurrence rate. First, our technique was stapled side-to-side anastomosis with two 75–80 mm linear staples. Thus, avoiding narrow anastomosis and fecal stasis that may trigger disease recurrence. Second, we didn't include patients with recurrent asymptomatic disease that were given medical treatment. We included only recurrent symptomatic clinical diseases that needed surgical intervention. Third, some losses to follow-up are also possible. Despite advances in the medical treatment of CD, clinical relapse after intestinal resection can occur in approximately 50% of the patients at 5 years (6, 7), and 9.5% to 43% of recurrent CD after primary resection need reoperation at 5 years (8, 9).

One patient with medically refractory disease in our cohort developed short bowel syndrome due to repeated intestinal resections for disease relapse at early postoperative period. She was not eligible for strictureplasty due to perforations and peritonitis. Strictureplasty has the advantage of small bowel preservation and prevention of short bowel syndrome, since 30%–70% of the affected patients will require repeated operations through their lifetime (3).

There were 30 patients with a history of previous abdominal operations at other centers. We were not able to retrieve the data about their previous operation details and indications. For this reason, in these patients, all previous abdominal operations were considered as operations due to CD. The relationship between postoperative complications and previous operations for CD is controversial. Unpublished data from our experience, although with a small number of cases, showed that previous operations did not affect the postoperative complication rates. However, Brouquet et al. (10) demonstrated that reoperation for recurrence of CD was associated with an increased postoperative morbidity and a longer hospital stay than primary resection.

The incidence of EIMs in this study was 21% (n=35), and 8 of these patients had colonic CD. The most commonly recognized EIMs were abnormalities involving the axial and peripheral joints of the musculoskeletal system, which were most frequently seen when CD affected the colon (4, 11). Our series was in line with the literature regarding the most common EIM being arthralgia (n=14, 40%).

In our study, 2 patients developed cecal adenocarcinoma at their 8th and 9th years of the follow-up period, and 1 patient developed cecal adenocarcinoma at the 1st year of the follow-up period. Despite the controversy related to the risk of colorectal carcinoma in CD, an increased surveillance program is advised for these patients (3). It is recommended that, patients with CD after 8 years or longer duration of chronic colitis should be enrolled in an endoscopic surveillance program (3, 4).

In our series, 36% of the surgical approaches were either laparoscopic (n=56) or robotic (n=4) intestinal resections. Robotic surgery has some promising advantages, and we have used this approach since December 2014, after the introduction of the robotic platform at our institution. In our current practice, we generally start with laparoscopy and continue as appropriate. In case of thickened mesentery and diffuse inflammation, the role of the laparoscopic approach in CD may be challenging (3). Riss et al. (12) stated that laparoscopic intestinal resection in CD could be performed safely in the majority of affected patients. They proposed that, even in complex cases, with all the advantages of the minimally invasive surgery, postoperative complication rate could be reduced by the laparoscopic approach.

The limitations of this study are that it is a retrospective study and that it has a relatively small-sample size.

CONCLUSION

Due to the complexity of CD, a combination of surgical and medical treatment is essential. Effective multidisciplinary care may improve the quality of pre- and postoperative management.

Further trials with prospective structure may elucidate the benefits of teamwork in the management of a lifelong CD.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Acıbadem University School of Medicine (2016-12/8).

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Case Report

The role of co-administration of damage control surgery and vacuum-assisted closure in the treatment of perineal wounds

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ABSTRACT

Perineal wounds caused by high-kinetic-energy shotgun blasts have a high mortality risk because they are often accompanied by injuries of the anus, rectum, genitourinary system, and extremities. Mortality often results from hemorrhage in the early stage and from multiple organ failure caused by sepsis in the late stage. The primary step in the treatment of patients presenting with perineal wound and hemodynamic instability caused by severe hemorrhage is to control hemorrhage and contamination using damage control surgery. After achieving hemodynamic stability, vacuum-assisted closure can be used to reduce the risks of infection and sepsis. In this report, we present a case who had a perineal wound caused by a mine blast and was successfully treated by damage control surgery and vacuum-assisted closure.

Keywords: Perineal wound, mine blast, vacuum-assisted closure

INTRODUCTION

Experience in the management of traumatic perineal wounds has been largely gained through the management of battlefield traumas. Perineal wounds caused by high-kinetic-energy shotgun blasts have a high mortality risk because they are often accompanied by injuries of the anus, rectum, genitourinary system, and extremities. Mortality often results from hemorrhage in the early stage and from multiple organ failure caused by sepsis in the late stage (1-3). Recent attempts have been made to decrease mortality rates by effectively using damage control surgery (DCS) techniques and by inducing protection against infection (4).

In this study, we report a case who had a perineal wound caused by a mine blast and was successfully treated by DCS and vacuum-assisted closure (VAC).

CASE PRESENTATION

The 24-year-old male patient was transferred to our hospital from a neighboring country where he had been wounded due to a mine blast during a civil war. A statement from paramedics revealed that the blast occurred approximately five hours before transportation, and the patient was transferred to the border following ginitial surgery at a location close to the combat arena. Physical examination revealed a body temperature of 35.6°C and a systolic blood pressure of 75 mmHg. The patient had a midline abdominal surgical incision. The perineal skin had been closed using a Y-shaped suture pattern. The patient was transferred to the intensive care unit (ICU). Heating pads and radiant heaters were used to prevent further heat loss. Fluid and electrolyte resuscitation was started. All fluids were warmed to body temperature before transfusion. The patient's arterial blood gas pH was 7.15, and his whole blood count revealed a hemoglobin level of 6.9 mg/dL and an international normalized ratio (INR) of 2.1. On the basis of these values, resuscitation was continued with the administration of 3 units of erythrocyte suspension that were previously warmed to body temperature and 2 units of fresh frozen plasma. At 24 h after admission to the ICU, the patient's parameters were as follows: systolic blood pressure; 95 mmHg, body temperature: 36.9°C, arterial pH: 7.31, hemoglobin: 9.0 mg/dL, and INR: 1.5.Abdominal and pelvic computed tomography revealed fragmented fractures and multiple foreign bodies suggestive of compressin the perineal region. The orthopedics department was consulted regarding the fragmented pelvic fractures. On this basis of the consultation, the patient was immobilized for one month. The surgical procedure was started by removing the sutures and compresses in the perineal region. Exploration revealed a 30x25 cm necrotic wound around the anus with no hemorrhage. No anorectal wound was observed by perioperative anoscopy. After debridement, the external sphincter was completely intact. The wound site was irrigated with physiologic serum and dressing was performed using the VAC method. The abdomen was entered through the previous incision site. Surgical exploration revealed that the sigmoid colon had been split at the distal end and had been primarily closed at both the proximal and distal ends. The sutures at the proximal end of the sigmoid colon were opened and sigmoid end colostomy was performed. The patient was extubated on postoperative day 1. Dressing was performed by applying negative pressure using the VAC method. Following the formation of granulation tissue, the perineal defect was closed by a skin graft obtained from the anterior surface of the left femur. The patient was discharged on postoperative day 15. Written informed consent was obtained from patient who participated in this case.

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DISCUSSION

Uncontrollable hemorrhage and sepsis are the most common challenges in the management of traumatic pelvic wounds. The pelvis is a complex anatomical region that is neighbored by several organs and systems. Therefore, no standard treatment has been established for the management of pelvic wounds. Treatment is commonly based on a multidisciplinary approach including the disciplines of general surgery, orthopedics, and anesthesiology. However, because the combat arena is generally characterized by irregular warfare, riots, and uprisings, the healthcare facilities present in combat arenas are usually disrupted by poverty and battle. Moreover, the transportation of casualties to health centers is hindered by destroyed roads, difficult terrain conditions, and long distances. In addition, the extensive number of casualties often outweighs the capacity of healthcare facilities available in the combat arena. Due to these factors, combat casualties generally present to health centers with deep hemorrhagic shock (4, 5).

Damage control surgery remains the mainstay treatment for casualties presenting with acidosis, hypothermia, coagulopathy, and hemodynamic instability. The principle aims of DCS are to achieve primary repair of major arterial injuries, to perform arterial ligation, or to prevent hemorrhage by packing with compression bags. In addition, in the treatment of hollow organ wounds, a subsequent primary repair should be performed to prevent contamination. In these patients, the duration of surgery should not exceed one hour. Procedures such as ileostomy and colostomy should be avoided because they are highly time consuming. The patient should be directly transferred to the ICU, and the initial aim should be to correct acidosis and hypothermia. After hemodynamic stability is achieved, definitive surgery should be performed. The decision to perform DCS should be made depending on the initial evaluation of the patient or the findings obtained within the first 15 minutes of surgery (6, 7).

Our patient had a perineal wound caused by a mine blast that occurred during a civil war in a neighboring country. The patient had undergone surgery at a location close to the combat arena before transportation. In such cases, amajor problem is that no medical document ation regarding the condition of the patient is transported with the patient or that the document is lost during transportation.The medical condition of our patient indicated that the hemorrhage may have been controlled by placing compresses on the perineum. Moreover, it is likely that the surgeons decided to perform DCS because no colostomy had been performed during laparotomy and both ends of the sigmoid colon had been closed. Ultimately, the surgeons probably decided to transfer the patient to our hospital due to the absence of appropriate facilities for postoperative resuscitation. Upon initial examination at our hospital, the patient presented with acidosis, hypothermia, and hemodynamic instability. The definitive surgery was performed after achieving resuscitation.

High-kinetic-energy shotgun wounds lead to large amounts of devitalized and contaminated tissues that have a high risk of infection. To reduce this risk, aggressive debridement and daily dressing changes hould be performed. Perineal wounds have a particularly high risk of infection because fecal contamination is inevitable. In these wounds, daily dressing changes are another challenge for treatment. VAC can be an ideal option for overcoming these difficulties. This method allows continuous drainage of contaminated and complicated wounds. It also reduces the level of exudate, debris, and bacteria. Moreover, it facilitates the removal of large amounts of fluid in deep wounds. After initial debridement and irrigation, VAC is performed to apply negative pressure, and the dressing is changed every 24 to 48 h. Following revitalization of the tissues and the formation of granulation tissue, the wound is closed using either primary closure, flap advancement, or skin graft (8, 9).

Our patient had a large necrotic wound in the perineal region. The wound was closed after creating negative pressure by VAC. The dressing was changed every 48 h. The tissues were revitalized and granulation tissue was formed on postoperative day 10. The defect was closed by a whole-layer skin graft obtained from the anterior surface of the left femur. No complications were observed in the follow-up period. The patient was discharged on day 15and was advised to visit our clinic for colostomy closure 8 weeks later. However, the patient has not returned for colostomy closure although more than 8 weeks have passed since discharge.

CONCLUSION

Damage control surgery and the proper administration of its principles can be lifesaving in patients with high-kinetic-energy shotgun wounds who present with hemodynamic instability. In addition, VAC may facilitate treatment by preventing the risks of soft tissue necrosis and serious infection, particularly in wounds that are located in difficult regions of the body.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Case Report

Pancreatic extragastrointestinal stromal tumor invading the duodenum

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ABSTRACT

Extragastrointestinal stromal tumors that arise in the pancreas are extremely rare and managing them can be difficult, particularly if located in the head of pancreas. This case report aims to contribute to the existing data in the literature regarding extragastrointestinal stromal tumors with rare and unusual locations. We present a 56-year-old man who presented with recurrent mild right upper quadrant abdominal pain. Abdominal computed tomography and magnetic resonance imaging revealed a mass lesion with a diameter of 10 cm localized in the head of pancreas. Pancreaticoduodenectomy with complete tumor excision was performed. He was discharged on the postoperative day 14. Only 15 extragastrointestinal stromal tumors cases have been reported. Of these 15 cases, tumors were located in the head of pancreas in six cases. Here we report the seventh case of pancreatic extragastrointestinal stromal tumor arising in the head of pancreas and also the largest of these seven tumors.

Keywords: Pancreas, extragastrointestinal tumor, stromal tumor

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are low-grade malignancies of mesenchymal origin in the gastrointestinal tract, and these tumors arise from the intestinal cells of Cajal (1-3). These tumors may originate from any location in the entire gastrointestinal tract, and the most susceptible sites are the stomach (40%-60%), small intestine (30%-40%), colon and rectum (5%), and esophagus (5%), whereas only 3%-5% of GISTs occur in the duodenum (4-6). There are also sporadic reports of GISTs that arise from the peritoneum, omentum, mesentery, and retroperitoneum (2, 3, 7). GISTs that originate from the soft tissues of the abdomen and retroperitoneum are called extragastrointestinal stromal tumors (EGISTs). EGISTs that arise from the pancreas are extremely rare, and only 15 cases have been previously reported (7-9). Here we report a case of a large pancreatic EGIST that invaded the duodenum.

CASE PRESENTATION

A 56-year-old man presented with recurrent mild right upper quadrant abdominal pain that radiated to the back of his torso. The patient had a history of melena, which required blood transfusion. After his admission owing to melena, a series of endoscopic and radiologic investigations was conducted, but it failed to reveal the source of bleeding; however, only hyperemia of the antrum and hiatal insufficiency were detected. There was no remarkable finding in his medical history and no weight loss. Abdominal examination revealed right upper quadrant tenderness. Laboratory test findings showed that the peripheral blood cell count and blood chemistry were within normal limits, except anemia (hemoglobin, 9 g/dl; reference range, 13-17 g/dL). Tumor markers were negative for CA 19-9, CA 125, and CEA. Abdominal computed tomography (CT) revealed an 11-cm-diameter mass lesion that originated from the head of pancreas and extended to the right paranephritic fat tissue. The fat plane between the duodenum and the pancreas was obliterated by the tumor. MRI (Figure 1, 2) also revealed a 10.5-cm-diameter mass lesion localized at the head of pancreas; however, there was no dilatation or invasion of the common bile duct.

Pancreaticoduodenectomy (Whipple's procedure) was performed as the treatment of choice. The tumor was palpated as a hard mass in the head of pancreas. The tumor was 15 cm in diameter and extended from the duodenum through to the retroperitoneum and inferior cecal region. Macroscopically, there were no metastases in the peritoneum or liver. The postoperative course was uneventful, and the patient was discharged on the postoperative day 14. The histopathological examination the specimen confirmed EGIST, with predominant spindle cells and mitotic figures of fewer than three per 50 high-power fields. Wide necrotic areas in the tumor were also noted. The surgical margins were negative, and no metastasis was noted in the six regional lymph nodes, which were excised. Immunohistochemistry revealed that the tumor cells were positive for CD117, CD34, and vimentin (Figure 3-6) and negative for S100 and desmin. Imatinib (400 mg daily) administration was initiated in the third postoperative week as adjuvant therapy.

Written informed consent is obtained from the patient for the publication of this case report and accompanying images.

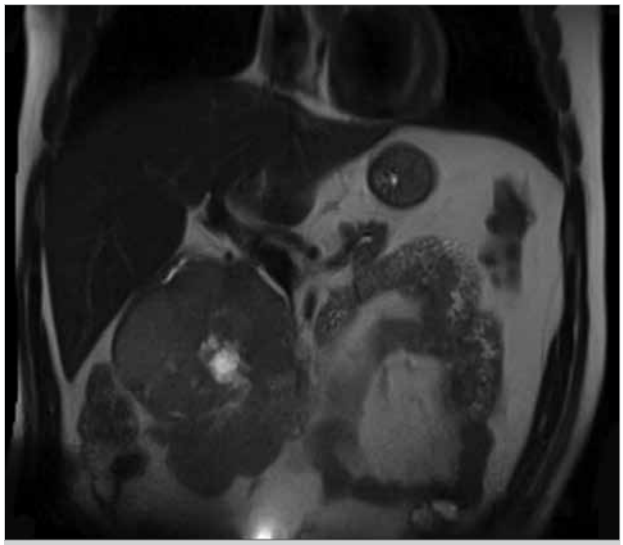

Figure 1. MRI demonstrating the pancreatic mass (coronal view)

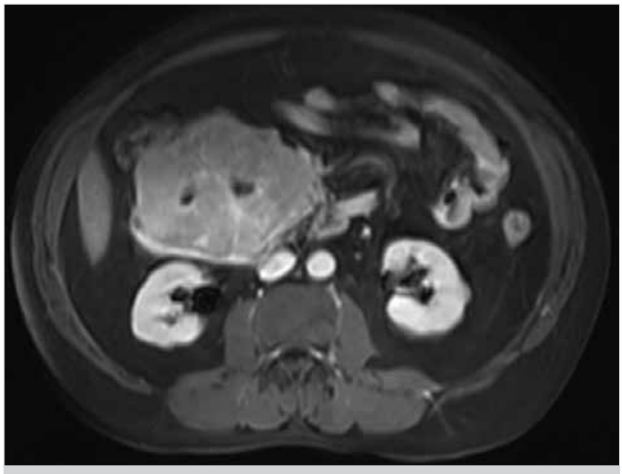

Figure 2. MRI demonstrating the pancreatic mass (axial view)

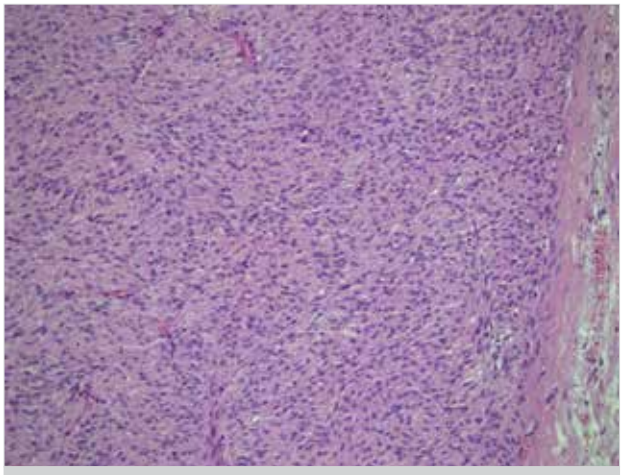

Figure 3. Tumor cells (H&E, 10×)

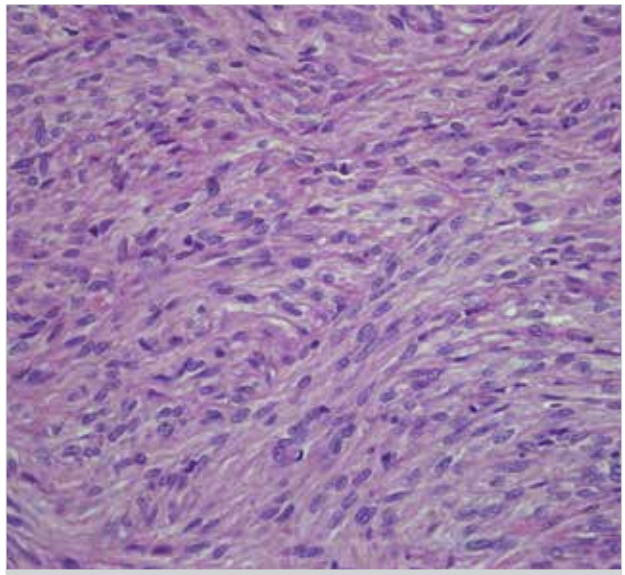

Figure 4. Tumor cells (H&E, 40×)

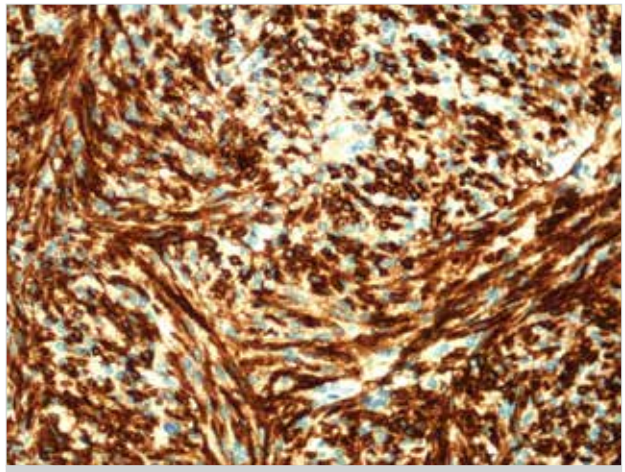

Figure 5. Tumor cells (CD34, 40×)

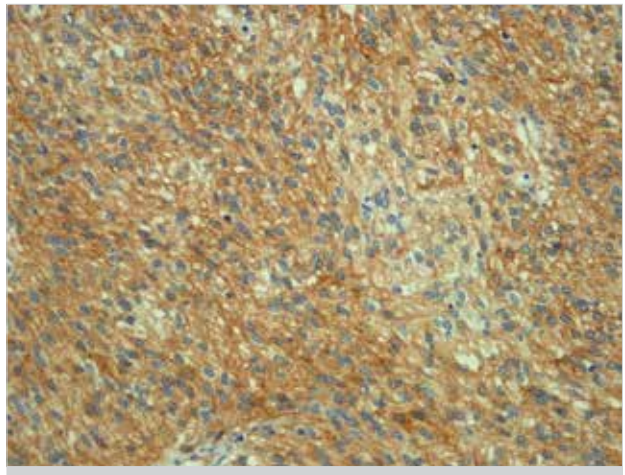

Figure 6. Tumor cells (CD117, 40×)

DISCUSSION

Gastrointestinal stromal tumors are low-grade malignant mesenchymal tumors and the most common non-epithelial tumor of the gastrointestinal tract, which is believed to originate from the interstitial cells of Cajal. Cajal cells are located in the muscle layer of the gastrointestinal tract as the pacemaker cells of the gastrointestinal tract and commonly express c-kit proteins (CD117), myeloid stem cell antigen (CD34), and vimentin. Almost all GISTs express the CD117 antigen, which is a receptor tyrosine kinase protein that is considered to be the defining characteristic. Approximately 70% of all GISTs are positive for the CD34 protein, which is a hematopoietic progenitor cell antigen, whereas 20%-30% are positive for SMA and 10% are positive for the S-100 protein. Approximately 40%-60% of GISTs occur in the stomach, whereas 30%-40% occur in the small intestine, 10% in other parts of the gastrointestinal tract, and 5% elsewhere in the abdominal cavity (3, 5, 8-14). GISTs

are infrequent neoplasms. The overall incidence of GISTs has been estimated to be 10-20 cases per million per year, and 300-4000 new cases are reported each year in the United States. The mean age of the patients was 53 years (range, 40-80 years), and only 5% are aged <30 years (1, 3, 13). GISTs that arise from outside the bowel wall are termed as EGISTs. Pancreatic EGISTs are reported to be very rare, and only 15 cases have been reported. In this study, we present an extremely rare case of a primary pancreatic EGIST.

Preoperative diagnosis of GIST and EGIST is difficult owing to nonspecific signs and symptoms. Abdominal pain, palpable mass, and bleeding are the most common presentations. Small tumors are usually found incidentally during operation, endoscopy, CT, or MRI, which are conducted to investigate other conditions. GISTs and EGISTs are usually diagnosed using CT, MRI, gastrointestinal endoscopy, and barium study. However, these modalities may not always be helpful in specifying the origin of the mass, particularly that of EGISTs (5, 6, 12, 13).

Pancreatic GISTs are very rare mass lesions, with clinical symptoms such as abdominal pain, early satiety, bleeding, ileus, anemia, and flatulence. EGISTs are often asymptomatic compared with GISTs, and this clinical difference is explained by their locations, size of the tumors, and lack of mucosal involvement. EGISTs tend to grow larger than GISTs before resulting in any symptoms, and their histological features are similar to other GISTs. EGISTs that arise in the head of pancreas are extremely rare, and to date, only 6 cases have been reported in the literature. (3-6, 8, 9, 11, 12, 14, 15). Here we report the seventh case of pancreatic EGIST that arose in the head of pancreas and also the largest of these seven tumors. In our case, preoperative imaging studies showed that the mass lesion originated from the head of pancreas, and gastroduodenoscopy showed that the duodenum mucosa was normal. Therefore, this tumor was considered to be a primary pancreatic head tumor with an exophytic growing pattern (5, 6, 10). The most important prognostic factors for GISTs are the tumor size and mitotic count. Additional factors such as histological variant, mutation type, and anatomic location have been associated with varying prognoses. Optimal surgical treatment of GISTs entails complete tumor removal with clear surgical margins and avoidance of tumor rupture and in some cases, necessitating the resection of adjacent organs. Local and regional lymph node involvement is infrequent in GISTs; therefore, systematic lymph node dissection is not considered necessary. Imatinib mesylate is used in the management of GISTs as adjuvant therapy and in patients with recurrent disease (1, 3-5, 11, 12-17). Our patient had adjuvant treatment with imatinib initiated in the third postoperative week because the patient was evaluated in the high-risk group with the tumor diameter of >10 cm.

CONCLUSION

There are very few reports regarding EGISTs that arise from the pancreas. The tenor in our case was considered to arise from the head of pancreas, and Whipple's procedure was performed for its treatment. This report will contribute to the existing data in the literature regarding EGISTs in rare and unusual locations.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Case Report

Goblet cell carcinoid of the appendix accompanied by adenomatous polyp with high-grade dysplasia at the cecum

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ABSTRACT

Goblet cell carcinoid tumor of the appendix is an uncommon neoplasia that shares the histological attributes of both adenocarcinoma and carcinoid tumors. Its prognosis has a more aggressive course than the other known carcinoid tumors. Clinical diagnosis of goblet cell carcinoid is seldom made preoperatively. The most common clinical presentation of goblet cell carcinoid tumor is acute appendicitis. In this study, we report a patient on whom right hemicolectomy was performed because of a cacal sessile polyp with high grade dysplasia; goblet cell carcinoid tumor of the appendix was revealed incidentally during microscopic evaluation of the appendectomy specimen. The patient healed uneventfully and no recurrence was observed after the 12-month follow-up period. Careful microscopic examination of the appendectomy specimen is key for the diagnosis of appendiceal tumors such as goblet cell carcinoid, especially in elderly patients.

Keywords: Goblet cell carcinoid, appendix, adenomatous polyp

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INTRODUCTION

Primary appendiceal tumors are detected in 0.9%-1.4% of all appendectomy specimens (1). Since carcinoid tumor was first described by Merling (2) in 1838, three different histological subtypes have been described: argentaffin-positive carcinoid; non-argentaffin carcinoid; and goblet cell carcinoid (GCC) (3). GCC shows attributes of both carcinoid tumor and adenocarcinoma. GCC constitutes less than 5% of primary appendix tumors, and the mean age for GCC was determined to be 58.9 years (4, 5). Because its behavior is more aggressive than that of the other standard carcinoid tumors, more extensive surgical approaches may be required (6). A five-year survey revealed a survival rate of 60%-84% (7). Metastatic disease develops in approximately 20% of patients. GCC of the appendix has various clinical presentations ranging from asymptomatic to acute appendicitis, which is the most common presentation; toward the other end of the spectrum, metastatic presentations such as Krukenberg's tumor or peritoneal carcinomatosis can be observed. Acute appendicitis occurs due to luminal stenosis of the appendix (8). Other clinical presentations of GCCs are lower abdomen pain, gastrointestinal bleeding, and palpable mass (8, 9). In this study, a rare combination of GCC of the appendix and high grade displasia polyp of the cecum is reported with a review of the relevant literature.

CASE PRESENTATION

A 46-year-old female patient was admitted to our surgical department with complaints of rectal bleeding, weakness, and fatigue. Her physical examination was unremarkable. Neither hemorrhoid nor anal fissure was detected upon anorectal examination, and her anal sphincter tone was normal. No palpable mass was detected upon rectal digital examination. Laboratory tests were as follows: hemoglobin: 10.1 g/dL, hematocrit: 32%, leukocyte: 12.000 K/mm^3, and platelet: 247.000 K/mm^3. Colonoscopy was performed to determine the source of the bleeding. Colonoscopy revealed a sessile polyp 3 cm in diameter at the distal part of the cecum. The patient underwent hot snare polypectomy, and the sessile polyp was partially resected piecemeal. The pathological assessment of the specimen showed adenomatous polyps with high-grade dysplasia, and the surgical margin was positive. Abdominal tomography was unremarkable; neither abdominal tumoral lesion nor metastatic lesion was detected. Serum CA19-9 and CEA levels were found to be 12.25 U/mL and 1.98 ng/mL, respectively. Right hemicolectomy and end-to-side ileotransversostomy were performed on the patient. Intraluminal rigid and irregular areas that did not extend beyond the serosa were palpated in the cecum. No other intra-abdominal pathologic findings were detected during surgery. The patient healed uneventfully, and no complications occurred.

The pathological analysis of the specimen revealed a 1-cm-long adenovillous polyp with high-grade displasia in the distal part of the cecum. Focal hemorrhage and edema areas were observed in the cecal mucosa. No tumoral lesion was detected in the cecum except for a remnant of the polyp. The serosal surface of the appendix was hyperemic, and its lumen was of obliterated appearance in the section. Tumoral infiltration to all layers of the appendix wall expanding through the periappendicular area was

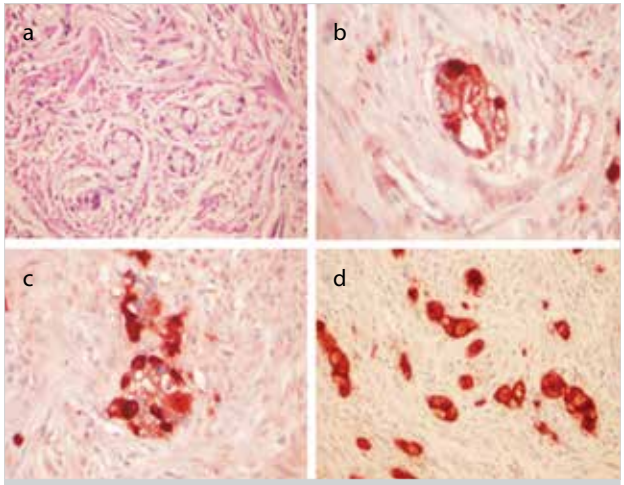

Figure 1. a-d. (a) Adenocarcinoid tumor of goblet cell type. (b) strong immunoreactivity with chromogranin. (c) strong immunoreactivity with synaptophysin. (d) strong immunoreactivity with CEA

observed in the microscopic examination. The size of the tumor was 1 cm. The tumor was composed of either single cell infiltrations or groups of four to five cells that were larger than normal goblet cells, with mild atypia (Figure 1). Perineural invasion was detected. Diffuse positivity of the tumor cells was determined by Alcian blue/PAS staining. Immunohistochemical analysis revealed strong diffuse positivity between the tumor cells as well as positive chromogranin, synaptophysin, and CEA results (Figure 1). Sustentacular cells between S-100 and cell nests were observed to be positive. The patient healed uneventfully and was discharged on the postoperative fifth day. After a twelve-month follow-up period, recurrence was not observed. The patient signed an informed consent form to participate in this study.

DISCUSSION

Malign tumors of the appendix are rare and are seen at a rate of 0.5%-1.4% following appendectomies (10). While the most common neoplasia of the appendix is carcinoid tumor, the appendix is the most common localization of carcinoid tumors. Adenocarcinoma is the second most common appendix neoplasia (1). GCC constitutes less than 5% of all carcinoid tumors of the appendix (7). These tumors present both endocrine and glandular differentiations; therefore, they demonstrate both epithelial and carcinoid tumor attributes (11). Various theories have been proposed on the histological origin of GCC (12, 13). In 1979, Warner et al. (13) described GCC as a neoplasm of endodermal origin arising from root cells located in the basal part of the gland and crypta. Ratzenhofer et al. (14) defined this tumor as an amphicrine neoplasm (endo-exocrine) in 1980. Some studies showed that p53 gene mutation plays an important role in the pathogenesis of GCC. Another remarkable genetic factor of GCC is the frequent loss of alleles in chromosomes 11q, 16q, and 18q (15).

Goblet cell carcinoids are usually accompanied by acute appendicitis symptoms and findings (8). They can also be detected incidentally during surgery that is performed for other organ diseases. These tumors rarely compose a discrete mass; therefore, they can be diagnosed only by postoperative histological analysis (6). Abnormal thickening of the appendix wall or deposition of mucinous material in its lumen are determinative signs for GCC (16). Luminal stenosis develops due to the circumferential involvement of the appendiceal wall, with longitudinal extension.

Goblet cell carcinoid tumors manifest more aggressive behavior than other carcinoid tumors. The metastasis rate of appendix carcinoids is 2%-5%, while it is 15%-30% for GCCs (4). Carcinoembriyonic antigen (CEA) has been found to be increased in metastatic cases (11). GCC can cause various complaints, such as abdominal mass, mesenteric lymphadenitis, and gastrointestinal bleeding (8, 9, 17). These tumors may rarely lead to pseudomyxoma peritonei, similar to other mucinous tumors. Appendix goblet cells secrete MUC2 and MUC5AC. MUC2 measurement is a specific indicator in the case of psesudomyxoma peritonei related to appendix GCC (18). There are rare cases in the literature regarding GCC tumors accompanied by Krukenberg tumors or colorectal adenocarcinoma (19, 20). In our case, right hemicolectomy was performed due to a sessile polyp of the cecum with high grade dysplasia; GCC of the appendix was later diagnosed coincidentally.

The clinical behavior of GCC tumors can vary; therefore, there are still controversial issues regarding both evaluating the malignant potential of the tumor and choosing an appropriate treatment. The initial reports regarding treatment options for GCC recommended appendectomy as an adequate treatment. Then, Varisco et al. (21) emphasized that appendectomy is adequate in the case of low-grade tumor histology without involvement of the cecum. Conversely, some authors suggest the necessity of right hemicolectomy because of the unpredictable behavior of GCC (9). While appendectomy is adequate for most patients, more radical approaches may be required in cases that present more complicated profiles, such as diffuse appendix involvement, tumor size greater than 2 cm, cellular undifferentiation, increased mitotic activity, presence of cecal wall involvement, or lymph node metastasis (3, 6). Due to the high risk of metastasis to the ovaries in female cases, bilateral oophorectomy is recommended in addition to right hemicolectomy (19). In our case, the tumor was 1 cm in diameter. Furthermore, perineural invasion and periappendicular expansion with involvement of all layers of the appendiceal wall were determined.

Goblet cell carcinoids do not form distinctive tumoral tissue; therefore, surgical resection borders in the appendectomy specimen should be examined microscopically in detail. To differentiate GCC from standard appendix carcinoid tumors, measurement of the amount of mucin production can be useful. The presence of a few amin precursor uptake decarboxylase (APUD) cells and positive staining of tumor cells with lysozyme and IgA are the other differentiating attributes (12).

Metastasis occurs in nearly 20% of GCC tumors, and the ovarium is the most common metastatic site for GCC (21). Studies revealed the presence of distant metastasis in 11.2% of patients and lymph involvement in 8.7% of patients during diagnosis (22). Intraperitoneal chemotherapy should be provided to patients if GCC is accompanied by peritoneal carcinomatosis. Intraperitoneal chemotherapy is also recommended if the tumor tissue is perforated during the surgery. Among metastatic GCC cases, survival rates are higher in patients who

received intraperitoneal chemotherapy than in patients who underwent surgery alone (23). Ovarian, lymphatic, and distant metastasis were not detected in our patient after a 12-month follow-up period. Marked octreotide scintigraphy is the most sensitive imaging method for diagnosis and follow-up of GCC. Plasma chromogranin A is also known as a hematological indicator for GCC. Thus, plasma chromogranin A and 5-hydroxyindoleacetic acid (5-HIAA) should be tested in a 24-hour urine sample, and marked octreotide scintigraphy should be performed in the follow-up period (9).

Goblet cell carcinoid tumors are located between carcinoid tumors and well-differentiated adenocarcinomas in terms of prognosis (6). The most important prognostic factor is the stage of the tumor (22). However, discussion regarding tumor size is controversial because tumors do not always form a significant mass (6). Metastasis to the ovaries and expansion into the abdominal cavity influence the prognosis very negatively. The five-year survival rate of GCC tumors was determined to be 60% to 84%, and the recurrence rate was found to be 16% (11, 15).

CONCLUSION

Goblet cell carcinoid should always be considered as a differential diagnosis in patients with suspected appendicitis with or without a mass formation. In cases of appendectomy due to appendicitis or other intra-abdominal pathologies, detailed histological examination of the appendectomy specimen is very important, especially for older patients, to not miss appendicular tumors that could be asymptomatic but aggressive.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.A.Ö., R.Y., O.A.; Design - İ.A.Ö., E.Z., H.B.; Supervision - İ.A.Ö., R.Y., O.A.; Resource - İ.A.Ö., E.Z., C.B.; Materials - İ.A.Ö., E.Z., C.B.; Data Collection and/or Processing - İ.A.Ö., E.Z., C.B.; Analysis and/or Interpretation - İ.A.Ö., H.B., O.A.; Literature Search - A.Ö., H.B., C.B.; Writing Manuscript - A.Ö., E.Z., C.B.; Critical Reviews - İ.A.Ö., R.Y., O.A .

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Case Report

Cutaneous metastasis of colon adenocarcinoma

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ABSTRACT

Skin metastasis originating from colorectal cancer is a rare entity and usually signifies poor prognosis. We present a case of a 62-year-old male patient who presented with a cutaneous metastatic focus on his forehead after five years of the primary treatment of colon cancer. Complete response from the cutaneous metastasis nodule was achieved with radiotherapy. The patient is still alive and under a second-line palliative chemotherapy regimen because of the multiple liver metastases. It is important for physicians to be aware of skin metastasis in patients with an oncology history.

Keywords: Colorectal cancer, skin metastasis, prognosis

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INTRODUCTION

Cutaneous metastases arising from an internal malignancy are extremely rare, occurring in 0.001% of all skin biopsies performed (1). Of these, 6.5% originate from a primary colorectal cancer (1). If a colon cancer metastases to the skin, it typically presents with a painless flesh-colored nodule or as a mass with occasional ulceration (2). Cutaneous metastasis typically signifies widespread disease with poor prognosis (3, 4). The case presented here is of a 62-year-old male with a large skin metastatic focus on his forehead 5 years after the resection of a colon adenocarcinoma.

CASE PRESENTATION

This paper is written under the permission of the patient. A 62-year-old male presented at the outpatient clinic with a growing mass on his forehead skin (Figure 1). On clinical examination, a diffuse erythematous multinodular lesion was evident. The patient had a history of colon adenocarcinoma. Five years previously, colonoscopy had been performed due to constipation and an ulcerated mass was found in the sigmoid region. Colonoscopic biopsy revealed adenocarcinoma of the colon, and the patient underwent left hemicolectomy in May 2009. Pathological diagnosis was adenocarcinoma with lymphovascular invasion. No distant metastasis was found. The colon cancer was classified as T3, N1, M0, stage III. Adjuvant 5-fluorouracil-based chemotherapy was administered for 6 months and then follow-up was performed, according to the National Comprehensive Network (NCCN) guidelines.

Five years later, the patient was admitted to hospital with a mass on his forehead. A biopsy specimen was obtained from this nodular mass. On microscopic evaluation, the dermis was seen to have been infiltrated by a number of adenomatous glands, which suggested a metastatic focus of the known colon adenocarcinoma (Figure 2, 3). Abdominal computed tomography also showed multiple liver metastasis. After the restaging work-up, the patient was discussed at a multidisciplinary team meeting and it was decided to administer palliative radiotherapy because of the pain and cosmetic problems. The tumor on his skin was irradiated with daily fractions of 250 cGy with 6 mV energy of electron (Total dose: 60 Gy) to relieve the pain and for palliation and systemic chemotherapy, and Folinic acid, 5-Fluorouracil, Irinotecan (FOLFIRI)+bevacizumab treatment was commenced as the K-RAS test identified a mutation. Complete response from the cutaneous metastatic nodule was achieved with radiotherapy (Figure 4). The patient is currently receiving the second-line palliative chemotherapy regimen [FOLFOX-4 (folinic acid, 5-fluorouracil, oxaliplatin)+bevacizumab] and is in good overall condition. There has been no relapse in the radiotherapy field.

DISCUSSION

Metastatic skin cancer is defined as skin metastases from visceral cancer, excluding primary skin cancer and hematological malignancies. Skin metastases are rare and the reported incidence range from 1.4% to 10% of all visceral cancers (2, 4). In males, lung cancer is the leading form of cancer, followed by colorectal, esophageal, and kidney cancers, and in females, the most prevalent is breast cancer followed by colorectal, ovarian, and lung cancers (5, 6). Although skin metastases from colorectal

Figure 1. Nodular mass on the forehead

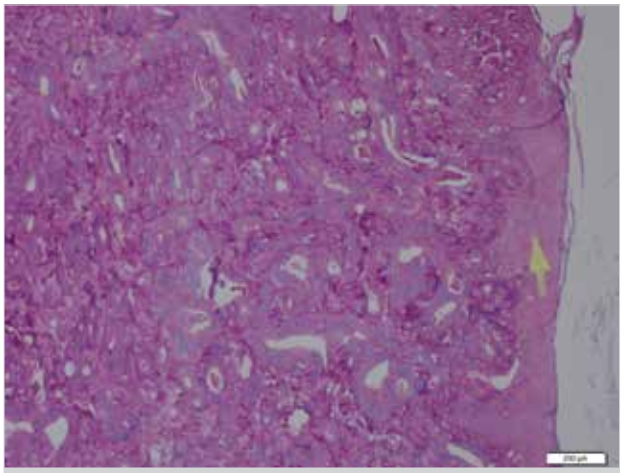

Figure 2. Pathologic section of metastatic foci of the skin: irregular and atypic cells forms abortif adenoidal glands with pseudostratified columnar epithelium; luminal mucus and inflammatory cells. (Hematoxylin and eosin X100)

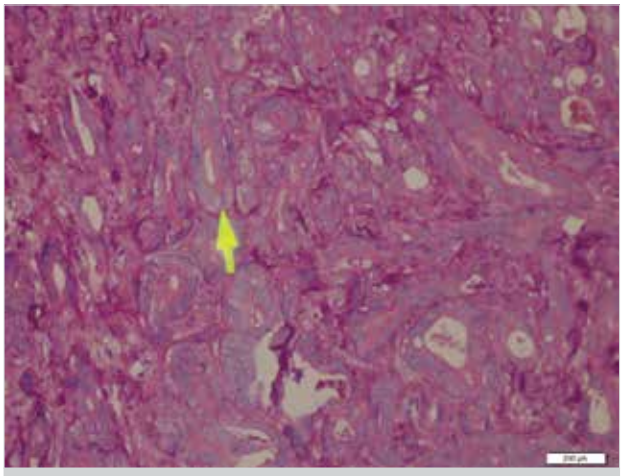

Figure 3. Adenoid glands of the metastatic dermis (Hematoxylin and eosin X 200)

Figure 4. Complete response of the metastatic cutaneus nodule

cancer account for nearly 5%, metastases on the face, scalp, and forehead, as seen in this case, are very rare (7). Atalay et al. (8) reported a case series of 8 patients from 263 colorectal cancer patients in 2009. According to this report and other previous reports, if a primary tumor has been previously diagnosed and treated, the onset to the development of cutaneous metastases usually occurs in the first two years (3). This is considered stage IV disease and usually has a poor prognosis.

The exact mechanisms of cutaneous metastasis are still unknown, although several probable ways have been discussed, including direct extension, hematogenous or lymphatic spread, or spread along the ligaments of embryonic origin and implantation of tumor cells (9). It has also been suspected that the vertebral venous plexus plays a role in hematogenous spread to distant sites, as this system may bypass other organs in the circulatory system (10). Despite these hypotheses, the exact mechanisms of metastasis to the skin remain unknown, and the means of metastasis may be different in each patient.

Through various means, metastatic lesions can assume a variety of morphological appearances (11), although the usual presentation is single or multiple nodules of a red color (2). An erythematous ring may be seen around the nodules, as in the current case. They may also resemble epidermal cysts, lipomas, morphea-like plaques, or zona zoster (2). Lookingbill et al. (2) reported in a large study that all the removed skin metastases were nodular. The histological features of metastatic lesions generally mimic the primary tumor, although metastases are generally more anaplastic. Microscopically most skin metastases from colon tumors have a nodular configuration and are located in the dermis, then spreading to the epidermis and subcutaneous tissue (4).

Identification of skin metastasis is a poor prognostic sign and indicates that the disease is widespread. Survival after diagnosis of cutaneous metastasis ranges from 1 to 34 months (2). The current patient is still alive 12 months after presentation with skin metastasis. If possible, wide local excision of the metastatic lesion is recommended. However, reconstruction may often be problematic and palliative options are preferred (11). A multidisciplinary team meeting at our hospital decided on palliative radiotherapy (because of the pain and cosmetic problems) followed by palliative chemotherapy. Interestingly, complete response was achieved after radiotherapy on this skin lesion.

CONCLUSION

There are very few reports in literature of skin metastasis as the first sign of metastatic disease after five years of the primary treatment of colon cancer. The region of the metastatic site and treatment success with radiotherapy are distinctive characteristics of our case report. It is important for physicians to be aware of skin metastasis in patients with an oncology history who present with cutaneous lesions. Early biopsy may be a good option. The opportunity for local treatment should be given to the patients, especially if the metastasis is located on the face, head, or more visible regions of the body.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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Case Report

Symptomatic hepatic metastasis of insulinoma 15 years after pancreatic resection

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ABSTRACT

Malignant insulinomas are infrequent endocrine tumors with miscellaneous clinical courses. In this report, we present a rare case of insulinoma that recurred with solitary hepatic metastasis 15 years after the initial resection of the primary tumor from the pancreas. A 20-year-old woman first presented with the symptoms of hypoglycemia in 1996. The diagnosis of pancreatic insulinoma was confirmed by laboratory findings, and the initial surgery had been performed involving complete enucleation of the pancreatic mass. Histopathologically, the tumor was diagnosed as a benign adenoma. After 15 years, the patient experienced symptoms of hypoglycemia again, and laboratory findings and abdominal computed tomography identified a lesion in the liver. Intraoperative ultrasound did not show any lesion in the pancreas, and wedge resection was performed for the hepatic lesion. Postoperative blood glucose levels returned to normal. Histopathologic examination confirmed the diagnosis of liver metastasis of a neuroendocrine tumor. This is the longest interval between primary tumor and the metastasis reported in the literature, for insulinoma. Thus, it should be remembered that long-term follow-up is mandatory for the patients with insulinoma even after resection of the primary tumor. Resection is recommended when a metastatic lesion is observed.

Keywords: Insulinoma, pancreas, liver, metastasis

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INTRODUCTION

Insulinomas are the most common pancreatic neuroendocrine tumors. The incidence is 3-10 cases per million individuals per year (1). Standard treatment is surgery, although accurate localization and resection of the tumor can be challenging. Five to 10% of insulinomas are malignant. Malignant insulinomas are very rare neuroendocrine tumors with varied clinical courses. After successful surgical removal, the long-term risk of recurrence is not high and for patients with a benign disease, long-term survival is expected (2). It is generally difficult to differentiate malignant and benign insulinomas. Differentiation is based on intraoperative evidence such as liver metastasis, regional lymph nodes, or local invasion, and in some patients, the metastases are diagnosed together with the recurrence of the symptoms related with hypoglycemia after surgical resection (3). In this report, we present a rare case of insulinoma that recurred with solitary hepatic metastasis 15 years after the initial pancreatic resection.

CASE PRESENTATION

A 20-year-old woman had first presented in 1996 with episodes of apathy, cloudy consciousness, syncope, and hypoglycemia. After spontaneous hypoglycemia had been confirmed by laboratory tests, a 15×20 mm mass was detected in the pancreas by abdominal computed tomography (CT). Complete enucleation of the pancreatic mass was performed, and after surgical excision, symptoms related to hypoglycemia disappeared. There were no characteristics of multiple endocrine neoplasia syndrome either clinically or histologically. Nuclear atypia was not observed in hematoxylin and eosin (H&E) staining, and the histopathologic diagnosis was benign adenoma.

Throughout the subsequent 15 years, patient did not show any symptoms or findings related with hypoglycemia. However, in 2011, the patient presented to our clinic with syncope and concomitant hypoglycemia. Recurrence of insulinoma was diagnosed with laboratory tests, which revealed plasma glucose, insulin, and C-peptide levels of 38 mg/dL, 23.2 mcU/mL, and 2.71 ng/mL, respectively.

After the biochemical diagnosis had been made, abdominal CT was conducted. Abdominal CT scan could not show any pancreatic mass; however, it identified a 12.5-mm hypervascular lesion in the segment 8 of the liver (Figure 1) and a 24-mm liver hemangioma in the segment 7. A somatostatin-labelled isotope scan did not show any marked uptake of the radiopharmaceutical by the liver or the pancreas. Endoscopic ultrasound was performed for detecting a possible recurrent insulinoma but did not show any suspected lesion suggesting insulinoma. Resection of the hepatic lesion was planned. Verbal and written informed consent was obtained from the patient for both surgery and potential medical reports before the operation.

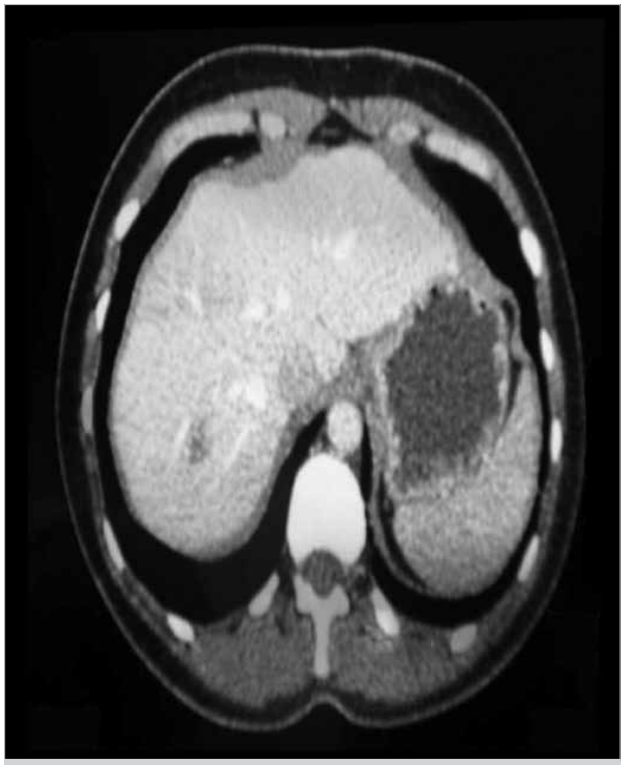

Figure 1. Hypervascular lesion in the segment 8 of the liver

Intraoperative ultrasound was performed and did not show any suspected lesion in the pancreas. Wedge resection of the hepatic lesion was performed. Postoperative blood glucose levels were returned to normal and no symptoms of hypoglycemia were seen. Histopathologic examination confirmed the diagnosis of neuroendocrine tumor metastasis. The tumor was positive for synaptophysin and chromogranin A immunostaining (Figure 2). The proliferative rate, measured by KI-67 index was 1.6%. Surgical margins were free of tumor. The patient was discharged on postoperative day 6 without any complication. The patient has been asymptomatic for subsequent 4 years.

DISCUSSION

Approximately 80% of insulinomas are single benign lesions, 10% are malignant tumors, and the remaining 10% are multiple benign tumors (4). Patients with benign insulinomas generally have good prognosis if complete resection of the primary tumor can be performed. Even some patients with malignant insulinomas may survive for long periods due to the slow growth characteristic (2). The time interval between the presentation of the primary tumor and the metastasis may be long. Kobayashi et al. (5) reported a solitary non-functioning metastasis 14 years after the resection of a malignant pancreatic insulinoma. The case was diagnosed as malignant after the initial surgery. Further, Gonzalez et al. (6) reported a symptomatic hepatic metastasis 9 years after the initial pancreatic resection and the case had

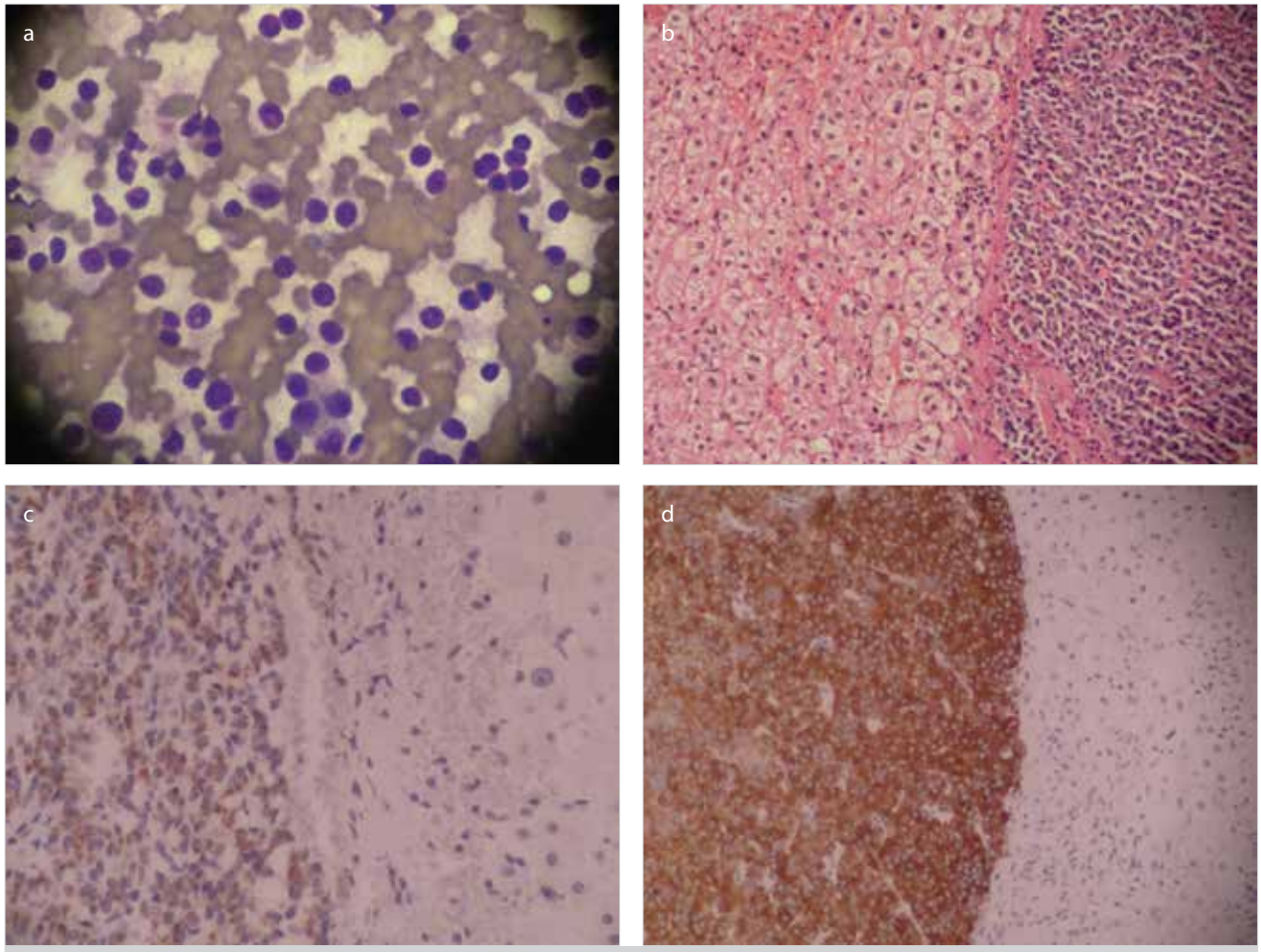

Figure 2. a-d. Microscopic features of the excised liver mass. (a) Individually localized neoplastic cells with neuroendocrine characteristics (400×, May-Grünwald Giemsa). (b) Liver metastasis of neuroendocrine tumor (200×, Hematoxylin and eosin). (c) Liver tumor with positive synaptophysin staining (200×, immunohistochemistry). (dd) Liver tumor with positive chromogranin A staining (200×, immunohistochemistry)

initially been considered as benign. This was the longest interval between primary tumor and the metastasis that is reported in the English literature until our report. We should remember that long-term follow-up is mandatory for these patients. Further, this case illustrates that metastasis of a pancreatic insulinoma can cause hypoglycemia, and symptomatic treatment can be achieved with the resection of the metastasis.

Liver resection is the most effective treatment of liver metastasis of neuroendocrine tumors. Other treatment options, including arterial chemo-embolization, radiofrequency ablation, radionuclide therapy, and liver transplantation, can be used for curative purposes when liver metastases are unresectable; the morbidity and mortality in patients with insulinoma are predominantly the result of the persistent hypoglycemia rather than wide-spread dissemination of the tumor (7). Thus, palliative debulking of tumors might improve survival (8). Unfortunately, however, curative cytoreduction is possible in less than 10% of all patients with metastatic insulinomas (9). The patients who have multiple unresectable metastases in the liver can be treated with chemotherapy via a catheter introduced in the hepatic artery (10). This patient had a solitary resectable lesion in the liver and was treated with liver resection.

CONCLUSION

We reported a case of metastatic insulinoma 15 years after the resection of the primary tumor. Life-long follow-up and resection when possible are recommended for even benign, resected islet cell tumors of pancreas.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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Conflict of Interest: The author have no conflicts of interest to declare.

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Case Report

A case report of left paraduodenal hernia diagnosed preoperatively and treated laparoscopically

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ABSTRACT

Paraduodenal hernia is a rare congenital anomaly; however, it is the most common cause of internal herniation. Clinical findings are often indeterminate. Computerized tomography is usually diagnostic; however, the diagnosis is often made intra-operatively. Paraduodenal hernia carries a risk of incarceration leading to bowel obstruction and strangulation; therefore, it should be repaired surgically when diagnosed. Here we present a case of left PDH that was diagnosed preoperatively and repaired laparoscopically.

Keywords: Laparoscopy, paraduodenal, hernia

INTRODUCTION

Internal hernias result from the extension of the intestine through a defect within the peritoneum or mesentery (1). They may be either congenital or acquired. Paraduodenal hernia (PDH) is a rare congenital anomaly that results from an error of rotation of the midgut (2). PDHs are the most common form of internal hernias, accounting for 53% of all internal hernias (1, 3). PDHs are difficult to diagnose because the clinical symptoms are variable (4). PDH can begin with symptoms of acute obstruction or recurring abdominal pain (43%) or can be asymptomatic throughout the patient's life. Between 10% and 50% of internal hernias are discovered during unrelated abdominal surgeries or imaging exams and autopsy (5). Preoperative computerized tomography scan of the abdomen is usually diagnostic; however, the diagnosis is often made intra-operatively. Surgical treatment can be performed with traditional open methods or minimally invasive laparoscopic techniques. We describe herein the preoperative radiological diagnosis and successful laparoscopic repair of a left PDH in an adult man.

CASE PRESENTATION

A 39-year-old man was admitted to the emergency department with complaints of epigastric cramps and nausea and vomiting that persisted for almost one day. It was known that he had been suffering from similar problems for a long time, and he had applied to 3 different hospitals in the last 10 days. There was no specific finding except for upper left quadrant tenderness. He had no history of abdominal surgery. His vital signs were normal. On his plain abdominal film, vague and limited air-fluid levels and a mass-like lesion were found in the left quadrants. Laboratory results were normal, except his leukocyte count was 11600. He was hospitalized for follow-up. It was noticed that he was comfortable while resting on his left side; however, his pain worsened in the supine position. Encapsulated and moderately dilated small bowel loops were detected in the upper left quadrant between the stomach and pancreas by CT (Figure 1). He was preoperatively diagnosed with left PDH. Four ports were inserted; one 10 mm supraumblical port for the camera, another port 10 mm from the upper left quadrant, and two 5 mm ports in the upper right quadrant. During exploration, left PDH was observed on the left side of Treitz's ligament behind the inferior mesenteric vein. An entrapped jejunum loop of approximately 80 cm was then reduced from the hernia sac into the abdominal cavity with an atraumatic tool. The loop was easily released by gentle traction. There was no ischemic or necrotic intestinal loop. The hernia sac was not resected, and the orifice was then closed intracorporeally with interrupted sutures using non-absorbable multifilament 3-0 material from the tissue around the inferior mesenteric vein to the tissue on the posterior abdominal wall and the serosa of the jejunum, avoiding injury to the inferior mesenteric vessels (Figure 2). Surgery time was 25 minutes. Loss of blood was approximately 30 ml. The patient's postoperative course was uneventful. The patient was given oral nutrition 8 hours after the surgery and was discharged 36 hours after operation. No recurrence was observed at one-year follow-up.

DISCUSSION

Paraduodenal hernia is a rare condition; however, it is the most common cause of internal hernia (2). The first PDH was evidently described during an autopsy by Neubauer in 1786. In 1857, Treitz defined PDHs as "retroperitoneal hernias"; he believed that they were caused by herniation of the intestine into the duodenojejunal fossa. Jonnesco, in 1889 and 1890, divided these hernias into two distinct types: left

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Figure 1. a-d. Radiologic findings in this case (a) A plain radiograph of the abdomen shows a mass-like lesion (arrows). Computerized tomography scan of the abdomen in coronal (b), axial (c) and sagittal (d) cuts

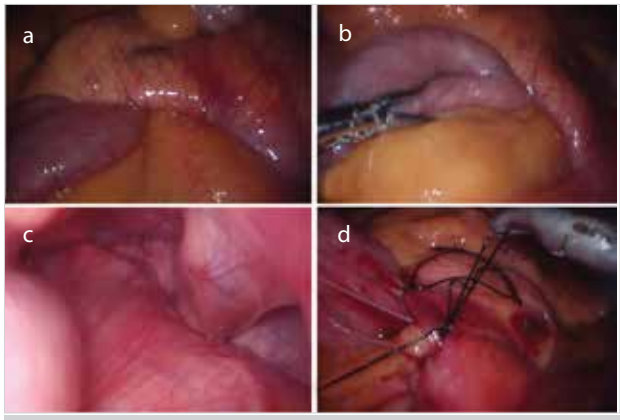

Figure 2. a-d. Laparoscopic view of the left PDH (a) Hernia orifice and distal part of entrapped jejunum, (b) Reduction of the entrapped jejunal loop (c) Hernia sac and cavity (d) Closure of the hernia orifice with intracorporeal sutures

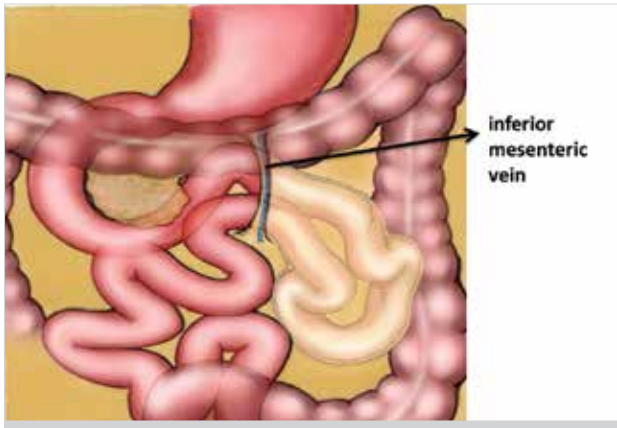

Figure 3. Graphic illustration of a left PDH depicts jejunal loop prolapsing through posterior of left mesocolon, lateral to Treiz's ligament, behind inferior mesenteric vein

and right. In 1923, Andrews first described the basis of the embryogenic origin of right PDH as a result of defective or incomplete midgut rotation. A clear description of the mechanism of left PDH as a fusion defect between the left mesocolon and the mesentery of the duodenum was provided by Callander in 1935 (6). In the present case, the bowels were observed to have completed their rotation; therefore, it was thought that the left PDH was due to a fusion defect. 25% of PDHs develop on the right side of Treitz's ligament and involve the mesentericoparietal fossa (Waldeyer's fossa). Approximately 75% occur on the left and involve the paraduodenal fossa (Landzert's fossa). The Landzert's fossa is situated immediately lateral to the ascending duodenum, posterior to the inferior mesenteric vein (IMV) and the ascending branch of the left colic artery, directly beneath the posterior parietal peritoneum. Left PDH extends in a retrocolic fashion into the left portion of the transverse mesocolon and the descending mesocolon (7) (Figure 3). PDH can present at any age but is usually seen between the 4th and 6th decades of life (mean age 38.5 years). Males are affected three times more than females (4, 6).

Paraduodenal hernias can be asymptomatic and can be found by laparotomy or autopsy (8). Symptomatic presentation can range from intermittent and mild digestive complaints to acute intestinal obstruction. Complaints are usually relieved by changes in position. Symptoms are often postprandial (especially after a large meal), and pain may be relieved when the patient lies supine (4, 8). In this case, the patient had colic and postprandial growing pain for a long time; however, it is notable that the pain was relieved in the left lateral supine position. Symptoms such as postprandial abdominal pain, nausea, and vomiting can lead the physician to misdiagnose PDH as biliary disease and peptic ulcer (4). Due to its nonspecific symptoms, PDH can even be misinterpreted as FMF in countries such as Turkey, which contains a large proportion of patients who suffer from FMF (9).

There is no specific physical examination finding for left PDH. However, it can be felt as a palpable mass in the left upper quadrant. Correct preoperative diagnosis of PDH is difficult and can only be made radiologically. In abdominal plain radiographs or gastrointestinal contrast studies, left PDH presents as an encapsulated circumscribed mass of a few intestinal loops in the left upper quadrant, lateral to the fourth part of the duodenum. The first diagnosis of an internal hernia by CT was presented by Harbin in 1982 (10). Abdominal CT is the gold standard to provide a correct diagnosis; the CT findings for a left PDH may show entrapped intestinal loops with the appearance of a smooth encapsulated border, called Donnelly's border, between the stomach and pancreas (5, 11). In this case, CT was ordered after vague air-fluid levels and a mass-like lesion were detected in the left quadrants on plain x-ray. As classic CT findings were observed, a definitive diagnosis was made preoperatively.

Paraduodenal hernia carries an approximately 50% lifetime risk of incarceration, leading to bowel obstruction and strangulation; therefore, it should be repaired surgically when diagnosed (4, 8). Surgical treatment can be performed with conventional open methods or minimally invasive laparoscopic techniques. The standard surgical approach for PDHs involves reduction of the entrapped intestinal loops, with resection if

Table 1. Published cases from Turkey in the national and international literature

Author	Published date	Age	Sex	Previously abdominal surgery	Preoperative examination	Side of hernia	Surgical technique	Hernia repair technique	Discharge time
Cebeci et al. (13)	1976	70	F	None	x-ray, PE	Right	Laparotomy	Primary closure	P.O.-1 exitus
Tireli et al. (14)	1982	18	M	None	x-ray, PE	Left	Laparotomy	Primary closure	UD
Kebudi et al. (15)	1989	43	M	None	x-ray, PE	Right	Laparotomy	Primary closure	10 days
Yüceyar et al. (16)	1993	49	M	None	x-ray, PE	Left	Laparotomy	Wide opening	13 days
Özçelik et al. (17)	1993	21	M	None	x-ray, PE	Left	Laparotomy	Primary closure	UD
Şahin et al. (18)	1998	44	M	None	x-ray, PE	Left	Laparotomy	Primary closure	10 days
Şahin et al. (18)	1998	63	M	None	x-ray, PE	Left	Laparotomy	Primary closure	7 days
Ovalı et al. (19)	2005	52	F	None	CT	Left	Refused surgery		
Cingi et al. (9)	2006	30	M	None	CT	Left	Laparotomy	Resection of the hernia sac	4 days
Şen et al. (20)	2007	24	F	None	x-ray, PE	Left	Laparotomy	Primary closure	5 days
Şen et al. (20)	2007	20	M	None	CT	Right	Laparotomy	Primary closure	6 days
Tekin et al. (21)	2007	53	M	None	x-ray, PE	Right	Laparotomy	Primary closure	4 days
Tekin et al. (21)	2007	48	M	None	x-ray, PE	Right	Laparotomy	Primary closure	11 days
Akın et al (22)	2009	23	M	None	x-ray, PE	Left	Laparotomy	Resection of the hernia sac	3 days
Okan et al. (23)	2010	43	M	None	CT	Left	Laparotomy	Primary closure	8 day
Polat et al. (24)	2010	25	M	None	x-ray, PE	Left	Laparotomy	Primary closure	4 days
Acu et al. (25)	2010	29	M	Appendectomy	CT	Left	Laparotomy	Primary closure	UD
Arslan et al. (26)	2012	49	M	None	CT	Left	Laparotomy	Primary closure	3 days
Akbulut et al. (27)	2012	42	M	None	x-ray, PE	Left	Laparotomy	Primary closure	5 days
Öztaş et al. (28)	2013	42	M	Appendectomy	CT	Left	Laparoscopy convertion laparotomy	Primary closure	4 day
Cengiz et al. (29)	2013	43	M	Appendectomy	CT	Left	Laparotomy	Primary closure	UD
Gemici et al. (30)	2014	45	F	None	CT	Left	Laparotomy	Primary closure	4 days

M: male; F: female; CT: computed tomography; PE: physical examination; UD: undeclared

necessary in the case of nonviable segments, and repair of the defect by either closure or wide opening of the hernia orifice so the hernia sac becomes a part of the general peritoneal cavity (2, 7). Left PDH can usually be reduced easily. The closure of the hernia orifice with sutures is sufficient. If reduction is difficult, widening of the hernia orifice by an incision along an avascular plane of the descending mesocolon or division of the IMV is performed (2). Excision of the hernia sac is generally not mandatory. Recurrent cases can be repaired with a mesh (3). In this case, because the left PDH was easily reduced, expansion of the hernia sac and IMV scarification were not necessary. Primary closure of the hernia orifice was sufficient.

There are many reports in the literature of left PDH, although the total number of reported cases is less than 500 (12). The approach of minimally invasive techniques for hernia is relatively new; the first successful laparoscopic repair of PDH was reported by Uematsu in 1998 (7). Since then, several successful laparoscopic PDH repairs have been reported in various countries. After searching the national and international literature, we found 22 cases related to adult PDH in Turkey (9, 13-30). This is summarized in the Table 1. This is the first case report of laparoscopically repaired PDH from Turkey. Öztaş et al. (29) preoperatively diagnosed a case by CT and began laparoscopic surgery; however, the operation was converted to open surgery.

Early and correct preoperative diagnosis may play an important role in determining the surgical strategy. In the present case, preoperative diagnosis and no ischemic sign in the CT findings enabled us to decide on a laparoscopic surgery approach. The major benefits of laparoscopic surgery can be cited as less postoperative pain, short hospital stay, and early return to normal activity.

CONCLUSION

Paraduodenal hernia is very rare, and preoperative diagnosis is difficult because there are no specific symptoms or physical examination findings. CT is the gold standard for preoperative diagnosis. Laparoscopic surgery is technically easy and may be the best surgical method for left PDHs without bowel necrosis.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Transcervical resection of two parathyroid adenomas located on the anterior mediastinum

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ABSTRACT

The mediastinum is a possible location of ectopic parathyroid adenoma. Most ectopic parathyroid glands in the mediastinum are found in the superior mediastinum within the thymus. In this article, two cases with ectopic mediastinal parathyroid adenomas that were excised via transcervical resection are presented. Preoperative examination of the two cases was performed. Laboratory tests supported hyperparathyroidism. For both patients, the results of radiologic and scintigraphic examinations of the cases were compatible with parathyroid adenoma masses in the anterior mediastinum. Transcervical resection was performed via suprasternal incision through the sternal notch and the posterior wall of the sternum space by blunt dissection with the finger. The soft lesions were removed en bloc in both cases. The parathyroid hormone levels of the two cases decreased dramatically after the operation. Transcervical resection may be an alternative method to major surgery in anterior mediastinal small masses.

Keywords: Mediastinum, ectopic parathyroid adenoma, transcervical resection, minimally invasive surgery

INTRODUCTION

Primary hyperparathyroidism is accompanied by oversecretion of parathormone, leading to hypercalcemia and hypophosphatemia. The major cause of primary hyperparathyroidism is parathyroid adenoma. In some patients, adenomas can be found ectopically. The mediastinum is an ectopic location for parathyroid adenomas (1). Parathyroid glands are ectopically positioned in almost in 15%-20% of cases (2). Retrospective studies have demonstrated that 1%-3% of all patients experiencing parathyroid operations have functional mediastinal parathyroid tumors (2, 3)

Most of these tumors are found in the superior aspect of the anterior or posterior mediastinum and are thus permeable through a cervical incision; 1.4%-20% of patients require sternotomy (4). This may require surgical intervention in the form of parathyroidectomy, which is workable through a cervical incision in most cases; however, 1%-2% of these patients may require a transsternal or transthoracic approach due to a deeply seated mediastinal parathyroid gland (1, 5). Minimally invasive strategies have lately been found to be an alternative to traditional open approaches due to their lower morbidity and improved results. We describe our experience with a minimally invasive versus a traditional open approach for ectopic mediastinal parathyroidectomy.

CASE PRESENTATIONS

Case 1

A 40-year-old woman (Table 1) with high levels of calcium, phosphate, and parathormone was referred to our clinic for suspected primary hyperparathyroidism. There was no relevant medical or family history. Physical examination was normal. Abnormal calcium, parathormone, and phosphate levels were detected in blood analysis. At presentation, her biochemical levels were as follows: serum calcium and phosphorus levels were 11.6 mg/dL (normal range (NR) 8.8-10.2 mg/dL) and 1.85 mg/dL (NR 2.7-4.5 mg/dL), respectively. Her intact parathormone level was 882 pg/mL (NR 15-68 pg/mL). Her thyroid function test results were within the normal range. The thyroid gland appeared normal, and no other pathologic lesion was found by cervical ultrasonography (USG) or magnetic resonance imaging (MRI). Ectopic parathyroid adenoma was suspected, and a mediastinal mass was identified in a chest computer tomography (CT) scan. CT study of the thorax revealed a nodule, 2×3 cm in diameter, located on the anterior mediastinum superior to the aortic arch (Figure 1, 2). By technetium-99 m pertechnetate methoxy-isobutyl-isonitrite (Tc-99 m MIBI) scan, the nodule was seen as an intense focus in the anterior mediastinum, and ectopic parathyroid adenoma was diagnosed. After surgery, the patient's intact parathyroid hormone level reverted to 86 pg/mL.

Case 2

A 57-year-old woman (Table 1) was referred to our clinic from another center for suspected primary hyperparathyroidism. She had been experiencing common bone pain and nephrolithiasis. Her symptoms had become more severe over time. At presentation, her biochemical levels were as follows: serum calcium 11.7 mg/dL,

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Table 1. Inter-observer measurement reliability

Patient data	Sex	Age	Size (cm)	Pre-op serum PTH (15-68 pg/mL)	Pre-op serum Ca (8.8-10.2 mg/dL)	Post-op PTH	Post-op Ca
Case 1	F	40	3×2×1.5	882	11.6	86	8.6
Case 2	F	57	3×3×2	1412	11.7	126	10

PTH: parathyroid hormone; Ca: calcium

Figure 1. Axial contrast-enhanced CT imaging shows an ectopic parathyroid adenoma, 1.5 cm in diameter, located on anterior mediastinum (arrow)

Figure 2. Sagittal contrast-enhanced CT imaging shows a small mass located in front of the arcus aorta (arrow)

parathyroid hormone 1412 pg/mL, and phosphorus level 2.67 mg/dl. The thyroid gland appeared normal, and no other pathologic lesion was found by cervical USG. Ectopic parathyroid adenoma was suspected, and a mediastinal mass was identified in a chest CT scan. CT study of the thorax revealed a nodule, 32×20 mm in diameter, located posterior to the manubrium sterni and in front of the left brachiocephalic vein. By Tc-99 m MIBI scan, the nodule was seen as an intense focus in the anterior mediastinum, and ectopic parathyroid adenoma was diagnosed. After the operation, the patient's intact parathyroid hormone level reverted to 126 pg/mL.

In both cases, rapid PTH was not considered due to the absence of rapid PTH facilities at the center. Postoperative pathologic diagnosis was parathyroid adenoma. A whole-body Tc99 m sestamibi parathyroid scan showed an increased tracer concentration in the anterior mediastinum, which suggested the presence of active parathyroid tissue, while the same activity was not observed in the neck. Thorax CT was performed after the sestamibi parathyroid scan. The level of the lesion is of great importance in these cases because lesions under the manubrium sterni can be difficult to access by this method.

A written informed consent was obtained from each patient.

Surgıcal Approach

Both patients underwent the same procedure. The patients were in the supine position under general anesthesia. The neck was brought to hyperextension to ensure maximum exposure. The skin and subcutaneous soft tissues were passed via a 3 cm transverse incision made from the sternal notch entrance. A sharp and blunt dissection was performed from the anterior mediastinum through the substernum (Figure 3a). It was descended to the lesion level located on the anterior mediastinum. The adenoma was held with Babcock forceps and was ligated from the surrounding fatty tissue with a LigaSure Atlas vessel sealing instrument (Valleylab; Tyco Healthcare Group LP Boulder, CO) (Figure 3b). The adenoma was removed en bloc (Figure 4). As the dissection of the substernal area was performed through adipose tissue, no bleeding or soft tissue injury occurred. The operation was terminated after hemostasis. Histopathological examination results of the specimens were compatible with parathyroid adenoma.

DISCUSSION

Churchill was the first to recognize hyperfunctioning ectopic parathyroid glands in 1932. The patient, Captain Charles E. Martell, underwent six prior unsuccessful cervical explorations and had severe osteitis fibrosa cystica until the ectopic gland was removed by a transsternal approach (1). Primary hyperparathyroidism is accompanied by hypersecretion of parathyroid hormone, which results in hypercalcemia and hypophosphathemia. Parathyroid adenoma is the major cause in most cases. In 11%-25% of cases, ectopic mediastinal hyperfunctional parathyroid tissue can be found (3).

Two different mediastinal parathyroid glands have been defined in the literature: the first type originates in the neck and descends into the chest with continuing glandular enlargement in the presence of negative intrathoracic pressure; the second type is the outcome of developmental malascent, which usually affects the inferior parathyroid glands or is due to supernumerary parathyroid glands. The first type can be removed by the transcervical approach; the second is usually deeply rooted in the mediastinum and may require an additional or an alternative access, either transsternal or transthoracic (1).

Diagnosis of ectopic mediastinal parathyroid glands is difficult, and their localization is even more so. The methods used to identify ectopic parathyroid glands include chest CT scan, MRI, or MIBI scan (1). If the parathyroid adenoma is located in the mediastinum, median sternotomy, thoracotomy, mediastinotomy, mediastinoscopy, or thoracoscopy may be required for resection, similar to other mediastinal masses (6-8). Successful and accurate preoperative localization of the ectopic glands is important, especially if minimally invasive approaches are

Figure 3. a, b. (a) A sharp and blunt dissection was performed from anterior mediastinum through substernum, (b) Adenoma was kept with bebcoock forceps and removed

Figure 4. Adenoma was removed en block

considered (1). 98% of these mediastinal parathyroid adenomas are resectable through a neck collar incision, whereas 2% require a different approach (9). In such cases, it is important to plan the operation to enable complete surgical resection of the ectopic parathyroid adenoma.

The traditional approaches to ectopic mediastinal parathyroid glands include median sternotomy or thoracotomy to access the ectopic glands. Recently, minimally or less invasive approaches are being seen as alternatives, with reported lower morbidity and earlier return to normal life (1). The diverse minimally or less invasive strategies reported in the literature include splitting the manubrium (manubriotomy), closed mediastinal exploration with dedicated equipment followed by excision of the gland via transcervical approach, video-assisted mediastinoscopy, video-assisted thoracoscopic surgery (VATS), and robot-assisted exploration (1, 10). Surgery is the preferred treatment. Surgical excision should be planned based on thorax CT and parathyroid scintigraphy findings. In such cases, cervical incision can also be applied (3). The transcervical approach was applied for our patients; parathyroidectomy was completely successful, with no complications.

CONCLUSION

Minimally invasive surgery for upper mediastinal parathyroidectomy is safe and can be applied with low morbidity. It may be equivalent to the traditional open approach in terms of morbidity; however, it provides the patient with a significantly shorter length of hospital stay.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Case Report

Idiopathic renal replacement lipomatosis: A diagnostic and therapeutic challenge

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ABSTRACT

Renal replacement lipomatosis is a rare benign renal disorder where the renal parenchyma is replaced by mature fatty tissue. It poses a diagnostic challenge to the clinicians due to an unusual presentation and clinical features. The disease usually presents in middle age with vague pain in the affected flank and variable urological symptoms. Although the condition is preceded by calculus disease or chronic inflammation, as an extremely rare occurrence, it can occur without any pre-existing condition, as in our case. Increasing awareness among the surgeons about the existence of such a condition will help the surgical fraternity to diagnose and manage such cases properly.

Keywords: Benign, lipomatosis, inflammation, pyelonephritis, nephrectomy

INTRODUCTION

Idiopathic renal replacement lipomatosis is an extremely rare benign condition of the kidney wherein the kidney parenchyma is replaced by mature adipocytes. The replacement process usually starts from the renal sinus to proceed toward the progressive involvement of the renal parenchyma and finally the perirenal space. It usually presents as a mass, posing a diagnostic challenge to the clinician. Here we present one such case in a middle-aged lady.

CASE PRESENTATION

A 45-year-old woman presented to our outpatient department with complaints of dull aching pain in the left flank of 2 years without any urinary complaints. The patient was obese with no positive findings on clinical examination duration, except for minimal left renal angle tenderness only on deep pressure. The case was presented after obtaining written informed consent from the patient.

Patients' blood and biochemical investigations were within normal limits. Ultrasound of the abdomen and pelvis could not provide any clue toward a definitive diagnosis other than showing a distorted contracted left kidney. Computed tomography (CT) scan of the abdomen revealed distorted, shrunken left kidney with the thinned-out cortex. There was loss of corticomedullary differentiation and delayed excretion of contrast. The kidney was surrounded by perinephric fat, which had pushed the abdominal organs inferiorly and medially (Figure 1). This information did not help in a definitive preoperative diagnosis. Hence, the retroperitoneum was explored through a flank incision to find a fatty mass in the left renal fossa. Due to the densely adherent mass in that region, we performed a subcapsular nephrectomy to retrieve a contracted and distorted fatty mass with very little vascularity, which could be recognized as the kidney only by the fact there were some structures of the pelvicalyceal system in the region of renal sinus and its connection to the ureter (Figure 2).

Histopathological examination revealed total replacement of the renal parenchyma with fat with very few sclerosed glomeruli with thyroidized tubules (Figure 3). The diagnosis of renal replacement lipomatosis could be made only after extensive literature study as the gross and microscopic features aptly fitted the features described in literature.

DISCUSSION

Renal replacement lipomatosis is a degenerative process that consists of progressive replacement of renal parenchyma by mature fatty tissue. It is a rare form of end stage kidney condition resulting from chronic inflammation. The condition was unheard of till Kurtzmann described it in detail during his study of 33 cases in 1931 (1). Even now, the condition is rarely seen in clinical practice wherein it presents a diagnostic and management challenge.

The disease usually presents in the fourth and fifth decades of life, although there are cases reported in the pediatric age group too. The usual presentation is in the form of a vague pain in the involved

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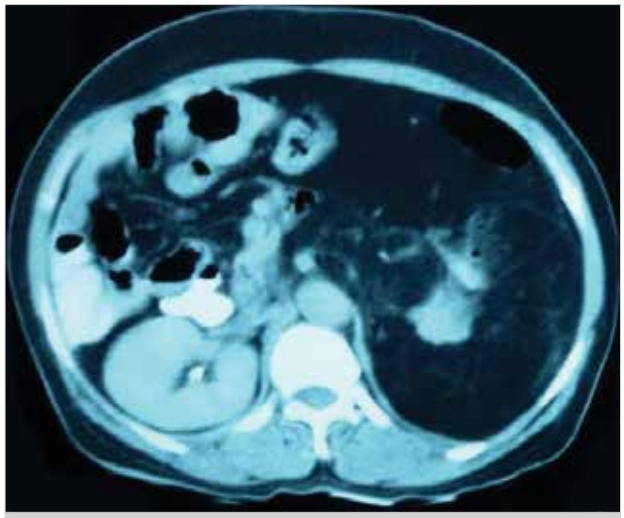

Figure 1. Computed tomography scan abdomen picture showing distorted left kidney surrounded by fat pushing abdominal content inferomedially

Figure 2. Cut surface of the specimen

flank with variable urinary symptoms. Although the condition is preceded by either a calculus disease or chronic pyelonephritis, there are very rare instances where no such preceding condition exists, such as ours (1, 2). It is important to promptly diagnose this condition as there are reports of coexisting malignancy too (3). Clinical examination hardly yields any positive finding.

In most of the cases reported, preoperative diagnosis could not be made. This is due to the paucity of classical features either on clinical examination or on investigation. Routine ultrasound of the abdomen can detect distorted renal parenchyma and presence of calculus. CT can further characterize the lesion as a fatty infiltration of the poorly functioning renal moiety. Magnetic resonance imaging can add to anatomic details (4). However, none of these can definitely point to the diagnosis of renal replacement lipomatosis.

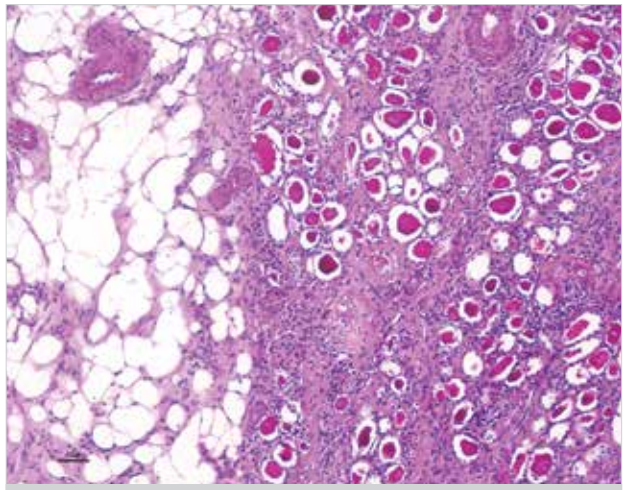

Figure 3. Photomicrograph of the histopathological examination of the specimen showing mature adipocytes, sclerosed glomeruli, thyroidized tubules, and inflammatory infiltrates (H&E stain, size: 40 µm)

As of today, histopathology is the only accurate diagnostic tool. The kidney is usually shrunken in size as in our case, although it may be enlarged as in cases associated with calculus disease and there is decreased vascularity of the renal parenchyma with replacement of parenchyma by mature adipocytes. There is infiltration by the inflammatory cells to certain extent. Xanthogranulomatous pyelonephritis is the closest mimicker of this condition, especially in case of calculus. The absence of xanthoma cells confirms diagnosis in favor of renal replacement lipomatosis (2, 4).

Differential diagnoses other than xanthogranulomatous pyelonephritis are malakoplakia and fat-containing tumors of the kidney and perirenal structures. Malakoplakia is characterized by Michaelis-Gutmann bodies, which are foamy histiocytes with basophilic inclusions. The diagnosis of malakoplakia is also made by histopathological examination in almost all cases, and there are suggestions that malakoplakia is also a stage in the formation of xanthogranulomatous pyelonephritis (5, 6).

The fat-containing tumors of the kidney such as angiomyolipoma and liposarcoma usually arise from the sinus fat and not from the renal parenchyma, hence cause mass effect rather than renal parenchymal lesions. The mass effect can cause vague pain and sometimes obstructive features when the mass causes obstruction at the level of the renal pelvis. They are usually identifiable by their specific imaging features unlike renal replacement lipomatosis, which has no specific features on imaging that can confirm diagnosis (6).

Preoperative diagnosis is important as it is challenging to plan the treatment for this condition. As such renal replacement lipomatosis itself is not of much clinical significance as it denotes a degenerative process. The rarity of its occurrence and

paucity of literature in contemporary medical textbooks about the condition adds to the difficulty of the clinician to diagnose the condition preoperatively. Although it is easy to diagnose a fatty mass on CT, to characterize this entity preoperatively as renal replacement lipomatosis is a clinical challenge. In almost all reported cases, the diagnosis was confirmed on histopathology only (1-6). Hence, the best treatment in such cases is excision of fatty mass intotal. However, this may not be possible due to severe adhesions, as in our case.

CONCLUSION

The rarity, nonspecific clinical features, and absence of classical investigative findings in case of renal replacement lipomatosis pose a diagnostic and therapeutic challenge to clinicians. With reporting of cases of all types and variants of this clinical condition, awareness about renal replacement lipomatosis can increase among clinicians, radiologists, and pathologists, which will help in accurate preoperative diagnosis and treatment planning.

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Case Report

Perforation of the small intestine caused by enteropathy-associated T cell lymphoma

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ABSTRACT

Enteropathy-associated T cell lymphoma is a rare lymphoma specific to the gastrointestinal system, arising from intraepithelial T lymphocytes, that is often associated with celiac disease. We report a 53-year-old female patient with no previous disease who presented with severe abdominal pain. Physical examination revealed diffuse abdominal tenderness and abdominal guarding and the patient underwent emergency surgery with a diagnosis of acute abdomen. During the operation, a 20-cm mass was found located on Treitz ligament, invading the duodenum and pancreatic head and perforating the jejunum. Histologically, medium-sized monomorphic atypical lymphocyte infiltration with dark nucleus and narrow cytoplasm was seen in the layers of mucosa, submucosa, muscular wall, and serosa of the duodenum. The final pathological diagnosis was "enteropathy-associated T cell lymphoma type 2" based on immunohistochemical and serological findings. Based on the World Health Organization 2008 criteria, enteropathy-associated T cell lymphoma has two subtypes. Type 1 enteropathy-associated T cell lymphoma is associated with celiac disease and has HLA DQ2 and HLA DQ8 genotype. Enteropathy-associated T cell lymphoma 2 enteropathy-associated T cell lymphoma seldom occurs and is not associated with celiac disease.

Keywords: Lymphoma, enteropathy, small intestine

INTRODUCTION

Enteropathy-associated T cell lymphoma (EATL) is an extranodal lymphoma that has a poor prognosis arising from intestinal intraepithelial T lymphocytes. Although it has a very rare incidence in most parts of the world, it is more common in societies where celiac disease is widespread (1, 2).

According to the World Health Organization (WHO) criteria, it has two subtypes: type 1 and type 2. Type 1 EATL is associated with celiac disease and it comprises 80%-90% of cases observed in Europe. Type 2 EATL, occurring sporadically, is less frequently associated with celiac disease and is more common in Asian countries (3).

A case of EATL presenting with intestinal perforation is reported due to its rare incidence and discussed with the literature.

CASE PRESENTATION

A 53-year-old female patient with no previous disease presented with severe abdominal pain. Physical examination revealed diffuse abdominal tenderness and abdominal guarding. Laboratory data revealed leukocytopenia (1780/mm^3) with normal values for hemoglobin (13.3 g/dL) and platelets (237×10^6/mm^3). Her other routine laboratory findings were normal. With these findings, the patient underwent emergency surgery with a diagnosis of acute abdomen. During operation, a 20-cm mass was found, located on Treitz ligament, invading the duodenum and pancreatic head and perforating the jejunum. An intraoperative biopsy specimen was sent for pathological diagnosis, which suggested a malignant lymphoid cell infiltration, and accordingly a partial intestinal resection and Roux-en Y anastomosis was performed.

Grossly, the resected specimen contained 5 cm of duodenum and 35 cm of jejunum with adjacent tissues. A 7×5 cm submucosal mass, invading the wall of duodenum and jejunum and resulting in mucosal ulcer and perforation, was found. It was a gray-white colored tumoral mass with occasional bleeding areas.

Microscopically medium-sized monomorphic atypical lymphocyte infiltration with dark nucleus and narrow cytoplasm was seen in the layers of mucosa, submucosa, muscular wall, and serosa of the duodenum (Figure 1). There was no inflammatory background but tumor cell necrosis was found in some areas. In the non-neoplastic intestinal mucosa, villous atrophy, cryptal hyperplasia, intraepithelial lymphocytosis, and lymphoplasmacytic infiltration in lamina propria were observed (Figure 2). In the im-

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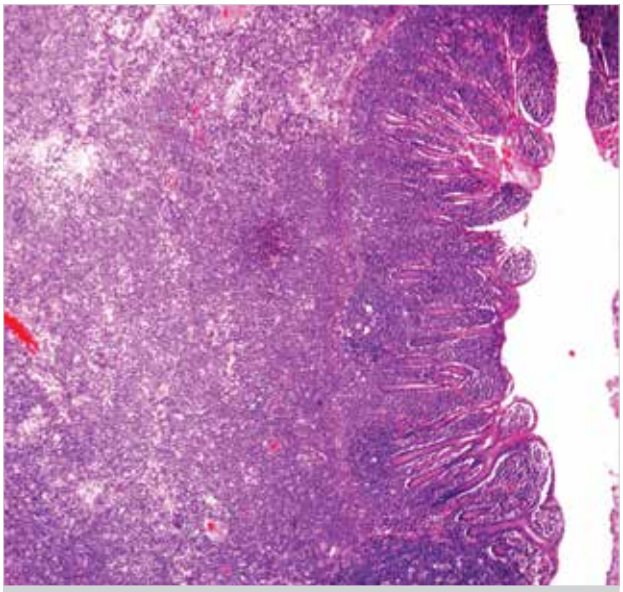

Figure 1. Infiltration of mucosa, submucosa, muscular wall, and serosa of the duodenum by atypical lymphocytes (H&E; 200×)

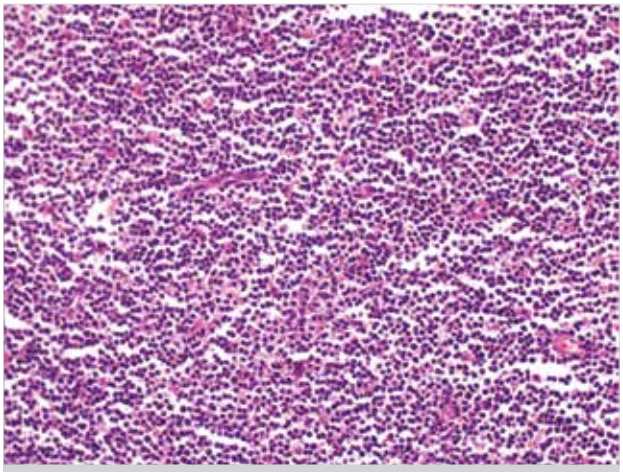

Figure 2. Medium-sized monomorphic atypical lymphocytes (H&E; 400×)

munohistochemical analysis, the tumor cells were positive for LCA, CD3, CD7, CD8, and CD56, and negative for CD20, CD5, CD4, CD79a, CD10, CD99, and CK. Ki67 proliferation activity was 70%. The intraepithelial lymphocytes in the adjacent mucosa had identical immunophenotype with tumor cells. The serological examination was negative for HLA DQ2 and HLA DQ8 expression. The final pathological diagnosis was "EATL type 2" according to above mentioned findings. The patient have been informed and also her consent have been taken for this case report.

DISCUSSION

The most common site for primary extranodal lymphomas is the gastrointestinal tract and majority have B cell phenotype. Primary T/NK cell lymphomas seldom occur but are more aggressive tumors (4).

Enteropathy-associated T cell lymphoma is a rare lymphoma, which is specific to gastrointestinal system, arising from the intraepithelial T lymphocytes, and is often associated with celiac disease. EATL is often observed in middle-aged men and is localized in the small intestines. Almost half of cases are presented with intestinal obstruction or perforation. Although rarely observed, EATL is one of the main causes of mortality in untreated or refractory celiac disease (5, 6).

Based on the WHO 2008 criteria, EATL has 2 subtypes. Type 1 EATL is associated with celiac disease, and has HLA DQ2 and HLA DQ8 genotype (7). On microscopic examination, the tumor cells are medium- or large-sized cells with round or angulated vesicular pleomorphic nuclei and abundant cytoplasm. They are positive for CD3 and negative for CD8 and CD56 immunohistochemically. Typically, the tumor has extensive necrosis areas and an inflammatory background rich of eosinophils, neutrophils, and histiocytes. Large cells with CD30 expression are occasionally seen in the type 1 EATL. In type 2 EATL, which seldom occurs and is not associated with celiac disease, tumor cells have small- to medium-sized round, darkly staining monomorphic nuclei and narrow cytoplasm. There is no inflammatory background and marked necrosis. As seen in our case, the neoplastic cells are stained positively for CD3, CD8, and CD56 immunohistochemically. In both types, the adjacent mucosa shows villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes, having same immunophenotype with the tumor cells (3, 8).

Differential diagnosis of EATL includes B cell lymphomas, especially diffuse large B cell lymphoma, which is the most common type of lymphoma in the small intestine. The positivity of B lymphocyte markers in all types of B cell lymphomas helps distinguish these tumors from EATL. Extranodal NK/T cell lymphomas, in general presenting with facial mass, are rarely diagnosed with intestinal metastasis and confused with EATL due to its morphological heterogeneity. Distinctive features of NK/T cell lymphomas are the positivity of NK (CD2) and EBV markers and absence of histopathological findings of enteropathy in the surrounding mucosa (9).

The poorly differentiated carcinomas and malignant melanomas, subject to differential diagnosis, can easily be excluded immunohistochemically. In absence of mass formation, EATL can be confused with an inflammatory ulcer, but the presence of atypical cells in EATL excludes this diagnosis (10, 11). B cell lymphomas, poorly differentiated carcinomas, and benign lesions were excluded in our case with the presence of monomorphic atypical tumor cells stained positively for T lymphocyte markers. Our case was diagnosed as intestinal EATL type 2, because of the monomorphic and small appearance of tumor cells, absence of inflammatory background, positive staining for CD3, CD8, and CD56, and lack of celiac disease findings, although focal necrosis was seen in some areas. Cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) protocol was planned for treatment. The patient was lost within two months postoperatively due to fever, pleural effusion, and respiratory failure.

CONCLUSION

Gastrointestinal lymphomas can be presented with the symptoms of acute abdomen, but not with systemic findings as in our case.

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Case Report

Foreign body: A sewing needle migrating from the gastrointestinal tract to pancreas

Fatih Dal, Engin Hatipoğlu, Serkan Teksöz, Metin Ertem

ABSTRACT

Of all ingested foreign bodies, 2.4% comprise of sewing needles. Through perforation of gastrointestinal tract, which occurs in 1% of cases, they can migrate into the liver and pancreas. Foreign bodies in pancreas should be considered in the differential diagnosis of chronic abdominal pain. Computed tomography scans provide valuable information for the localization of the lesion, which guide the surgeon during the operation. Secondary to foreign bodies that migrate to the pancreas, complications with high mortality such as pancreatitis, pseudoaneurysm, and pancreas abscess can be seen. Thus, for this patient group, diagnostic laparoscopy is recommended, considering its advantages of decreased postoperative pain, decreased wound infection, and faster recovery time. Here we present a case of a 23-year-old female patient, from whom an ingested needle that migrated from the back wall of the stomach to the pancreas was extracted by laparoscopic surgery.

Keywords: Sewing needle, pancreas, laparoscopy

INTRODUCTION

Out of all the ingested foreign bodies, 43.7% are organic, 56.3% are inorganic, and 2.4% are sewing needles. Most of the ingested foreign bodies are excreted spontaneously (1). These foreign bodies may reach pancreas and liver in 1% of patients, through penetration of small intestine or stomach wall (1, 2). Foreign bodies in pancreas might cause serious complications such as pancreatitis, pancreatic abscess, and pseudoaneurysm. These should be removed either endoscopically or surgically (1, 3, 4). In few cases, foreign bodies can also be removed using open surgical techniques (2, 5). However, the suggested technique is the laparoscopic approach before open surgery (3, 6, 7). Here we report the case of a 23-year-old female patient, who presented with epigastric pain and a sewing needle was removed laparoscopically from her pancreas parenchyma.

CASE PRESENTATION

A 23-year-old female patient presented with epigastric pain and retrosternal burns that continued intermittently for seven years. She had used proton pump inhibitors (PPI) and as her symptoms did not resolve, she presented to the hospital. In her physical examination, there was minimal tenderness and discomfort in the epigastric area without rebound sign or defense. Laboratory blood tests including her hemogram, biochemical markers, liver function tests, kidney function tests, and amylase levels were within normal limits. Her standing abdominal x-ray was also normal (Figure 1a). During gastroscopy, no sign of any pathology related to a foreign body was observed. We performed a barium follow-through x-ray with an initial diagnosis of gastroesophageal reflux disease, and in this test, we observed a foreign body in the epigastric area (Figure 1b). When patient's medical history was questioned again, it was found that she had accidentally swallowed a sewing needle seven years ago. She underwent computed tomography screening and we saw that a foreign body was present starting from the posterior side of the stomach reaching head and body of the pancreas. (Figure 2a) The patient was hospitalized, obtained the written informed consent for publication and prepared for operation, undergoing the whole routine preoperative workup. She underwent a laparoscopic surgery. During the laparoscopic exploration, the gastrocolic ligament was opened with the help of a laparoscopic instrument (Ligasure™; Vessel Sealing System, Covidien, MA, USA). Foreign metallic body (sewing needle), spanning from the posterior of a small curvature of stomach to the head and body of pancreas was visualized. (Figure 2b) Using a laparoscopic instrument (Endo clinch ™; single-use instrument, Covidien, MA, USA), the needle was (4 cm) removed from the abdomen in three pieces. (Figure 3a) The defect in the stomach wall was repaired laparoscopically using 3/0 vicryl sutures. The patient did not have any postoperative bleeding and she was mobilized 16 h postoperatively. She was started on oral diet on postoperative day four. She was discharged on postoperative day six. During her hospitalization, there was no wound infection or dehiscence (Figure 3b).

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DISCUSSION

Most of the foreign bodies such as fishbone, tooth, sewing needle, and chicken bone that are accidentally swallowed, are excreted spontaneously through anus. Only 1% of these penetrate the gastrointestinal tract (1, 2). Common perforation sites are crycopharyngeal ring, cardia, phylorus, C-loop duodenum, ligament of Treitz, Meckel diverticulum, ileocecal valve, appendix, and rectosigmoid junction (1-3). In some cases, these sharp foreign bodies can perforate the walls of stomach or duodenum and reach the liver. Foreign bodies reaching pancreas

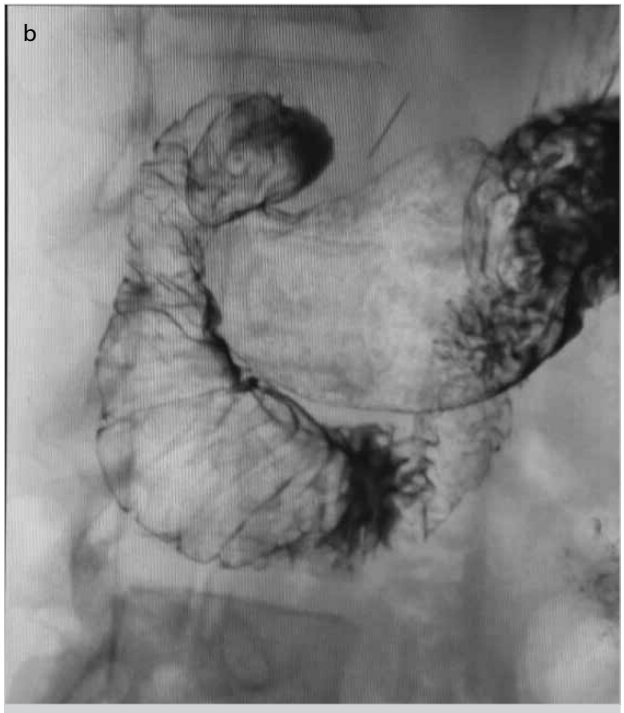

Figure 1. a, b. (a) Normal standing x-ray and (b) stomach passage x-ray and foreign body

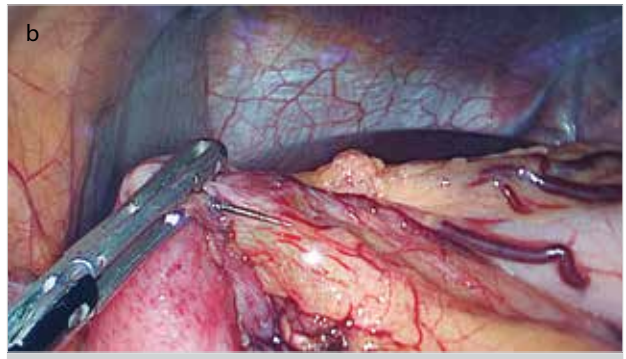

Figure 2. a, b. (a) Abdominal CT and (b) metallic foreign body

Figure 3. a, b. (a) Metallic foreign body and (b) postoperative day four

and liver parenchyma can cause abscess, pseudoaneurysm, pancreatitis, and high-mortality-risk complications (1, 4, 5).

Most patients cannot remember any accidental swallowing of foreign bodies. Therefore, diagnosis of these patients is not easy. Symptoms can mimic other diseases such as gastroesophageal reflux and gastritis, just like in our patient. Standing x-rays are used widely for diagnosis of foreign bodies in the abdominal area but may not provide exact localization like abdominal CT (3). Our patient presented to us with chronic abdominal pain with no mention of any foreign body ingestion seven years ago. Therefore, foreign body ingestion was not included in our initial diagnosis. We did not perform a double-sided standing abdominal x-ray, and one-sided standing abdominal x-ray did not reveal the sewing needle due to superposition. We believe that the first diagnostic test to perform, in patients with foreign body ingestion, should be a double-sided standing abdominal x-ray. Abdominal CT plays an important role in the diagnosis, localization, and determination of the surgical procedure in complicated cases comprising 1% of all patients.

Although open surgical approach is widely used for diagnosed abdominal foreign body extraction, in the modern surgical platforms, laparoscopic approach is advocated in stable nonacute patients due to its advantages of less postoperative pain, lower incidence of wound infection, and minimal surgical stress, in turn improving wound healing (2, 5, 8) . We found three cases of extraction of foreign body from the pancreas in literature, and here we present the fourth case (3, 6, 7, 9).

CONCLUSION

In stable patients with chronic abdominal pain, foreign bodies migrated into the abdominal cavity should be kept in mind for differential diagnosis and they should be questioned regarding this in the medical history. Abdominal CT presents an important advantage for both localization and decision of surgical approach. The treatment of such foreign bodies is surgical due to high-mortality-risk complications. Laparoscopic minimally invasive surgery should be preferred to open surgery due to advantages of better diagnosis, less postoperative pain, less wound infection, and faster recovery times.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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